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Should middle ear pressure and hearing loss be evaluated prior to septoplasty? A prospective cohort study

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Ethics Committee Approval
The study was conducted with the approval of the Scientific Research Investigation Commission of Goztepe Education Research Hospital (Ethical approval number: 02/98).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Nasal resistance is primarily caused by the deviation of the nasal septum at the level of the inferior turbinate and isthmus nasi. The pressure of the nasopharynx may decrease to less than that of the middle ear, from where the air would drain, thus creating a cavity with negative pressure. Therefore, pathological phenomena in the nasal cavity can affect the ventilation of the middle ear. In this study, we aimed to investigate how hearing is changed by septum deviation (SD) affecting middle ear pressure, and in case of hearing loss, whether there is any improvement after nasal surgery.
Methods: Sixty-seven patients were admitted to our Otorhinolaryngology clinic with nasal obstruction and hearing loss complaints, and 50 patients (≥18 years of age) with nasal congestion due to SD were included in this study. Septoplasty was performed to fifty patients and lateralization of SD was noted. Pure tone audiometric and tympanometric evaluations were performed preoperatively and postoperatively. Gain of hearing and gain of pressure after surgery were recorded, which were statistically compared between the groups.
Results: Of the 50 patients with nasal congestion and hearing impairment included in our study, 27 were male and 23 were female. The mean age of all cases was 32.08 (9.44) years, ranging between 18–56 years. Among forty-two patients with unilateral SD, thirty-seven (88%) had negative middle ear pressure. The lowest pure-tone-threshold was 1 dB, and the highest was 35 dB on the side with the deviation. On the side without SD, the lowest threshold was 8 dB, and the highest was 28 dB. Pure-tone-thresholds between 500 and 2,000 Hz were within normal range in seventy-six ears. Hearing loss was present in twenty-four ears. Postoperatively, the lowest hearing gain was 0 dB, and the highest was 15 dB on the side with the SD. On the side without SD, the lowest and highest hearing gains were 0 dB and 11 dB.
Conclusion: The negative pressure in the middle-ear due to SD may affect hearing. Hearing loss does not result from every deviation but occurs only when sufficient negative pressure is formed in the middle-ear.

Keywords: Septal deviation, Hearing loss, Middle ear

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Introduction

The physiological respiratory airway in humans passes through the nose [1]. Nasal resistance is primarily caused by deviation of the nasal septum at the level of the inferior turbinate and isthmus nasi. Nasal septal deviations due to developmental defects or trauma play a role in the formation of nasal resistance.

Ventilation of the middle ear is important for balancing the air pressure on either side of the tympanic membrane. The Eustachian tube provides ventilation of the middle ear and discharges secretions that accumulate within. The ability of the tympanic membrane to vibrate well depends on it being tensioned, with equal pressure on both sides. If the pressure on one side of the membrane exceeds the pressure on the other side, the tympanic membrane is tensioned to the side with less pressure, which prevents the formation of a normal vibration.

During swallowing in patients whose nasal cavities are obstructed for any reason, contact of the soft palate with the oropharynx can hold some air in the nasopharynx, increasing the air pressure. Therefore, in patients with septum deviation and in those whose nasal cavity is obstructed for any reason, the tube opens more easily with swallowing; however, in the second phase of swallowing, the palate is restored to its former position and the setting leads to a pressure drop in the nasopharynx. The pressure of the nasopharynx may decrease to less than that of the middle ear, from where the air would drain, thus creating a cavity with negative pressure. Therefore, pathological phenomena in the nasal cavity can affect the ventilation of the middle ear [2].

Flisberg et al. [3] applied a pressure of 680 mmH2O in the ear using the physiological environment, and when the nasal passage closed and opened during swallowing, they recorded changes in the middle ear pressure. Miller [4] performed the same test with the nasal passage closed, applying negative 400 mmH2O pressure to the ear, and determined that the pressure in the external auditory canal changed with swallowing. Brookler [5] applied negative 400 mmH2O pressure to the external auditory canal and measured residual pressure after 10 swallows, then measured the minimum positive air pressure capable of opening the tube without swallowing. All these studies showed hearing loss with negative middle ear pressure.

The aim of our study is to investigate how hearing is altered by septum deviation affecting middle ear ventilation, and if hearing loss occurs, whether there is any improvement after nasal surgery.

Materials and methods

Sixty-seven patients were admitted to the Goztepe Education and Research Hospital Otorhinolaryngology clinic within the last year with nasal obstruction and hearing loss complaints. Fifty patients over 18 years of age with nasal congestion due to septal deviation were included in the study group.

Study design and sample size

Study design has a major impact on the sample size. Descriptive studies need hundreds of subjects for acceptable confidence intervals for small effects. Experimental studies need fewer sample sizes while the cross-over designs need one-quarter of the number required compared to a control group because every subject gets the experimental treatment in a cross-over study. An evaluation study in a single group with pre-post type of design needs half the number for a similar study with a control group. For that reason, fifty patients were included the study. The definition of alpha is the probability of detecting a significant difference when the treatments are equally effective or in case of a risk of false positive findings. The alpha level used in determining the sample size in most academic research studies are either 0.05 or 0.01. The lower the alpha level, the larger the sample size. For example, a study with alpha level of 0.01 requires more subjects when compared to a study with alpha level of 0.05 for similar outcome variable. So, we used *P*-value as <0.05 to determine statistical significance. The difference between two groups in our study was explored in terms of estimate of effect, appropriate confidence interval, and *P*-value. The confidence interval indicates the likely range of values for the true effect in a population while *P* value determines how likely it is that the observed effect in the sample is due to chance. A related quantity is the statistical power of the study, which is the probability of detecting a predefined clinical significance. The ideal study is the one with high power. This means that the study has a high chance of detecting a difference between groups if it exists. Consequently, if the study demonstrates no difference between the groups, the researcher can be confident in concluding that none exists. The ideal power for any study is 80%, the same as ours.

The study was conducted with the approval of the Scientific Research Investigation Commission of Goztepe Education Research Hospital (Ethical approval number: 02/98). Informed consent was obtained from the patients. Patients with a history of allergic rhinitis or other causes of nasal congestion, who needed nasal plastic reconstruction, or who had sleep apnea, deformity of the columella, alar collapse, adenoid hypertrophy, acute or chronic sinusitis, nasal vestibular pathologies, a history of acoustic trauma, anamnesis of previously treated otitis media, and otitis media sequela in the otoscopic examination as well as patients with a history of using ototoxic drugs and those who had previously undergone nasal surgery were excluded from the study.

Nasal examination

The causes of nasal obstruction were evaluated through anterior and posterior rhinoscopic examination of the patients. Cotton pledgets with pantocaine (1% tetracaine-Hcl) were used to examine the nasal passage. The lateralization of the nasal septum and its localization were noted. The pharyngeal orifice of the Eustachian tube was examined. In the otoscopic examination, the shape of the auricle, the anatomical and structural differences between the external auditory canals, the appearance of the tympanic membrane, mobility, and perforation were examined. The patency of the Eustachian tube was checked using the Valsalva test. Rinne, Weber, and Schwabach tests were performed using 512 frequency diapasons.

Audiometric evaluation

Audiometric evaluations were performed using interacoustics AC3 and Madsen OE822 clinical audiometer devices. Pure-tone averages (PTA) of thresholds at 500, 1,000, and 2,000 Hz frequencies were measured in both ears.

Tympanometric measurements were made using interacoustic impedance audiometer AZ7 and XYT recorder AG3 devices to obtain tympanogram curves. During the acoustic impedance tests, patients were instructed not to cough or sniff. Measurement was performed by applying positive pressure to the middle ear. Patients with normal pure-tone thresholds at speech frequencies between 0 and 26 dB and middle ear pressures between +25 and -25 mmH2O were considered the normal group. The Student's-t test was used to compare groups.

Surgical procedure

In septoplasty operation, submucosal resection under local anesthesia was performed using the Killian method to correct patients' septal deviations. The anterior pack inserted into the nose was removed after 48 hours. Patients were given amoxicillin for five days and paracetamol as an analgesic. Postoperative audiometric and tympanometric measurements were conducted on the 21st day following the operation in accordance with the literature [6].

Statistical analysis

One of the most important tests within the branch of inferential statistics is the Student's t-test. The Student's t-test for two samples is used to test whether two groups are different in terms of a quantitative variable, based on the comparison of two samples drawn from these two groups. Our groups' sizes were sufficient for statistical analysis, which was performed using SPSS for Windows version 21 (IBM SPSS Inc., Chicago, IL, USA). The minimal level of significance was fixed at *P*-value ≤0.05.

Results

Of the 50 patients with nasal congestion and hearing impairment included in our study group, 27 were male and 23 were female. The mean age of all cases was 32.08 (9.44) years with an age range of 18–56 years. Decreased tympanic membrane tension was detected in 72 (72%) of 100 ears with a pneumatic otoscope. Eustachian tube permeability, detected with a Valsalva test, was within the normal range in 57 (57%) of 100 ears.

In all patients, bone conduction thresholds were between 0 and 20 dB, which was within normal range. In diapason tests, the Rinne test was positive in 79 ears. The Weber test was not lateralized in 79 ears; in 21 ears, the test was lateralized to the right or the left. The Schwabach test results were within the normal range in 79 ears and extended in 21 ears.

We found that 23 of 42 patients with unilateral septal deviation had a right deviation, and 19 had a left deviation. In eight patients, bilateral septal deviation was present. In 42 patients with unilateral septal deviation, the middle ear pressure on the side without the deviation ranged between 50 mmH2O-175 mmH2O. Of the 42 patients with unilateral septal deviation, 37 (88%) had negative middle ear pressure. Middle ear pressures in eight patients with bilateral septal deviation were negative in both ears. The lowest pure tone thresholds were 10 dB, and the highest were 35 dB on the side with deviation. On the side without septum deviation, the lowest threshold was 8 dB, and the highest threshold was 28 dB. Pure tone thresholds between 500 and 2,000 Hz were within normal range in 76 ears. Hearing loss was present in 24 ears.

In the postoperative period, the lowest hearing gain was 0 dB, and the highest was 15 dB on the side with the septum deviation. On the side without a deviated septum, the lowest and highest hearing gain values were 0 dB and 11 dB, respectively. The preoperative and postoperative period hearing gains in 12 (12%) ears were similar (Table 1) (*P*=0.064).

Table 1: Pure tone audiometry results in preoperative and postoperative period and gains of hearing in patients after surgery

Patient no	Age/Sex	Deviation	Pure Tone Audiometry (dB)				Gain of Hearing	
			Preoperative		Postoperative			
			(R)	(L)	(R)	(L)	(R)	(L)
1	36/M	Right	25	20	10	10	15	10
2	21/M	Bilateral	23	1 8	15	10	8	8
3	18/M	Left	28	24	17	1 1	11	13
4	24/F	Left	18	20	16	14	2	6
5	33/F	Right	31	17	25	13	6	4
6	46/M	Right	27	24	20	16	7	8
7	23/F	Bilateral	25	23	16	16	9	7
8	27/F	Left	18	21	14	12	4	9
9	18/F	Left	15	10	14	10	1	0
10	29/M	Right	14	10	11	8	3	2
11	37/F	Right	16	1 0	10	10	6	0
12	19/M	Left	18	12	8	7	10	5
13	24/M	Left	13	27	10	13	3	14
14	18/F	Right	15	1 1	6	6	9	5
15	30/M	Bilateral	30	18	21	12	9	6
16	24/F	Right	12	8	12	8	0	0
17	18/F	Left	15	20	15	I5	0	5
18	31/M	Right	21	13	14	1 1	7	2
19	27/F	Bilateral	16	21	10	14	6	7
20	48/M	Right	17	14	10	12	7	2
21	32/F	Right	19	14	15	10	4	5
22	34/M	Bilateral	21	16	16	1 5	5	1
23	41/M	Right	35	17	23	14	12	3
24	46/F	Left	13	24	10	1 4	3	10
25	31/M	Right	18	11	13	9	5	2
26	37/M	Bilateral	15	17	15	17	0	0
27	51/F	Right	18	21	14	19	4	2
28	38/M	Right	30	15	21	13	9	2
29	29/M	Left	14	18	10	10	4	8
30	31/M	Right	21	13	13	8	8	5
31	56/M	Left	10	18	10	12	0	6
32	38/F	Left	17	26	15	18	2	8
33	30/M	Right	16	11	11	7	5	4
34	45/M	Left	18	1 1	14	7	4	4
35	33/F	Left	8	17	6	10	2	7
36	27/M	Right	19	16	16	16	3	0
37	29/F	Left	12	14	12	14	0	0
38	34/F	Right	26	13	18	10	8	3
39	34/F	Right	12	10	8	8	4	2
40	31/M	Bilateral	24	14	20	10	4	4
41	29/F	Left	14	18	12	13	2	5
42	34/M	Right	20	16	14	10	6	6
43	27/F	Left	13	18	11	12	2	6
44	56/M	Bilateral	21	12	15	10	6	2
45	34/F	Right	18	14	14	14	4	0
46	39/M	Left	14	12	11	8	3	4
47	24/F	Right	18	14	12	9	6	5
48	26/M	Left	17	14	12	10	5	4
49	39/F	Right	17	11	13	8	4	3
50	18/M	Left	14	20	10	12	4	8

R: Right, L: Left.

The otoscopic examination results did not differ from preoperative findings. The results of the diapason tests performed in the postoperative period were as follows: Rinne was positive in 88 ears and negative in 12 ears; Weber was not lateralized in 88 ears and lateralized in 12 ears; Schwabach detected normal ranges in 86 ears and extended in 14 ears; the Valsalva test showed that the tubal patency in 81 of 100 ears in the postoperative period was normal (positive). In 19 ears, tubal patency was impaired (negative). When the middle ear pressure gains were examined, the lowest pressure gain obtained on the side of the septum deviation was 0 mmH2O, and the highest pressure gain was 150 mmH2O. On the side where there was no deviated septum, the lowest and pressure gains were 0 mmH2O and 75 mmH2O, respectively. There was no pressure gain in 13 of 100 ears (Table 2) (*P*=0.058).

Table 2: Tympanometry results in preoperative and postoperative period and gains of pressure in patients after surgery.

Patient no	Age/sex	Deviation	Pressure of Middle Ear (mmH2O)				Gain of Pressure	
			Preoperative		Postoperative			
			(R)	(L)	(R)	(L)	(R)	(L)
1	36/M	Right	-75	-1 00	-50	-50	25	50
2	21/M	Bilateral	- 1 00	-125	-25	0	75	12
3	18/M	Left	-150	-200	-75	-50	75	1 5
4	24/F	Left	-75	-50	-50	-25	25	25
5	33/F	Right	-150	-100	-75	-75	75	25
6	46/M	Right	-100	-100	-50	-75	50	25
7	23/F	Bilateral	-175	-150	-25	-50	150	10
8	27/F	Left	-100	-200	-100	- 150	0	50
9	18/F	Left	-50	50	-25	-25	25	25
10	29/M	Right	-150	-100	0	-25	1 50	75
11	37/F	Right	-50	-25	0	0	50	25
12	19/M	Left	-100	-125	-50	-50	50	75
13	24/M	Left	-50	-125	0	25	50	150
14	18/F	Right	-75	-50	25	25	100	75
15	30/M	Bilateral	-100	-50	0	0	100	50
16	24/F	Right	-75	-75	-50	-75	25	0
17	18/F	Left	-50	- 150	-25	-50	25	100
18	31/M	Right	100	50	50	25	50	25
19	27/F	Bilateral	-150	-125	-75	-75	75	50
20	48/M	Right	-100	-50	-25	0	75	50
21	32/F	Right	25	25	25	25	0	0
22	34/M	Bilateral	-150	-100	-75	-50	75	50
23	41/M	Right	-200	-150	-100	-75	100	75
24	46/F	Left	25	50	25	25	0	25
25	31/M	Right	-25	-25	-25	-25	0	0
26	37/M	Bilateral	-150	-100	-125	-100	25	0
27	51/F	Right	-100	-125	-75	-100	25	25
28	38/M	Right	-50	-75	0	-25	50	50
29	29/M	Left	25	25	0	0	25	25
30	31/M	Right	-50	-50	0	-25	50	25
31	56/M	Left	-125	-175	-100	-100	25	75
32	38/F	Left	-150	-175	-100	-100	50	75
33	30/M	Right	-100	-75	-50	-50	50	25
34	45/M	Left	-175	-150	-100	- 100	75	50
35	33/F	Left	-50	-50	0	0	50	50
36	27/M	Right	-50	-75	-25	-75	25	0
37	29/F	Left	-125	-100	-50	-50	75	50
38	34/F	Right	-100	-50	-75	-5O	25	0
39	34/F	Right	- 175	-100	-100	-75	75	25
40	31/M	Bilateral	-200	-150	-150	-75	50	75
41	29/F	Left	25	25	25	25	0	0
42	34/M	Right	-150	-100	-75	-50	75	50
43	27/F	Left	-75	-100	-50	-50	25	50
44	56/M	Bilateral	-100	-50	-50	0	50	50
45	34/F	Right	-75	-50	-50	-25	25	25
46	39/M	Left	-100	-150	-50	-50	50	100
47	24/F	Right	-75	-50	-50	-50	25	0
48	26/M	Left	-100	-125	-50	-75	50	50
49	39/F	Right	-75	-75	-25	-50	50	25
50	18/M	Left	-150	-200	-75	-100	75	100

Discussion

Nasal septal deviations narrow the respiratory tract, causing various complications in neighboring structures. The role of septal deviations in pathologies of the middle ear is undisputed. However, opinions differ about the frequency and importance of these middle ear complications among other upper respiratory complications [7].

As a result of nasal septal deviation, breathing through the nose is disturbed, the lumen of the Eustachian tube narrows, and the ventilation of the middle ear is disrupted. Insufficiency in the tubal canal creates negative pressure in the middle ear, which causes hearing loss before forming a collection of fluids of a transudate character in the middle ear [3]. In studies on the prevention of this fluid formation, it has been proven that negative pressure formed in the middle ear disrupts hearing. Hearing is especially decreased in speech frequencies, while no loss was detected in frequencies greater than 2,000 Hz [7].

In the literature, the effects of air pressure on the middle ear have been investigated, and a direct relationship was found between negative pressure and hearing loss. It is known that nasal septal deviations disrupt the ventilation of the middle ear. In our study, we investigated the effect of air pressure on hearing during the preoperative period and found that the middle ear air pressure on the side with nasal septal deviation was negative in 90% of cases [3]. Negative pressure values slightly reduced hearing in 24% of cases (21–35dB). Hearing was unaffected in 76% of cases. Hearing loss was the conductive type. In our study, hearing loss rate on the side with nasal septal deviation was 24%, and negative pressure in the middle ear was 90%.

Negative pressure and hearing loss levels were not in complete harmony. Negative pressure in the middle ear may not occur in all nasal septal deviations [8, 9]. In our study, hearing gain occurred in 88% of patients by the 21st postoperative day, but a hearing gain of <10dB occurred in only seven ears. We found that postoperative hearing gain of <10dB occurred in 18 ears by the 60th postoperative day. On the 90th postoperative day, a hearing gain of <10dB was detected in 25 ears. Thus, postoperative recovery in hearing occurs over time [3]. Also Kaya et al. [10] showed that septoplasty may have a beneficial effect on middle ear ventilation and Eustachian Tube in their study. Duran et al. [11] found that approximately 30% improvement occurs in the middle ear pressure after septoplasty. In contrast, Eyigör et al. [12] described that the success of septoplasty operation does not affect the ventilation and pressure of the middle ear significantly.

Rhinosinusitis can be induced by impaired ventilation and drainage in patients with a deviated nasal septum (especially those with a high deviation) due to a moved middle turbinate under consistent pressure [9]. Tubal collapse due to septum deviation affects both ears to varying degrees. In the postoperative period, hearing loss on the side with nasal septal deviation and gains of air pressure in the middle ear are correlated with the numerical values on the side without septum deviation. The cause of unilateral aural fullness is usually same-side obstructions in the nasal cavity. Negative pressure affecting the ear is the cause of the nasal congestion, and sometimes it can bilaterally affect the tubal orifice. With this mechanism, inflammation and edema in the nasal cavity drained by peritubal lymphatics leads to tubal obstruction and causes effusion of the middle ear. As a result of nasal obstruction, ciliary activity is disturbed. With the lymphatic plexus pathway on the side with nasal obstruction, the contralateral nasopharynx may also be affected [13]. Negative pressure resulting from nasal septal deviation can affect both ears over time.

Limitation

One minor limitation to this study might be the limited number of participants. Also, a major limitation of our study is lack of evaluations of allergic rhinitis with laboratory tests.

Conclusion

The negative pressure in the middle ear occurring because of nasal septal deviation may affect hearing. On the other hand, hearing loss does not result from every deviation, but occurs only when sufficient negative pressure is formed in the middle ear. The tympanometric findings that we detected in our study showed that middle ear pressure was significantly affected in patients with deviation but returned to normal values during the postoperative period. In most patients in the postoperative period, there was an improvement in hearing over time.

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Retrospective cohort study of pregnancy terminations before the 24th week of pregnancy

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Ethics Committee Approval
TC. İzmir Governorship İzmir Provincial Health Directorate, S.B.Ü. Tepecik Training and Research Hospital Clinical Research Ethics Committee, Decision No: 2020 / 13-40, 16/11/2020.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Termination, which indicates ending the pregnancy process, should be performed in fetal anomalies incompatible with life or maternal-life threatening pregnancies. Pregnancy termination involves a challenging process for both the clinician and the patients. Identifying the pathology indicating termination and sharing this decision with the family should include certain strategies. In this study, the indications for termination decision were examined. We think that these indications may help the clinician make a termination decision.

Methods: In this retrospective cohort study, the indications, and termination procedures performed on 707 pregnant women in the Perinatology clinic of Izmir Tepecik Training and Research Hospital between November 2016 and November 2020 were analyzed retrospectively.

Results: The total number of patients who underwent termination was 707. Their ages varied between 14 and 45 years (median 29.6). The median number of pregnancies among all patients was 2.5 (range: 1-12). The minimum and maximum gestational weeks of termination were 10 and 24 weeks, respectively (median 17.4). Termination indications were divided into groups: a) Congenital malformations (without karyotype diagnosis) (n=400, 56.5%) b) Congenital malformation with diagnosed karyotype anomalies (n=27, 3.8%) c) Only karyotype anomalies (n=146, 20.6%) d) Other fetal / obstetric disorders (anhydramnios, Preterm Premature Rupture of Membranes (PPROM), teratoma, Twin-to-twin transfusion syndrome (TTTS), drug use (n=115, 16.2%) e) Maternal causes (n=19, 2.6%). In addition, each group was divided into three groups according to the weeks of termination as 11-14 weeks, 15-22 weeks, and 23-24 weeks. The total number of patients for these groups were 170, 503 and 34, respectively. Patients without fetuses with karyotype anomalies and who were terminated due to congenital malformations were grouped according to the origin of the malformation: a) Central nervous system anomalies (57.2%) b) Multiple anomalies (18.7%) c) Hydrops fetalis (8%) d) Urinary system anomalies (6.5%) e) Skeletal system anomalies (5.7%) f) Cardiac anomalies (1.7%) g) Conjoined twins (1%) h) Congenital pulmonary airway obstruction (0.5%) i) Congenital diaphragmatic hernia (0.2%).

Conclusion: The continuation of abnormal pregnancies brings many problems. Termination of pregnancies that are incompatible with life or involving serious anomalies is necessary in most cases. In daily practice, making the decision of termination and sharing it with the family should include an important algorithm.

Keywords: Termination of pregnancy, Congenital malformations, Fetal indications

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Introduction

Pregnancy terminations in Turkey can be grouped into three categories in general. The first group of terminations can be performed until the 10th gestational week per the family's request. According to the 13th article of the "regulation on the execution of population planning services" published in 1983, the termination process was approved by law until the 10th week, with the consent of the mother and father [1]. Termination in pregnancies over the 10th week is limited with certain indications. While pregnancies that endanger maternal life make the second group, pregnancies involving fetal genetic anomalies or malformations make the third group.

It is important to base the termination decision on concrete evidence and provide options to the family accordingly. During fetal evaluation, diagnosis should be made using all current evaluation parameters. In cases where ultrasound and diagnosis are not clear, using magnetic resonance is important for the diagnosis of fetal malformation [2-4]. In addition, obtaining a fetal karyotype sample (chorionic villus biopsy, amniocentesis, cordocentesis) to detect genetic problems will help the clinician in terms of definitive diagnosis. Maternal problems should be evaluated and those that may prevent the continuation of pregnancy should be revealed with a multidisciplinary approach. Regardless of the indication, in our perinatology clinic, termination is performed to pregnancies below 24 weeks only.

In this study, we retrospectively analyzed the patients who decided to terminate due to fetal/maternal problems under 24 weeks of gestation and analyzed the indications for termination.

Materials and methods

A total of 707 patients who decided to terminate between November 2016 and November 2020 were retrospectively analyzed. Terminations under 10 weeks of gestation performed per the wishes of the family were not included in this study. Pregnancies with serious fetal congenital malformations incompatible with life and those with serious maternal disease which threaten maternal life were included in the study. Anomalies were determined with ultrasound and fetal magnetic resonance.

Data were obtained from the digital archive of İzmir Tepecik Training and Research Hospital and patient files. The demographic and obstetric characteristics of the patients are shown in Table 1, Figure 1, and Figure 2.

Table 1: Demographic and obstetric characteristics of the patients

	Median	Minimum	Maximum
Age	29.6	14	45
Gravida	2.5	1	12
Parity	1.08	0	1
Gestational week	17.4	10	24

All patients underwent routine pregnancy examinations (blood tests, maternal blood pressure measurements and systemic examinations during pregnancy). Prenatal screening tests were performed to all patients. In addition, chorionic villus sampling, amniocentesis or cordocentesis procedures were performed for prenatal diagnosis in necessary cases.

In the council where the termination decision is made, there are experts from all relevant branches (perinatology, neurosurgery, radiology, neurology, pediatric cardiovascular surgery, pediatric cardiology, pharmacology, pediatric nephrology, and neonatology). According to the characteristics of the patient, a termination decision was made by obtaining expert opinion from the required branch.

Figure 1: Age range of patients

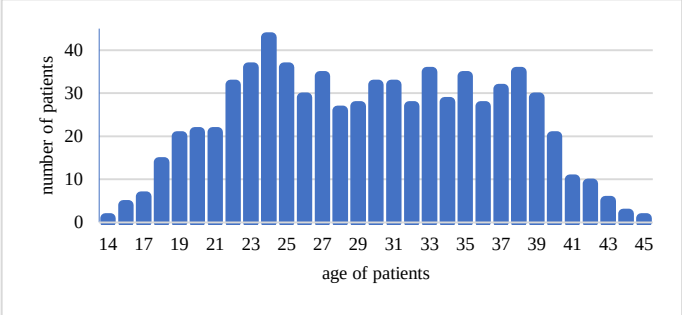
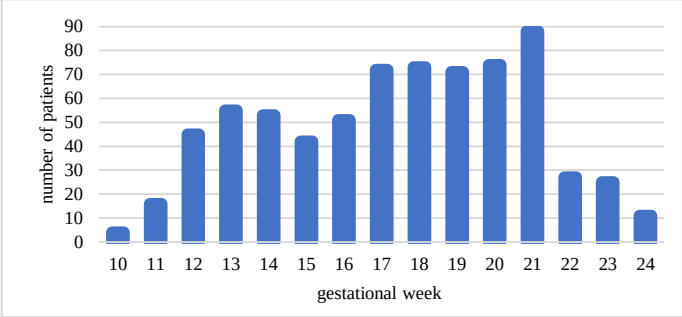


Figure 2: Distribution of the gestational weeks of the patients



The patients were divided into five subgroups: a) Congenital malformations (without karyotype diagnosis) b) Congenital malformations and diagnosis of karyotype anomalies) c) Only karyotype anomalies d) Other fetal / obstetric disorders e) Maternal causes.

Pregnancies with congenital malformations were examined in two separate groups. The first group comprised pregnancies with congenital malformations who did not undergo invasive karyotyping (patients who did not consent to invasive sampling or did not need karyotyping due to the presence of multiple major anomalies). The second group included pregnancies with congenital malformations who were diagnosed with karyotype disorders. The third group included pregnancies deemed risky during prenatal screening, later found to have karyotype anomalies as revealed by invasive karyotype sampling. Anhydramnios, premature rupture of membranes (PPROM), teratoma, twin to twin transfusion syndrome (TTTS) and iatrogenic drug use were categorized as a separate group. The last group included patients with terminated pregnancies due to maternal reasons.

The five groups were also divided into categories according to the week of gestation in which termination took place. Those performed between the 11th and 14th weeks constituted the first group, those performed between the 15th and 22nd weeks were included in the second group, and finally, the ones performed between the 23rd and 24th weeks constituted the third group.

This study was approved by Izmir Tepecik Training and Research Hospital Ethics Committee (2020/13-40, 11/16/2020).

Statistical analysis

A total of 707 patients were included in the study. The minimum, maximum and median values of the ages of the patients, the number of previous pregnancies, and the weeks of

gestation at termination were analyzed. The results were classified according to the patients' ages and weeks of gestation. Termination indications were also classified and those in the same group were indicated in the table together with their percentages.

Results

The ages of 707 patients included in our study ranged from 14 to 45 years (mean: 29.6 years). The ages at termination were similar between the patients. Median gravida and parity values of the patients who underwent termination were 2.5 and 1.08, respectively. The gestational weeks of the patients ranged from 10 to 24 weeks (mean 17.4). We found that the most common week of termination was between the 20^{th}-21^{st} weeks (86 patients).

Fifty-six percent of the patients (n=400) were recommended termination due to congenital malformations without karyotype diagnosis (Table 2). While 14.4% of these patients (n=102) were between the 11^{th} and 14^{th} gestational weeks, 38.6% (273 patients) were between the 15^{th} and 22^{nd} gestational weeks and 3.5% were between the 23^{rd} and 24^{th} gestational weeks. We categorized the patients in this group according to the origin of their congenital malformation. Anomalies related to the central nervous system were the most common (57.2%), followed by multiple anomalies (18.7%), hydrops fetalis (8%), urinary system anomalies (6.5%), skeletal dysplasia (5.7%), cardiac anomalies (1.7%), conjoined twins (1%), congenital pulmonary airway obstruction (0.5%) and congenital diaphragmatic hernia (0.2%) (Table 3).

Table 2: Termination indications

Number of patients (%)		Distribution of patients according to the week of termination		
	total	11^{th} -14^{th} weeks	15^{th}-22^{th} weeks	23^{th}-24^{th} weeks
Congenital Malformations (without karyotype diagnosis)	400 (56.5%)	102 (14.4%)	273 (38.6%)	25 (3.5%)
Congenital Malformation + Karyotype Anomaly	27 (3.8%)	6 (0.8%)	19 (2.6%)	2 (0.2%)
Isolated Karyotype Anomaly	146 (20.6%)	31 (4.3%)	109 (15.4%)	6 (0.8%)
Other Fetal/Obstetric Disorders	115 (16.2%)	19 (2.6%)	95 (13.4%)	1 (0.1%)
Anhydramnios	40 (5.6%)	4 (0.5%)	35 (4.9%)	1 (0.1%)
PPROM	54 (7.6%)	3 (0.4%)	51 (7.2%)	
Teratoma	5 (0.7%)	1 (0.1%)	4 (0.5%)	
TTTS	4 (0.5%)		4 (0.5%)	
Iatrogenic Drug Use	12 (1.6%)	11 (1.5%)	1 (0.1%)	
Maternal Causes	19 (2.6%)	12 (1.7%)	7 (0.9%)	
Total	707 (100%)	170 (24%)	503 (71.1%)	34 (4.8%)

PPROM: Preterm Premature Rupture of Membranes, TTTS: Twin to Twin Syndrome

Table 3: Congenital malformations by systems

Congenital Malformation	Number of Patients (percentage in group)			Total
	11^{th} -14^{th} weeks	15^{th} -22^{th} weeks	23^{th}-24^{th} weeks	
Central Nervous System	65 (16.2%)	148 (37%)	16 (4%)	229 (57.2%)
Skeletal System	4 (1%)	19 (4.7%)		23 (5.7%)
Cardiac Abnormality		7 (1.7%)		7 (1.7%)
Hydrops Fetalis	13 (3.2%)	18 (4.5%)	1(0.2%)	32 (8%)
Urinary System	5 (1.2%)	21 (5.2%)		26 (6.5%)
Congenital Diaphragmatic Hernia		1 (0.2%)		1 (0.2%)
Congenital Pulmonary Airway Obstruction		2 (0.5%)		2 (0.5%)
Conjoined Twin	3 (0.7%)	1 (0.2%)		4 (1%)
Multiple anomaly	12 (3%)	56 (14%)	8 (2%)	75 (18.7%)
Total	102 (25.5%)	273 (68.25)	25 (6.2%)	400 (100%)

The number of patients who carried fetuses with karyotype anomalies in addition to congenital malformations were 27 (3.8%). Six (0.8%) were between the 11^{th}-14^{th} gestational weeks, 19 patients (15.4%), between the 15^{th}-22^{nd} gestational weeks, and 2 (0.2%) were between the 23^{rd}-24^{th} weeks. The number of patients who underwent invasive karyotyping after positive prenatal screening tests and found to have abnormal results was 146 (20.6%). While the pregnancies of 31 of these patients were terminated between the 11^{th} and 14^{th} weeks, 109 (15.4%) were terminated between the 15^{th} and 22^{nd} weeks, and 6 (0.8%) were terminated between the 23^{rd} and 24^{th} weeks.

We included 115 patients (16.2%), except those carrying fetuses with congenital malformations and genetic problems, in the other fetal/obstetric disorders group. In this group, anhydramnios (5.6%), PPROM (7.6%), teratoma (0.7%), TTTS (0.5%) and iatrogenic drug use (2.6%) were the reasons for termination.

Patients who were recommended termination of pregnancy due to maternal reasons only were included in a separate group (n=19, 2.6%).

Discussion

Making a pregnancy termination decision requires a serious algorithm. The patient should be evaluated with multidisciplinary approach and all auxiliary equipment that can be used in fetal diagnosis should be used when necessary. Although ultrasound findings provide a large amount of evidence, it is not sufficient in some cases to make a termination decision. Fetal magnetic resonance imaging, prenatal screening tests and invasive karyotype sampling methods should be used frequently [2-4].

Termination by family request is legal up to the 10^{th} gestational week in Turkey, according to 'the population planning services law' published in 1983 [1]. Termination after the designated period should depend on medical reasons. If the fetus is not alive, there is no week limitation for the termination decision [5, 6]. However, if the fetus is alive, it is legally considered an individual and has legal rights (Turkish Civil Code no: 4721/28 2001). After the 24^{th} week, it is not considered ethical to terminate the pregnancy without feticide (Maternal-Fetal and Perinatal Association of Turkey, Ankara Declaration, 2011) [7]. In Izmir Tepecik Training and Research Hospital, a termination decision made over the tenth week of gestation involves multidisciplinary approach and the decisions are thoroughly discussed with the family.

Congenital heart diseases, which are the most common anomalies in the literature, are not an indication for termination because some types of heart anomalies are compatible with life [8]. Central nervous system anomalies are the most common reason for termination of pregnancy [9-12]. We found that the most common cause of congenital malformations in terminated pregnancies in our center was central nervous system anomalies (57.2%). Other reasons for termination appear at different rates in different publications [13]. We found that multiple anomalies (18.7%) and urinary system anomalies (6.5%) were the second and third most frequent, respectively. We think that the

differences may be due to different geographical features or the diverse characteristics of the population admitted to the hospital.

The rate of patients with congenital malformations and concomitant chromosomal anomalies was lower in our study compared to others [10]. Invasive karyotype analysis is recommended for patients with multiple anomalies in our center. However, some patients we follow with multiple anomalies do not accept this procedure and they want termination without invasive karyotyping. For this reason, we think that we found a lower rate than that reported in the literature.

The number of patients who received invasive karyotyping and were diagnosed with chromosomal anomalies of the fetus after positive prenatal screening tests is 146 (20.6%). This rate was similar with the other publications in the literature [14, 15].

In the literature review conducted in terms of the upper limit of gestational week for termination, it is seen that different weeks are considered in different countries [11]. In Turkey and many other countries, because the limit of viability, 24th gestational week is accepted as the upper limit for termination without feticide [5]. After this week, feticide process should be added to pregnancy terminations. Also, after the 24th gestational week, the termination procedure should be implemented cautiously [16, 17].

Limitations

The retrospective nature of this cohort study limited us in terms of generalizing the results. Studies involving more patients are needed to evaluate the causes of termination. In future studies where each country or ethnic origin is examined much more broadly, it can be determined whether there are differences in pregnancy termination indications between the communities.

Conclusion

Pregnancy termination involves difficulties for both the family and the clinician. Due to different legal regulations in different countries, it is not possible to clearly standardize the termination indications. Thorough knowledge of the legal and medical requirements will ensure that more accurate decisions are made when making a termination decision as a physician. Since there is a wide spectrum of diseases that may cause pregnancy termination, the most accurate information and recommendations should be provided to the patient by following up-to-date diagnosis and treatment protocols.

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Investigating the particle amount hanging in the air in the operating room during instrumented and non-instrumented neurosurgery operations

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Ethics Committee Approval
Administrative permission and local ethics board consent (Kutahya Health Sciences University - approval date and number: 2019/5) were obtained for the study.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: To improve patient safety and surgical results, it is highly significant to understand the factors which cause high particle matter (PM) levels in the air of the operating room. The objective of this study was to investigate the particle amounts hanging in the air in the operating room in instrumented and non-instrumented cases during Neurosurgery operations.

Methods: This was an analytical study comparing PM amounts measured in 21 non-instrumented and 22 instrumented cases performed in Kütahya Evliya Çelebi Training and Research Hospital NRS operating room between March-May 2019. Five spots were identified in the operating room and measurements were performed at these spots by the same researcher during the operation. "Particles Plus 8306" particle measurement device was used for the measurements performed for 11 weeks. Also, detailed information such as operation duration, number of team members in the operating room and operating time of vaporizers per operation were registered on a form.

Results: PM0.5 and PM1 amounts were higher in instrumented operations compared to non-instrumented operations. All PM amounts (except PM 0.5) measured in instrumented and non-instrumented operations decreased towards the end of the operation compared to the beginning (P=0.001, P=0.001, P=0.001, P=0.001 for all).

Conclusions: PM smaller than one micron were detected more in instrumented operations compared to non-instrumented operations, and the amounts of these particles increased with the number of team members present. All PM amounts increased with operation durations, and all PM (except PM 0.5) amounts measured in non-instrumented and instrumented operations gradually decreased towards the end of the operation compared to the beginning. Regularly checking the air flow and restricting entry and exit in and out of the operating room are necessary.

Keywords: Clean room, Instrumentation, Neurosurgery, Operating room, Particles

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Introduction

To prevent the wound site infections and contamination during the surgical operations, it is important to provide sterility in the operating room and observe the air quality [1]. Although no consensus exists regarding the best method, the correlation between the number of particles hanging in the air and microbial contamination was reported in some studies and it was suggested that the particle count could be used to observe contamination [1-3]. This measurement is performed by counting particle matters (PM) of 0.3, 0.5, 1.0 and 5.0 µm present in one m^3 to check whether the room meets ISO standards (ISO-14644-1 "Cleanrooms & Association Controlled Environment Part 1 Classification of Air Cleanliness").

To improve patient safety and surgical results, it is of great importance to understand factors such as staff mobility, which causes high particle levels in the operating room air, the type of the instruments used during the operation and the duration [2, 3]. The objective of this study was to investigate the particle amounts hanging in the air in the operating room in instrumented and non-instrumented cases during Neurosurgery (NRS) operations. Correlations between other variables such as particle count and door opening frequency, number of individuals in the operating room and duration of the surgical operation were also assessed.

Materials and methods

Descriptions

The neurosurgery clinic in our hospital performs 570 operations per year and twelve operations per week. In these, instruments exclusive for Neurosurgery operations, namely, cervical plate, monoaxial, polyaxial, transpedicular screw, lumbar intervertebral cage and implants are used, along with the routine surgical sets used during opening and closure in all operations. In this study, all operations performed with titanium screw to provide spinal stabilization were included in "instrumented" operations and the measurements used in these operations were included in the study group. Measurements made in all non-instrumented operations were included in the control group.

Measurement locations

Neurosurgery operating room where the study was conducted is a 24 square meter area and its ventilation is provided by a HEPA filter cleaning PM over 0.5µm. Measurements were performed five steps away from the door and near the air conditioner by the same researcher during the operation. The measurements began when the whole team was ready, and anesthesia was completely provided. "*Particles Plus 8306 particle measurement device*" was used for measurements performed for 11 weeks. This manual and mobile device with a sensor counts PM values between 0.3-25 µm with 0.1 CFM (2.83 LPM) air flow rate. It also measures temperature and relative humidity values. Measurements performed can be reported according to ISO 14644-1, E GMP Annex 1 or FS 209. Detailed information such as operation duration, number of team members in the operating room and operating time of vaporizers per operation were registered on a form for each operation.

Statistical analysis

Data were evaluated with SPSS 18 program. Mean, standard deviation (SD), median, minimum, and maximum values were provided for measurement data. Since data was not normally distributed, Mann Whitney U test was performed for the comparison of group medians. Normal distribution was used for the analysis of the linear logarithm and PM amount, which are dependent variables. Operation duration, number of individuals in the operating room, operating time of vaporizers per operation, temperature, and moisture measurement results, which were independent variables, were assessed with Pearson correlation test. The statistical significance of PM measurement results at the beginning and end of the operation were examined with Wilcoxon test for paired comparisons. $P<0.05$ was considered statistically significant.

Results

G*Power 3.1.9.2 software was used to determine sample size. The power of this data was 1-β=0.80 with α=0.07 and an effect size of d=0.73, with 22 samples in each group.

This was an analytical study comparing PM amounts measured in 21 non-instrumented and 22 instrumented cases performed in Kutahya Evliya Celebi Training and Research Hospital NRS operating room between 4 March and 22 May 2019. A total of 644 measurements were made in forty-three operations.

Operation type-related comparison of Mean (SD), Median, Min-Max values of PM and factors such as operation duration, number of team members, operating time of vaporizer are provided in Table 1. The number of team members was higher in non-instrumented operations compared to instrumented operations. PM 0.5 and PM 1 amounts were higher in instrumented operations compared to non-instrumented operations ($P=0.011$, $P=0.010$, respectively) (Table 1).

Table 1: Factors affecting the operation and the comparison of PM measurements according to operation type

	Non-instrumented (n=21)	Instrumented (n=22)	Statistics
Operation duration (min)			
Mean (SD)	70.0 (23.76)	76.59 (17.95)	Z=-0.706
Median (Min-max)	80 (30-100)	80 (45-120)	*P*=0.480
Number of team members			
Mean (SD)	7.04 (0.97)	6.09 (0.29)	Z=-3.563
Median (Min-max)	7 (6-8)	6 (6-7)	*P*<0.001
Operating time of vaporizer			
Min, Mean (SD)	-	38.19 (9.19)	-
Median (Min-max)		40 (20-60)	
PM 0.5 (µg/m^3)			Z=-2.541
Median (Min-max)	0.10 (0.04-7.21)	0.31 (0.05-0.60)	*P*=0.011
PM 1 (µg/m^3)			Z=-2.564
Median (Min-max)	0.31 (0.10-15.07)	0.69 (0.12-1.54)	*P*=0.010
PM 2.5 (µg/m^3)			Z=-1.847
Median (Min-max)	1.85 (0.60-47.75)	2.46 (0.65-5.24)	*P*=0.065
PM 5 (µg/m^3)			Z=-0.632
Median (Min-max)	7.85 (3.14-177.17)	8.49 (3.83-15.93)	*P*=0.528
PM 10 (µg/m^3)			Z=-0.632
Median (Min-max)	21.22 (10.36-37.21)	20.34 (12.26-36.77)	*P*=0.528
Temperature			
Mean (SD)	19.89 (1.29)	19.32 (1.25)	Z= -1.555
Median (Min-max)	19.07 (17-21)	19.13 (17-21)	*P*=0.120
Moisture			
Mean (SD)	33.06 (7.26)	30.91 (6.57)	Z= -1.057
Median (Min-max)	33.07 (19-49)	28.90 (19.8-40.53)	*P*=0.291

The operation duration was a factor affecting all PM amounts and PM amounts increased with operation durations (r=0.575 $P<0.001$, r=0.576 $P<0.001$, r=0.528 $P<0.001$, r=0.439 $P=0.003$, r=0.339 $P=0.029$, respectively). PM5 and PM10 amounts increased in line with the number of team members participating in the operation and the moisture ratio during the

operation (r=0.321 *P*=0.036, r=0.380 *P*=0.012, respectively). No significant correlation was found between operation type (case-control), temperature, PM5 and PM10 amounts or between PM0.5, PM1 and PM 2.5 amounts and operation type (case-control), number of team members, moisture, and temperature (Table 2).

Table 2: Correlation results between dependent and independent variables

	PM0.5		PM1		PM2.5		PM5		PM10	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
Instrument	0.272	0.072	0.233	0.132	0.100	0.522	-0.054	0.733	-0.180	0.249
Time	0.575	<0.001	0.576	<0.001	0.528	<0.001	0.439	0.003	0.339	0.029
Number of team members	0.191	0.221	0.193	0.214	0.251	0.105	0.321	0.036	0.380	0.012
Temperature	0.089	0.569	0.098	0.534	0.157	0.314	0.196	0.207	0.186	0.232
Moisture	0.203	0.193	0.211	0.174	0.270	0.080	0.305	0.057	0.299	0.051

All PM (except PM 0.5) amounts measured in non-instrumented and instrumented operations decreased towards the end of the operation compared to the beginning (Z=-5.414 *P*=0.001, Z=-6.520 *P*=0.001, Z=-6.437 *P*=0.001, Z=-6.200 *P*=0.001, respectively for non-instrumented operations, and Z=-9.062 *P*=0.001, Z=-9.059 *P*=0.001, Z=-8.972 *P*=0.001, Z=-8.560 *P*=0.001, respectively, for instrumented operations) (Figures 1, 2). PM0.5 amounts measured in non-instrumented and instrumented operations were similar at the end and beginning of the operation (Z=-2.591 *P*=0.296, Z=-2.301 *P*=0.212, respectively) (Figures 1, 2).

Figure 1: Comparison of the mean PM amounts measured at the beginning, middle and end of non-instrumented operations

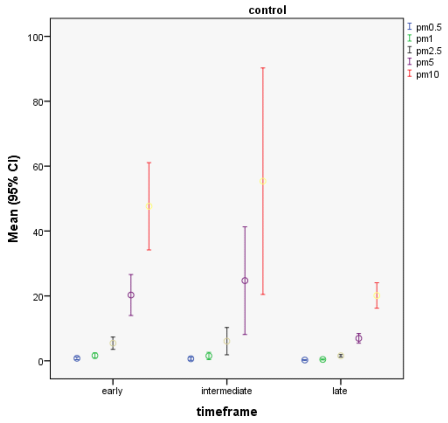
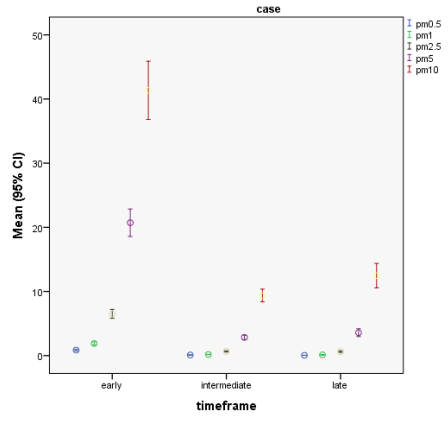


Figure 2: Comparison of the mean PM amounts measured at the beginning, middle and end of instrumented operations



Discussion

Isolated areas in healthcare services and the manufacturing sector involving medications and microelectronics, where the particle number in the environment is kept under control and the temperature, moisture and ventilation values are kept within a certain range, are called "Clean Rooms." [4-7]. Neurosurgery operating rooms should meet and sustain clean room standards [4]. The size and amount of the particles present in the ambient air constitute the main criteria used for the classification of clean rooms in the medical field. Microorganisms hold on to dust particles, shed skin and cloth pieces. They contaminate open wounds during an operation. They may cause infection if the wound location is convenient, and the defense system of the patient is inadequate. In our study, PM amounts measured in 21 non-instrumented and 22 instrumented cases operated in the Neurosurgery operating room were compared and analyzed.

ISO 14644-1 standard classifies air cleanliness in terms of the concentration of the particles in the air in a clean room and area [8]. In studies performed by Seal and Clark [9] and Stocks et al. [10], a correlation was found between the number of particles in the air and number of colony-forming units (CFU). Our operating room measurement results were within clean room limits and in accordance with ISO 14644-1 standards.

In our study, the number of team members was higher in non-instrumented operations compared to instrumented operations. Cranial cases constitute 66.6% of non-instrumented cases (n=14), and individuals other than the operating team are highly involved in cranial surgeries (neuromonitor, navigation, etc.). Thus, the number of individuals was higher in non-instrumented cases. In the literature, it was reported that increasing number of individuals in the operating room caused the increase in PM amount [11, 12]. In our study, PM 0.5 and PM 1 amounts in instrumented operations were significantly higher compared to non-instrumented operations. This result was related to longer operation duration in instrumented cases and the implants used. In the literature, implant use-related PM amount increased parallel to increasing operation duration [1, 11, 13].

Proper ventilation systems lower the infection risk. To suppress the static electricity and prevent bacterial grouping, the temperature should be between 20-23 degrees, the moisture, between 30-60% and to prevent the entrance of microorganisms and dust, the positive pressure should be 15% [14].

The number of individuals and the moisture ratio in the operating room were factors which increased PM amount and postoperative infection risk [6, 12]. In some studies, the number of individuals in the operating room was the key factor increasing the microorganism count [6]. In this aspect, our results were compatible with the literature and we found that moisture ratio and number of team members increased with PM5 and PM10.

The number of bacteria in the air is directly related to the human traffic in the room. Minimizing the number of people and human traffic in the operating room is important to prevent CAE by lowering the number of bacteria in the air. In modern operating rooms, conventional ventilation is available for filtering air particles ≥5µm. In the studies performed, staff activity in the room was the crucial reason for bacterial contamination of the air in the operating room [6, 15]. In the middle of the operation and towards the end, the operating room environment becomes more stabilized in non-instrumented cases (cranial and spinal) and the individuals in the room move less. Towards the middle of instrumented cases, there is more

movement. This is due to the variability of the mobility of the individuals and objects in the room.

Limitations

This study has several limitations. The sample group was small, and the microbiological population was not evaluated. Therefore, we believe that our results should be supported by studies conducted in different operations with larger samples and microbiological measurements.

Conclusion

PM smaller than one micron were detected more in instrumented operations compared to non-instrumented ones. The amounts of these particles increased with the number of team members during the operation. All PM amounts also increased with operation duration.

PM amounts measured in non-instrumented and instrumented operations gradually decreased towards the end of the operation compared to the beginning.

Considering these results, regular inspection of ventilation related policies and procedures, changing of air filters, regular checking of air flows entrances and exits, always keeping the doors of the operating rooms closed, and restricting the entrances and exits to the room are necessary in our hospital. This way, sterile room conditions including only filtered air entry without any particles can be provided for surgeries involving implants and prostheses.

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Psychosocial status and attitudes of healthcare workers amid the COVID-19 pandemic

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Ethics Committee Approval
The study was approved by the COVID-19 Studies Scientific Committee of Turkish Ministry of Health and Adıyaman University Non-Interventional Studies Local Ethics Committee (date:18.05.2020, number:2020/5-6).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: COVID-19 disease occurs in close contact due to its highly contagious nature. Healthcare workers (HCWs) are in the frontline of struggling with the COVID-19 pandemic. The thoughts, behaviors, attitudes, and psychosocial statuses of healthcare professionals working in this problematic condition have not yet been fully investigated in Turkey. We aimed to evaluate the mental health and psychosocial status, thoughts about the measures taken by the government, attitudes, and behaviors of healthcare workers facing the COVID-19 pandemic, and whether there is a difference between physician and non-physician HCWs.

Methods: In this cross-sectional survey, a 56-question multiple-choice test created based on similar surveys and scales was performed by a one-to-one interview with the HCWs in three registered hospitals fighting the COVID-19 pandemic from 20 May to 10 June 2020. Mental health variables were assessed via the Patient Health Questionnaire-4 (PHQ-4) and the Turkish Beck Depression Scale to specify psychological manifestations. A scoring system was applied using a four-point Likert scale, from no points (“strongly disagree”) to three points (“strongly agree”) to determine the levels of anxiety and depression. Participants were divided into two groups as physician and non-physician HCWs for subgroup analysis.

Results: A total of 300 HCWs (45 physicians, 255 non-physician health care workers) enrolled in the survey. Only 0.8% of HCWs received psychological support from a therapist or psychiatrist. The most common concern during the COVID-19 pandemic was about “the elderly and other risky population being infected” (37.9%). Compared with non-physician HCWs, physicians felt more concerned about the spread of COVID-19 (80% vs 47.1%, P=0.006 $\chi 2$=12.591) and they agreed at a higher rate that the number of tests performed was sufficient (53.3% vs. 41.2%, P=0.030, OR: 0.29-0.35, $\chi 2$=7.047). For all HCWs, the "feeling of being infected with COVID-19” item had the highest mean total score (2.60 (0.97). The mean score of the “feeling nervous/anxious/on edge” item was 2.53 (0.52) for physicians and 2.26 (0.86) for non-physician HCWs. Non- physicians HCWs had a higher mean score for “Feeling of increased body pain and agony” item than physicians 0.27(0.80) vs 0.76 (1.23), mean dif=-0.50, 95% confidence interval=-1.002 to 0.006, P<0.05).

Conclusions: The results of this study showed that healthcare professionals were most anxious about “being infected with COVID-19”. Both physician and non-physician HCWs were feeling nervous/anxious/on edge according to anxiety scores.

Keywords: Covid 19, Mental health, Healthcare workers, Physicians, Non-physicians

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Introduction

Coronaviridea are enveloped, non-segmented, single-stranded RNA viruses which replicate in epithelial cells of the upper respiratory tract and in some circumstances, spread to the lower respiratory tract. The disease may cause bronchiolitis, pneumonia, and even acute respiratory distress syndrome. Human coronaviruses were recognized since the 1960s, but in 2003 a novel coronavirus was introduced as an etiologic agent of the outbreak of severe acute respiratory syndrome (SARS). The outbreak in Jeddah, Kingdom of Saudi Arabia in June 2012 was named "Middle East Respiratory Syndrome" (MERS) and caused Middle East Respiratory Syndrome-coronavirus (MERS-CoV) [1]. A pneumonia outbreak of unknown cause was observed in Wuhan province, China, in December 2019-January 2020. After testing the samples collected from these patients, the cause was revealed as a novel coronavirus originating from coronavirus families such as SARS and MERS and was named Novel Coronavirus 2019 (2019-nCoV). In this new disease, the very infectious virus spread all over the world rapidly. Over 4 million cases and 275 thousand deaths have been reported until now (15/20). The first case in Turkey was observed on 11 March 2020 and over 140 thousand cases and four thousand deaths had been reported since then (15/2020) [2].

Coronaviridea may cause severe respiratory infections especially in the elderly, infants and in patients with underlying chronic diseases [1]. It spreads via small droplets produced during coughing, sneezing, or talking, and when people are in close contact [3]. Although the incubation period is not precisely known, it is estimated to be between 9 to 12 days when transmitted between humans. This period is noted as approximately 2 days for other infections caused by coronaviruses [4]. Based on these assumptions, the observation period of 14 days in COVID-19 is considered safe [5].

COVID-19 cases can be seen individually and/or as a group. Healthcare workers (HCWs) are in the frontline of the struggle against any disease and play a key role in the response to this pandemic, just as in other epidemics. Healthcare professionals such as physicians, nurses, and other auxiliary staff are all at risk because of the very infectious nature of the COVID-19 in close contact. While they all have been working under these circumstances, their thoughts and behaviors have not been fully investigated. Diminishing the anxiety levels of HCWs as much as possible might help them fight pandemics more effectively. In this study, we aimed to detect the anxiety levels, thoughts, attitudes, and behaviors of HCWs facing the COVID-19 pandemic and whether there is a difference between physician and non-physician health care workers in terms of these issues.

Materials and methods

This cross-sectional survey study was designed based on the American Association for Public Opinion Research (AAPOR) guideline for survey studies. The study was approved by the COVID-19 Studies Scientific Committee of Turkey Ministry of Health and Adıyaman University Non-Interventional Studies Local Ethics Committee (date:18.05.2020, number:2020/5-6). Informed consents were obtained from all participants before the questionnaire. Participants were free to withdraw from the study at any time and data were kept strictly confidential.

This multi-centered, cross-sectional survey study was performed with a one-to-one interview with the HCWs registered in the pandemic workforce in Adıyaman University of Training and Research Hospital, Gerger and Kızıltepe Public Hospitals, Turkey, between 20 May 2020 and 10 June 2020. We performed a questionnaire of fifty-six questions to the participants. All survey questions were created based on similar survey studies and revised anxiety score questions of patient Health Questionnaire-4 (PHQ-4) and Beck Depression Scale [5,6].

Measurements:

Demographic variables such as gender, age, profession (physician, nurse, administrative personnel, auxiliary personnel, other personnel), marital status (married, single, divorced) were asked in the questionnaire. Besides, the participants were asked whether they had any organic diseases, insomnia, or psychiatric symptoms. Participants were asked to state the factors affecting their anxiety levels during the COVID-19 outbreak in order of importance. The questions were prepared to determine the participants' self-protection from COVID-19, attitudes, behaviors, and opinions on preventions taken by the government using a 4-point Likert scale.

Survey questions were classified to determine the anxiety and depression levels, attributes, and behaviors of HCWs due to the COVID-19 outbreak. The Turkish modifications of Patient Health Questionnaire-4 (PHQ-4) and Beck Depression Scale were used.

Survey questions were established to specify psychological manifestations (Feeling nervous/anxious/on edge, not being able to stop worrying, loss of joy, feelings about increased risk of infection, avoidance from crowds, loss of interest in following news, difficulty in falling asleep, increased general body pain, feeling down/depressed/hopeless [5,6]. A scoring system was applied using a four-point Likert scale ranging from no points ("strongly disagree") to three points ("strongly agree") to determine the levels of anxiety and depression [7].

Study participants and three researchers who conducted face-to-face interviews were blinded to the hypothesis and purpose of the study. To avoid the bias of misinterpreting the survey results, a data analysis plan was created. A different researcher than the researchers who conducted the face-to-face interview performed the statistical analysis and was blinded to the purpose and hypothesis of the study.

Statistical analysis

All data analysis was performed with the Statistical Package for the Social Sciences software (SPSS 17.0 v). A power analysis was performed using the G*power v3.1.9.2 software. Categorical values were presented as percentage and number; numeric values were presented as mean (Standard deviation (SD)).

After survey data is obtained, group analyses were performed by dividing participants into two groups as physician and non-physician HCWs. The categorical variables were compared with the $\chi 2$ test. The student's t-test was performed on each group to compare the differences between mean values. Variant analysis was performed with the Levene test. A priori

power analysis revealed that a sample size of 180 participants in total would be required to detect medium effects (d = 0.50) with 80% power and alpha critical level (type 1 error) at 0.05 using a t-test. A 95% confidence interval (CI) was used for expressing the study data. For all statistical analyses, a *P*-value of <0.05 was considered statistically significant.

Results

Sociodemographic findings and knowledge levels:

A total of 300 HCWs were enrolled in the study and questionnaires were performed with one-to-one interviews. Of HCWs enrolled in this study, 15% (n=45) were physicians, 85% (n=255) were non-physician healthcare workers (71% nurse, 9% staff, 5% administrative personnel). Half were male, 64% were married, and most participants were aged between 26 and 40 years. All participants aged between 50 and 65 years were physicians. Eighty-six percent of the participants had no history of any diseases and there was no difference between professions regarding health problems (*P*=0.936, $\chi2$=0.007).

During the COVID-19 pandemic, 68% of HCWs thought that they had sufficient knowledge about the course of the outbreak and 21% thought their knowledge was at expert level. While 53.3% of physicians thought that they had expert-level knowledge, this ratio was 15.3% among non-physician HCWs (*P*=0.004, $\chi2$=11.121). Of all HCWs, 85% had not done any research on COVID-19 and this ratio was 90.6% among non-physician HCWs (*P*=0.058, $\chi2$=3.595).

Table 1 presents the sociodemographic characteristics of all participants and the comparison of physician and non-physician HCWs.

Table 1: Sociodemographic characteristics in Physician versus Non-physician HCWs

	Total %(n)	Physician n=45 %(n)	Non- physician n=255 %(n)	*P*-value
Gender				*P*=0.002
Female	50.0(150)	13.3(6)	56.5(144)	$\chi2$=9.490
Male	50.0(150)	86.7(39)	43.5(111)	
Marital status				*P*=0.007
Married	64.0(192)	33.3(15)	69.4(177)	$\chi2$=7.203
Single	36.0(108)	66.7(30)	30.6(78)	
Age, years				*P*=0.007
18-25	13.0(39)	13.3(6)	12.9(33)	$\chi2$=12.059
26-40	71.0(213)	66.7(30)	71.8(181)	
41-55	14.0(42)	6.7(3)	15.3(39)	
56-65	2.0(6)	13.3(6)	0	
Chronic Diseases				*P*=0.936
Yes	14.0(42)	13.3(6)	14.1(36)	$\chi2$=0.007
No	86.0(258)	86.7(39)	85.9(219)	
Anxiety				*P*=0.250
No	22.0(66)	33.3(15)	20.0(51)	$\chi2$=1.321
Yes	78.0(234)	66.7(30)	80.0(204)	
Somatization symptoms				*P*=0. 215
No	82.0(246)	93.3(42)	80.0(204)	$\chi2$=1.536
Yes	18.0(54)	6.7(3)	20.0(51)	
Insomnia				*P*=0.482
No	74.0(74)	66.7(10)	75.3(64)	$\chi2$=0.493
Yes	26.0(26)	33.3(5)	24.7(21)	
Wearing a mask outside				*P*=0.464
No	18.0(18)	26.7(4)	16.5(14)	$\chi2$=0.898
Yes	82.0(82)	73.3(11)	83.5(71)	
Research about COVID-19				*P*=0.058
No	88.0(264)	73.3(33)	90.6(141)	$\chi2$=3.595
Yes	12.0(36)	26.7(12)	9.4(24)	
Knowledge level				*P*=0.004
Inadequate	11.0(33)	6.7(3)	11.8(30)	$\chi2$=11.121
Adequate	68.0(204)	40.0(18)	72.9(186)	
At expert level	21.0(63)	53.3(24)	15.3(39)	

$\chi2$: Pearson Chi-square test

Information and anxiety sources of HCWs about COVID-19

Among concerned participants, 62.8% were between 26 and 40 years old (*P*=0.009, $\chi2$=11.520). There was no significant difference between the professions of HCWs and feelings of concern (*P*=0.250, $\chi2$=1.321). Only 0.8% received psychological support from a therapist or psychiatrist. HCWs were most concerned with "the elderly and other risky population being infected" (37.9%), while the rate of those concerned by being infected was only 3.1%. There were no significant differences between the HCWs in terms of rate and reasons of concern (*P*=0.294, $\chi2$=10.740).

Most HCWs had changed their thoughts about COVID-19 according to what they had learned from their friends and family members (25.4%), the WHO and other health agencies (20.8%). The rate of those who changed their opinions because of newspapers and the press were only 1%. Among concerned HCWs, 89.2% felt stated that they had changed their thoughts with the information they got from television (*P*=0.005, $\chi2$=20.271).

Responses of HCWs about the COVID-19 outbreak according to concern statements are shown in Table 2.

Table 2: Responses of health-care workers to concern statements about the COVID-19 outbreak

Questions	Characteristics	Total %(n)	Concern No, (n=66) n	%	Yes (n=234) n	%	*P*-value
Profession	Physician	15(45)	15	33.3	30	66.7	*P*=0.250
	Nurse and other staff	85(255)	51	20.0	204	80.0	$\chi2$=1.321
Age	18-25 years	13(39)	0	0	39	16.7	*P*=0.009
	26-40 years	71(213)	66	100	147	62.8	$\chi2$=11.520
	41-55 years	14(42)	0	0	42	17.9	
	56-65 years	2(6)	0	0	6	2.6	
Which factors changed your feelings about COVID-19?*	Friends, family	25.4(150)	27	18.0	123	82.0	*P*<0.001
	Health web sites	16.2(96)	27	28.1	69	71.9	$\chi2$=20.271
	TV	18.8111)	12	10.8	99	89.2	
	WHO	20.8(123)	21	17.1	102	82.9	
	Online health programs	3.6(21)	12	57.1	9	42.9	
	Social media and internet browsers	14.2(54)	15	17.9	69	82.1	
	Newspapers and journals	1.0(6)	6	100.0	0	0	
What are you most anxious about regarding the COVID-19 outbreak? *	Economy	20.3(138)	45	32.6	63	67.4	*P*=0.294
	Children being infected	21.6(147)	33	22.4	114	77.6	$\chi2$=10.740
	Elderly and risky populations being infected	37.9(258)	54	20.9	104	79.1	
	Fast spreading	9.7(66)	6	9.1	60	90.9	
	Dying of illness	2.6(18)	3	16.7	15	83.3	
	Inadequate medical facility	3.121)	6	28.6	15	71.4	
	Being quarantined	0.9(6)	0	0	6	100.0	
	Loss of income	0.9(6)	3	50.0	3	50.0	
	Being infected	3.1(21)	3	28.6	15	71.4	
What have you done to support your mental and emotional health during COVID-19 outbreak? *	Gathering information and doing research	33.9(129)	39	30.2	90	69.8	*P*<0.05 $\chi2$=5.449
	Asking specialists for information	8.7(33)	0	0	33	100.0	
	Getting Psychological support	0.8(3)	3	100.0	0	0	
	Taking medicine	2.4(9)	3	33.3	6	66.7	
	Using social media a lot more	20.5(78)	9	11.5	69	88.5	
	Suspending social media	5.5(21)	9	42.9	12	57.1	
	Doing exercise	17.3(66)	18	27.3	48	72.7	
	Allocating time to my hobbies	11.0(42)	6	14.3	36	85.7	

* Multiple responses, WHO: World Health Organization, TV: television

The attitudes and behaviors of HCWs about COVID-19 pandemic

In our study, only 6.7% of HCWs had no anxiety during the COVID-19 pandemic. Physicians significantly more commonly stated that they felt very anxious about the spreading of the COVID-19 pandemic compared to non-physician HCWs (%80 vs %47.1, *P*=0.006 $\chi2$=12.591).

Sixty percent of participants strongly agreed that COVID-19 affected their daily life very much, 49% thought that their future lives would be affected and 59% thought it had affected their social relations.

In terms of the responses to whether COVID-19 affected daily life, future life, and social relations, there was no statistically significant difference between the physician and non-physician HCWs (P=0.104, P=0.100, P=0.038, respectively, Table 3).

Because of the outbreak, 72% of HCWs did not use mass transport. Seventy-five percent stated that their handwashing habits increased very much in frequency. Eighty-five percent stated that they obeyed the precautions such as social distance. All those who did not believe that the social distance rule was protective were non-physician health workers and this rate was only 1.2%. The physician and non-physician HCWs were similar in terms of responses to questions regarding mass transport, handwashing, and social distance (P=0.089, P=0.085, P=0.212, respectively, Table 3).

Because of the outbreak, 43% of HCWs bought extra food and 64% bought extra cleaning supplies and stored them at home. Among physicians, 26.7% did not think they needed to buy extra food and 21.2% of non-physician HCWs said that they had no intention of buying extra cleaning supplies. There was no significant difference between the answers given by physicians and other HCWs (P=0.294, P=0.677, respectively).

Of HCWs, 82% responded that they wore masks outside the hospital since the outbreak emerged. 73.3% of physician and 83.5% of non-physician HCWs agreed on the importance of wearing a mask outside the hospital. Responses of all HCWs were similar with regards to wearing masks outside (P=0.815).

Seventeen percent of HCWs were certain about the preventiveness of precautions they had taken, while 10% were not sure. Among all participants, 13.3% who thought that the preventive measures taken were inadequate were physicians and 9.4% were non-physician HCWs. The two groups were similar in terms of their thoughts on the protectiveness of the precautions taken (P=0.742).

Forty-five percent of participants replied that their interest in patients who came for routine examination did not change at all. Almost half of physicians (46.7%) stated that their interest in patients who came for routine examination did not change and this rate was 18.8% for the rest of the participants.

Sixty-seven percent of HCWs stated that their perception of the risk of their occupation as a HCW increased after the COVID-19 pandemic. While 86.7% of the physicians strongly agreed with this statement, this rate was 62.7% non-physician HCWs (P=0.168). The distribution of attitudes and behaviors of physician and non-physician HCWs concerning COVID-19 is presented in Table 3.

The opinion of HCWs about the preventive measures the government has taken:

Forty-six percent stated that they were satisfied with the governmental precautions during Covid- 19 pandemic; 56% agreed that some precautions had been taken but criticized its inadequacy. Concerning governmental preventive measures, 66.7% and 13.3% of physicians were satisfied and extremely satisfied, respectively, while these rates were 42.4% and 12.8% among non-physician HCWs.

Forty-five percent thought that the government officially announced the latest data thoroughly whereas

%11 felt otherwise. Fifty-eight percent stated that the government adequately announced the transmission routes during the pandemic.

Sixty-five percent agreed that during a pandemic, the governmental policy of quarantine, travel restrictions, and closing some borders were sufficient. Forty-three percent thought that an adequate number of tests had been performed, whereas 41% thought the opposite. While 53.3% of physicians thought that the number of tests being performed was sufficient, 45.9% of non-physician HCWs did not agree (P=0.030 OR: 0.29-0.35 χ2: 7.047) (Table 4).

Psychological conditions of HCWs during COVID-19 pandemic:

Among the questions classified to determine the psychological status for all HCWs, "concern of being infected with COVID-19" item had the highest mean total score with 2.60 (0.97), and "Decrease in the joy of living" item had the lowest mean total score with 0.92 (1.09).

The mean score of "feeling nervous/anxious/on edge" item was 2.53 (0.52) among physicians and 2.26 (0.86) among non-physicians (P=0.102, mean dif.=0.28, 95% confidence interval= -0.06 to 0.61).

The overall mean total score of "Increased physical pain and agony" item was 0.69 (1.19), and it was higher among non-physician HCWs compared to physicians (0.27(0.80) vs 0.76 (1.23), mean dif.= -0.50, 95% confidence interval=-1.002 to 0.006, P<0.05).

Table 5 presents scores of mental health variables for psychological conditions of HCWs during COVID-19 according to two groups.

Table 3: The attitudes and behaviors of HCWs about Covid-19 pandemic

Questions % (n)	Physician (n=45)				Non-physician HCWs (n=255)				*P*-value
	Disagree	Neither agree nor disagree	Agree	Strongly agree	Disagree	Neither agree nor disagree	Agree	Strongly agree	χ^2
Covid-19 affects daily life very much	6.7(3)	13.3(6)	20.0(9)	60(27)	0	10.6(27)	29.4(75)	60.0(153)	*P*=0.104 χ^2=6.157
Our future life will be affected	6.7(3)	40.0(18)	40.0(18)	13.3(6)	0	23.5(60)	50.6(129)	25.9(266)	*P*=0.100 χ^2=6.249
Covid-19 deeply affected social relations	6.7(3)	0	20.0(9)	73.3(33)	0	8.2(21)	35.3(90)	56.5(144)	*P*=0.038 χ^2=8.420
My anxiety level increased very much since the Covid-19 outbreak emerged.	6.7(3)	6.7(3)	80.0(36)	6.7(3)	0	29.4(75)	47.1(120)	23.5(60)	*P*=0.006 χ^2=12.591
My handwashing frequency increased very much outside the hospital	0	13.3(6)	80.0(36)	6.7(3)	1.2(3)	24.7(63)	74.1(189)	0	*P*=0.085 χ^2=6.619
I have to maintain social/personal distance	0	13.3(6)	13.3(6)	73.3(33)	1.2(3	2.4(6)	9.4(24)	87.1(222)	*P*=0.212 χ^2=4.498
I have to buy extra food	26.7(12)	0	33.3(15)	40.0(18)	15.3(39)	22.4(57)	18.8(48)	43.5(111)	*P*=0.294 χ^2=3.712
I have to buy extra cleaning supplies.	20.0(9)	0	6.7(3)	73.3(33)	21.2(54)	8.2(21)	8.2(21)	62.4(159)	*P*=0.677 χ^2=1.523
I have to wear a mask outdoors	6.7(3)	6.7(3)	13.3(6)	73.3(33)	3.5(9)	4.7(12)	8.2(21)	83.5(213)	*P*=0.815 χ^2=0.942
The precautions I take are preventive enough.	13.3(6)	26.7(12)	40.0(18)	20.0(9)	9.4(24)	18.8(48)	55.3(141)	16.5(42)	*P*=0.742 χ^2=1.244
I had to minimize my choice of mass transport	0	20.0(6)	13.3(6)	66.7(30)	1.2(3)	3.5(9)	22.4(57)	72.9(186)	*P*=0.089 χ^2=6.505
My interest in patients who came for routine examination diminished	46.7(21)	26.7(12)	20.0(9	6.7(3)	18.8(48)	49.4(126)	23.5(60)	8.2(21)	*P*=0.077 χ^2=6.840
My feelings about having a risky occupation have increased	0	6.7(3)	6.7(3)	86.7(39)	4.7(12)	2.4(6)	29.4(75)	63.5(162)	*P*=0.168 χ^2=5.052

Table 4: Opinions of HCWs about governmental precautions against Covid-19

Questions, % (n)	Physician (n=45)				Non-physician HCWs (n=255)				*P*-value
	Disagree	Neither agree nor disagree	Agree	Strongly agree	Disagree	Neither agree nor disagree	Agree	Strongly agree	χ^2
I am satisfied with overall governmental policy	6.7(3)	13.3(6)	66.7(30)	13.3(6)	9.4(24)	29.4(75)	42.4(108)	18.8(48)	*P*=0.365 χ^2=3.180
The government has taken enough precautions to prevent the spread of the disease	6.7(3)	60.0(27)	26.7(12)	6.7(3)	10.6(27)	55.3(141)	24.7(63)	9.4(24)	*P*=0.946 χ^2=0.373
The government has imposed enough travel restrictions and quarantine	20.0(9)	0	80.0(36)	0	16.5(42)	0	62.4(159)	21.2(54)	*P*=0.144 χ^2=3.881
The government has done enough to publicly communicate about the latest news	13.3(6)	20.0(9)	60.0(27)	6.7(3)	10.6(27)	31.8(81)	42.4(108)	15.3(39)	*P*=0.525 χ^2=2.236
The government has done enough to inform the public about transmission routes of COVID-19	6.7(3)	0	53.3(24)	40.0(18)	0	8.2(21)	58.8(150)	32.9(54)	*P*=0.864 χ^2=0.292
The government has performed enough Covid-19 tests	13.3(6)	33.3(15)	53.3(24)	0	45.9(117)	12.9(33)	41.2(105)	0	*P*=0.030 χ^2=7.047

Table 5: The mean scoring system values for Psychological manifestation items according to physicians and non-physician healthcare workers

Questions related Psychological manifestations, mean (SD)	Total	Physician (n=45)	Non- physician HCWs (n=255)	*P*-value
Feeling nervous/anxious/on edge	2.01(0.69)	2.53(0.52)	2.26(0.86)	0.10
Not being able to stop worrying	2.29(1.21)	1.93(1.44)	2.35(1.17)	0.22
Loss of joy of living	0.92(1.09)	0.53(0.92)	0.95(1.02)	0.14
Concern of being infected with covid-19	2.60(0.97)	2.67(0.90)	2.55(1.05)	0.70
Avoiding crowds	0.92(1.09)	1.40(0.74)	1.34(0.63)	0.75
Loss of interest in following news	2.43(1.07)	2.53(1.06)	2.41(1.07)	0.69
Difficulty in falling asleep	1.00(1.31)	1.27(1.39)	0.95(1.30)	0.40
Feeling of increased body pain and agony	0.69(1.19)	0.27(0.80)	0.76(1.23)	<0.05
Feeling down/depressed/hopeless	1.93(0.71)	1.87(0.64)	1.94(0.73)	0.71

Discussion

This is the first study on HCWs regarding the behavioral effects and level of psychological distress of the COVID-19 pandemic and reflecting their thoughts about governmental policies and practices.

In their study including 1257 Chinese HCWs, Lai et al. [6] demonstrated that the majority of HCWs showed anxiety, depression, and sleep disorder symptoms, and more than 70% reported psychological problems during the COVID-19 pandemic. In a study conducted in 2016 by Alsahafi et al. [7], participants' source of information was the "Ministry of Health" during MERS-coronavirus (MERS-CoV) (74.3%). According to a survey performed by Khan et al. [8], the main source of information was the internet. In our study, the information sources of HCWs were family (25.4%), WHO and other health agencies (20.8%), printed media such as newspapers and journals (1%), television 18.8%, and social media (14.2%).

Lei et al. [9] studied 1593 Chinese individuals during the COVID-19 pandemic and stated that society felt more anxious about being infected, had no psychological support, and faced more financial damage. We also found that the HCWs were most anxious about infecting the elderly and susceptible ones in their family, followed by infecting children, and economic loss.

According to the study of Khan et al. [8] during the MERS-CoV outbreak in Saudi Arabia, most HCWs stated that they took precautions using gloves, laboratory coats, and personal protective equipment but believed that these precautions would not reduce the prevalence of MERS-COV. In our study, the participants also took precautions against infection; nevertheless, they thought that these precautions would reduce the spread of COVID-19. The same study also demonstrated that HCWs had a positive attitude towards and concrete knowledge of MERS. Yet, there were situations the HCWs showed negative attitudes and inadequate knowledge. Similarly, 33.9% of the participants received psychological support via trying to gather

information, and only 0.8% collaborated with a therapist or psychiatrist in our study.

Styra et al. [10] performed a study in 2008 during the SARS outbreak that revealed that HCWs had high-stress levels even they had cared only for one patient. We also found similar anxiety and stress levels among more than half of HCWs during COVID-19.

Bukhari et al. [11] reported that nurses had remarkably high anxiety levels during MERS. Most HCWs enrolled in our study were also very anxious during the COVID-19 pandemic, particularly about infecting the elderly and fragile people, yet they were less anxious about being infected. Wang et al. [12] reported that more than half of the normal population enrolled in the study also experienced moderate to severe psychological effects. Most participants washed their hands with soap after touching contaminated objects, closed their mouths during sneezing or coughing, and wore a mask regardless of the symptoms of the patients. At the very beginning of the COVID-19 outbreak in China, the internet was the main information source (93.5%) [12]. We found that the frequency of handwashing and wearing masks both inside and outside the hospital increased remarkably among HCWs. In our study, the main information source of HCWs was not the internet but WHO and other health agencies.

According to Wen et al [13], very serious psychological problems emerged in society during the COVID-19 pandemic and informing the public and following appropriate strategies were necessary. We similarly found that COVID-19 pandemic had deeply affected most HCWs' daily lives and social relationships and that they were very anxious. A survey consisting of 10754 Iranians showed that the severity of anxiety symptoms was normal in 49.1%, severe in 9.3%, and very severe in 9.8% of the participants. Anxiety levels were significantly higher among females than males. Although COVID-19 related infection and mortality rates seemed to increase with older age, this study showed that anxiety levels were much higher in the 21-40-year age group [14]. The anxiety level was higher in our study and 53% of participants had severe anxiety. There was no difference between the two genders.

Research on mental health problems in medical health workers during the COVID-19 epidemic is limited. Zhang et al. [15] found that compared with nonmedical health workers, medical health workers had higher total Patient Health Questionnaire-4 scores. In our study, both physicians and non-physicians HCWs were feeling nervous/anxious/on edge largely and the highest anxiety score for all healthcare professionals regarded getting infected with COVID-19 according to Patient Health Questionnaire-4 (PHQ-4) and the Turkish Beck Depression Scale.

Limitations

The prominent limitation of this survey is the small study population. However, this study exhibited some important results because data were collected with one-on-one, face-to-face interviews with HCWs working exceptionally long hours during COVID-19. One limitation is that the analysis of potential risk factors that might cause obsessive-compulsive disease, depression, anxiety, and somatization disorder could not be performed. Finally, another limitation is that gender differences were not taken into account when evaluating the level of knowledge and anxiety among the groups in our study. Novel studies are needed to show gender differences in knowledge and anxiety levels between physician and non-physician HCWs.

Conclusion

The results of this survey study showed that the issue that healthcare professionals worry most about was the infection of elderly and risky patients. Concerned HCWs were most likely to receive COVID-19 related information from television. Physicians worry more about the COVID-19 spread than other healthcare professionals and think the COVID-19 tests have been performed adequately. The highest anxiety score among all healthcare professionals regarded getting infected with COVID-19. Most physician and non-physicians HCWs were feeling nervous/anxious/on edge. Non-physicians HCWs felt more body pain and agony. During COVID-19 pandemic, healthcare workers did not seek enough psychological support. HCWs felt anxious in their work environment during the COVID-19 pandemic like the previous pandemics, MERS, and SARS. We observed that increased anxiety levels of HCWs reduced their ability to care for patients as well as their quality of life and caused negative feelings such as working in a risky job and worry of infecting other people. We pointed out that HCWs should be completely informed via education programs including transmission paths, infection control measures, and programs that help reduce anxiety levels so that HCWs could efficiently fight against a pandemic. We need more studies to maintain a concrete fight with pandemics all around the world.

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Prognostic factors and survival outcomes of uterine sarcomas in a reference gynecologic oncology cancer center

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Ethics Committee Approval
The study protocol was approved by the Tepecik Education and Research Hospital Ethics Committee with the number 2021/01-47 on 15/01/2021.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Uterine sarcomas are rare and aggressive tumors, and their clinical behavior is unpredictable. A clear-cut clinical course, proven treatment method or definitive prognostic factors affecting the survival of sarcoma patients are not reported in the literature. We aim to evaluate uterine sarcomas, determine clinicopathologic features, adjuvant therapies, and prognostic factors on survival while sharing our experience of these rare uterine tumors in light of the literature.

Methods: This retrospective cohort study was conducted in Tepecik Training and Research Hospital, Izmir, Turkey between 2002-2020. Out of the total of 205 uterine sarcoma patients, 173 patients who underwent surgical procedures and were followed up in our hospital's Gynecologic Oncology Clinic were included in the study. Data of patients were collected from the hospital database. Surgical interventions, clinicopathologic features, adjuvant therapies, and overall and disease-free survivals were evaluated. Patients were grouped as leiomyosarcoma (LMS), carcinosarcoma (CS), endometrial stromal sarcoma (ESS), adenosarcoma (AS), and undifferentiated sarcoma (US).

Results: The mean age of the patients was 57.6 (11.2) years. According to the International Federation of Gynecology and Obstetrics (FIGO2009), 115 patients (66.5%) had stage 1, 17 patients (9.8%) had stage 2, 31 (17.9%) patients had stage 3, and 10 patients (5.8%) had stage 4 disease. One hundred and sixty-two patients (93.6%) received adjuvant therapy. Median follow-up period was 39 months (range 3-214). The 120-month OS for the entire group was 87.1%.

Conclusion: Stage is a significant prognostic factor for survival in all sarcoma types and recurrence is a significant prognostic factor for survival for LMS and CS patients. Sarcoma type and adjuvant treatments have no impact on survival. ESS patients require extended surgical staging.

Keywords: Uterine sarcoma, Chemotherapy, Radiotherapy, Survival

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Introduction

Uterine sarcomas are rare and aggressive tumors of the uterus which account for up to 7% of all uterine cancers [1]. In 1959, Ober classified these tumors according to their origin and cell types. In 2009, a new FIGO classification and staging system was published [2]. Histological sarcoma types include malignant mixed Mullerian tumors (MMMT, or carcinosarcomas (CS)), leiomyosarcomas (LMS), endometrial stromal sarcomas (ESS) and undifferentiated sarcomas (US). Carcinosarcomas are still staged as uterine carcinomas. In all uterine sarcomas, the most common presenting symptoms are abnormal uterine bleeding and pelvic mass. Stage is the most important prognostic factor for uterine sarcomas [3]. Since uterine sarcomas are rare, risk factors and a definitive treatment protocol have not been established. In terms of adjuvant treatments, postoperative radiation therapy seems to improve local control [4].

The purpose of this study was to compare histological subtypes and clinical outcomes with analysis of the role of adjuvant therapies in the management of these patients and share our experience of management of these rare tumors in light of the literature.

Materials and methods

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Tepecik Training and Research Hospital Ethics Committee with the number 2021/01-47 on 15/01/2021. The data of 205 patients diagnosed with uterine sarcoma who were followed up in our clinic between January 2002- 2020 were retrospectively reviewed. Patients who did not undergo surgery in our hospital, the presence of another cancer, and patients with missing data (n=32) were excluded from the study, after which 173 patients were included. The age, surgical and adjuvant treatments, pathological results, follow-up information, treatments given, survival and recurrences of patients were retrieved from the medical records of our hospital. Pathology specimens were reviewed by expert pathologists. Patients were staged according to FIGO 2009. Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) with or without pelvic lymph node dissection (PLND) were performed for all operable patients. Additionally, low anterior resection plus colostomy, pelvic peritonectomy, implant resection were performed in indicated cases (Table 1).

We categorized the patients according to age and tumor size. A cut-off size of 5 cm was reported in FIGO 2009 staging system. According to this, we grouped patients with tumors below and above 5 cm. For CS there was no consensus regarding tumor diameter. We aimed to analyze whether a cut-off of 5 cm tumor size is a significant factor for outcome. We also categorized the patients as those younger and older than 50 years of age. Since 50 years is a significant factor for endometrial cancers, we aimed to assess whether the same is true for sarcomas as well. Cox regression analysis was used for the comparison of these groups.

Whether the patient was to receive adjuvant radiotherapy (RT), chemotherapy (CT), or combination therapy was decided by the members of the tumor board, depending on the age, stage, lymph node metastasis, medical comorbidities, and performance. Patients were followed up every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually.

Statistical analysis

Statistical analysis was performed with SPSS version 22 (SPSS for Mac Inc., Chicago, IL, USA). *P*-value <0.05 was considered statistically significant. To identify whether the data were normally distributed, Shapiro-Wilk's test, histograms, Q-Q plots tests were used. Descriptive statistics were presented as median (SD). Univariate and multivariate cox regression analysis were used to identify factors that affect overall (OS) and disease-free survival (DFS). The Kaplan-Meier method was used to assess survival. Log-rank statistical analyses were used when comparing lifetimes of cases with categoric variables.

Results

The mean age of the patients was 57.6 (11.2) years. Carcinosarcoma (50.9%) and leiomyosarcoma (27.7%) were the most common histopathological types. Most patients had stage 1 disease (n:115, 66.5%), 17 patients had (9.8%) stage 2, 31(17.9%) had stage 3 and 10 (5.8%) had stage 4 disease (Table 1).

Table 1: Clinicopathologic features of sarcomas

Type	n (%)	95%CI
LMS	48(27.7%)	(21.4-34.1)
CS	88(50.9%)	(42.8-58.4)
ESS	27(15.6%)	(10.4-21.4)
US	2(1.2%)	(0-2.9)
AS	8(4.6%)	(1.7-8.1)
Total	173(100%)	
OP	n (%)	95%CI
TAH	2(1.2%)	(0-2.9)
TAH BSO	59(34.1%)	(27.2-42.2)
TAH BSO PLND	11(6.4%)	(2.9-10.4)
TAH BSO PPLND	90(52%)	(43.9-59.4)
TAH USO	3(1.7%)	(0-4)
TAH BSO PPLND Low Ant Resec.	3(1.7%)	(0-3.5)
TAH BSO PPLND Implant Resec.	4(2.3%)	(0.6-4.6)
TAH BSO PPLND Pelvic Peritonectomy	1(0.6%)	(0-1.7)
Stage		
1	115(66.5%)	(59.5-72.8)
2	17(9.8%)	(5.8-14.5)
3	31(17.9%)	(12.1-23.7)
4	10(5.8%)	(2.3-9.8)
	Mean	(SD)
TM Size	6.46	3.8
Adjuvant Treatment	N (%)	95% CI
Yes	162(93.6%)	(89.6-97.1)
No	11(6.4%)	(2.9-10.4)
Mean OS	Mean	(SD)
Adj TX Yes	116	16.2
Adj TX No	168	8.7
	Mean	(SD)
Age	57.6	11.2
	n(%)	95% CI
Follow up (Month, Median)	39	
Local Recurrence		
Yes	3 (1.7%)	(0-4)
No	170(98.3%)	(96-100)
Distant Met		
Yes	20(11.6%)	(4.6-21.2)
No	153(88.4%)	(83.8-93.1)

LMS: Leiomyosarcoma, CS: Carcinosarcoma, ESS: Endometrial stromal sarcoma, US: Undifferentiated sarcoma, AS: Adenosarcoma, 95% CI: 95% Confidence Interval (lower-upper limits), TM Size: Tumor size, OP: Operation, ADJ TX: Adjuvant treatment, RT: Radiotherapy, CT: Chemotherapy

Three patients had local vaginal cuff recurrence and twenty patients (11.6%) had distant metastasis involving the liver, lung, pelvis, paraaortic lymph nodes and groin region. All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH BSO). Only one patient underwent TAH and unilateral salpingo-oophorectomy (USO) due to a former oophorectomy operation. Ninety (52%) patients underwent TAH+BSO and Pelvic (P) and paraaortic (PA) lymph

node dissection (LND). Among all, 162 (93.6%) received adjuvant therapy, while 11 (6.4%) did not. These patients were all stage 1A LMS patients. Mean tumor size was 6.46 (3.8) cm. Local recurrence occurred in three (1.7%) and distant metastasis occurred in twenty patients (11.6%).

The mean age of LMS patients was 53.3 (9.4) years and the mean tumor size was 8.06 (4.9) cm. Thirty-seven (77.1%) LMS patients had stage 1 disease, 6 (12.5%) had stage 2, 1 (2.1%) had stage 3, 4 (8.3%) had stage 4 disease. Out of the forty-eight patients, thirty-seven (77.1%) received adjuvant therapy, 23 (47.9%) patients received RT only, 4 (8.4%) received CT only, 10 (20.8%) patients received both RT and CT. Twenty-five (52.1%) patients underwent TAH BSO, 2 (4.2%) underwent only TAH, 5 (10.4%) patients underwent TAH BSO, P and LND, and 14 (29.2%) underwent TAH BSO, P, PA and LND. Local recurrence was seen in 1 (2.1%) patient while distant metastasis was seen in 9 (18.8%) patients. A mean of 15 (8.7) pelvic lymph nodes and 10 (2.9) paraaortic lymph nodes were dissected. No metastasis was detected among patients who underwent lymph node dissection (Table 2).

Table 2: Clinicopathologic features of LMS

	n=48 (27.7%)	
Age (mean (SD)	53.3 (9.4)	
Tm Size (mean (SD)	8.06 (4.9)	
Stage	n(%)	95%CI
1	37(77.1%)	64.6-97.5
2	6(12.5%)	4.2-22.9
3	1(2.1%)	0-6.3
4	4(8.3%)	2.1-16.7
Adj Treat.	n(%)	95%CI
Yes	37(77.1%)	64.6-89.6
No	11(22.9%)	10.4-35.4
Only RT	23(47.9%)	33.3-62.5
Only CT	4(8.4%)	2.1-16.7
RT+CT	10(20.8%)	8.4-33.3
Op	n(%)	95% CI
TAH	2(4.2%)	0-10.4
TAH BSO	25(52.1%)	39.6-66.7
TAH BSO PLND	5(10.4%)	2.1-18.8
TAH BSO PPLND	14(29.2%)	16.7-41.6
TAH USO	2(4.2%)	0-10.4
Local Recurrence	1(2.1%)	0-6.3
Distant Met	9(18.8%)	8.3-31.3
Pelvic Lymph Node Number median (SD)	15 (8.7)	
Paraaortic Lymph Node Number Median (SD)	10 (2.9)	
	n(%)	
Pelvic Lymph Node Met	0	
Paraaortic Lymph Node Met	0	

95% CI: 95% Confidence Interval (lower-upper limits), TM Size: Tumor size, OP: Operation, ADJ TREAT: Adjuvant treatment, RT: Radiotherapy, CT: Chemotherapy

Adenosarcoma (AS) and undifferentiated sarcoma (US) rates were 4.6% and 1.2% respectively. Factors (tumor size, age, recurrence, adjuvant treatments) affecting overall and disease-free survival were evaluated for LMS and CS patients (Table 3, 4 and 5). For OS and DFS, recurrence was a significant prognostic factor in LMS in univariate and multivariate (P<0.05 for all) analyses and in CS patients, in multivariate analysis (P=0.02 and 0.01 respectively for OS and DFS analysis).

The mean age and tumor sizes of CS patients were 58.2 (12.2) years and 5.7 (3.3) cm, respectively. Fifty-nine (67.8%) had stage 1 disease, 8 (9.2%) had stage 2 disease, 17 (19.5%) had stage 3 disease and 3 (3.4%) had stage 4 disease. Eighty (90.9%) patients received RT and CT, 8 (9.1%) received CT only, while no patients received RT only. Forty-eight (54.5%) patients underwent TAH BSO, P, PA and LND. Thirty-three (37.5%) patients underwent TAH BSO, P and LND. The mean number of dissected pelvic and paraaortic lymph nodes were 15 (5.4) and 9 (5.7), respectively. Ten (20%) pelvic and three patients (6.3%) had paraaortic lymph node metastasis, while 7 (8%) had distant metastasis (Table 4).

Table 3: Factors effecting overall and disease-free survival in LMS patients

Univariate analysis	Overall Survival			Disease Free Survival		
	P-value	OR	95%CI	*P*-value	OR	95%CI
Tm Size(≤5cm,>5cm)	0.06	0.14	0.19-1.14	0.06	0.14	0.01-1.15
Age (≤50,>50)	0.56	0.71	0.22-2.22	0.50	0.68	0.22-2.07
Adjuvant Therapy	0.60	1.41	0.38-5.75	0.72	1.25	0.34-4.60
Recurrence (local,distant)	0.00	0.09	0.02-0.35	0.00	0.02	0.00-0.13
Multivariate analysis	Overall Survival			Disease Free Survival		
	P-value	OR	95%CI	*P*-value	OR	95%CI
Tm Size(≤5cm,>5cm)	0.06	0.11	0.01-1.13	0.09	0.10	0.01-1.33
Age (≤50,>50)	0.64	0.75	0.22-2.53	0.38	0.5	0.18-1.91
Adjuvant Therapy	0.40	0.50	0.09-2.75	0.98	0.9	0.19-4.94
Recurrence (local,distant)	0.00	0.10	0.02-0.40	0.00	0.03	0.00-0.15

Tm: Tumor, Cox Regression Analysis. OR: odds ratio, CI: confidence interval.

Table 4: Clinicopathologic features of CS

	n=88 (50.9%)	
Age (mean (SD))	58.2 (12.2)	
Tm Size (mean (SD))	5.7(3.3)	
Stage	n(%)	95% CI
1	59(67.8%)	58.6-77.0
2	8(9.2%)	3.4-14.9
3	17(19.5%)	11.5-28.7
4	3(3.4%)	0-8
	n(%)	95% CI
RT+CT	80 (90.9%)	84.1-96.6
Only CT	8(9.1%)	3.4-15.9
Only RT	0	0
Op		
TAH BSO	2(2.3%)	0-5.7
TAH BSO PLND	33(37.5%)	27.3-47.7
TAH BSO PPLND	48(54.5%)	43.2-64.8
TAH USO	1(1.1%)	0-3.4
TAH BSO PPLND Low Anterior Resection	2(2.3%)	0-5.7
TAH BSO PPLND Implant Resection	1(1.1%)	0-3.4
TAH BSO PPLND Pelvic Peritonectomy	1(1.1%)	0-3.4
	n (median (SD))	
Pelvic Lymph node number Median (SD)	15 (5.4)	
Paraaortic Lymph Node Number Median (SD)	9 (5.7)	
	n(%)	95% CI
Pelvic Lymph Node Met	10(20%)	10.4-33.3
Paraaortic Lymph Node Met	3(6.3%)	0-14.6
Local Recurrence	0	0
Distant Met	7(8%)	3.4-13.6

95% CI: 95% Confidence Interval (lower-upper limits), TM Size: Tumor size, OP: Operation, ADJ TREAT: Adjuvant treatment, RT: Radiotherapy CT: Chemotherapy

Table 5. Factors effecting overall and disease-free survival in CS patients

Univariate analysis	Overall Survival			Disease Free Survival		
	P-value	OR	95%CI	*P*-value	OR	95%CI
Tm Size(≤5cm,>5cm)	0.30	3.0	0.37-24.3	0.23	3.5	0.43-28.3
Recurrence (local,distant)	0.18	2.9	0.60-14.6	0.17	2.9	0.6-14.5
Age (≤50,>50)	0.73	1.2	0.33-4.76	0.87	1.1	0.29-4.24
Multivariate analysis	Overall Survival			Disease Free Survival		
	P-value	OR	95%CI	*P*-value	OR	95%CI
Tm Size(≤5cm,>5cm)	0.10	0.15	0.01-1.48	0.05	0.07	0.00-1.03
Recurrence (local,distant)	0.02	0.10	0.01-0.70	0.01	0.05	0.00-0.50
Age (≤50, >50)	0.36	0.50	0.11-2.22	0.58	0.67	0.16-2.77

Tm: Tumor, Cox Regression Analysis, OR: odds ratio; CI: confidence interval. Bold *P*-values are <0.05 and statistically significant

The mean age in ESS patients was 62.8 (7.4) years and mean tumor size was 6.3 (2.9) cm. Thirteen (48.1%) patients had stage 1, 2 (7.4%) had stage 2, 10 (37.0%) had stage 3 and 2 (7.4%) had stage 4 disease. Seventeen (63%) patients received RT and CT, 5 (18.5%) received only CT, 5 (18.5%) received progesterone hormone therapy. Twenty-two (81.5%) patients underwent TAH BSO, P, PA and LND, and 2 (7.4%) underwent TAH BSO, P and LND. Local recurrence occurred in 2 (7.4%) patients while distant metastasis was seen in 4 (14.8%). The mean number of dissected pelvic and mean paraaortic lymph nodes were 15 (10.2) and 11(10.7), respectively. Pelvic and paraaortic lymph node metastases were detected in 9 (36%) and 6 (24%) patients, respectively (Table 6).

Table 6. Clinicopathologic Features of ESS

	n:27 (15.6%)	
Age (mean (SD))	62.8 (7.4)	
Tm Size (mean (SD))	6.3 (2.9)	
Stage	n(%)	95% CI
1	13(48.1%)	29.6-66.7
2	2(7.4%)	0-18.5
3	10(37.0%)	18.5-55.6
4	2(7.4%)	0-18.5
Adjuvant Treatment	n(%)	95% CI
RT+CT	17(63%)	44.5-81.5
CT	5(18.5%)	3.7-33.5
Hormone	5(18.5%)	3.7-33.5
Op	n(%)	95% CI
TAH BSO	1(3.7%)	0-11.1
TAH BSO PLND	2(7.4%)	0-18.5
TAH BSO PPLND	22(81.5%)	66.7-92.6
TAH BSO PPLND Implant Resection	2(7.4%)	0-18.5
Local Recurrence	2(7.4%)	0-18.5
Distant Met	4(14.8%)	3.7-29.6
Pelvic Lymph Node Number Median (SD)	15 (10.2)	
Paraaortic Lymph Node number Median(SD)	11 (10.7)	
	n(%)	95% CI
Pelvic Lymph Node Met	9(36%)	16-56
Paraaortic Lymph Node Met	6(24%)	8-44

95% CI: 95% Confidence Interval (lower-upper limits), TM Size: Tumor size, OP: Operation, ADJ TREAT: Adjuvant treatment, RT: Radiotherapy, CT: Chemotherapy

The median overall survival (OS) was 39 (range 3-214 months) months. All patients were followed-up for 200 months, during which 22 patients died. The 200-month OS rate of all patients was 60.9% (Figure 1). The patients were evaluated with respect to the diagnoses (Figure 2). Sarcoma type had no significant impact on OS (P=0.13). The mean OS in patients who did and did not receive adjuvant treatment were 116 (16.2) months and 168 (8.7) months, respectively (Table 1). The patients were evaluated with respect to the stages and adjuvant treatment. While early stages had a significant impact on OS (Figure 3), adjuvant treatment did not (P<0.001 and P=0.50, respectively) (Figure 4).

Figure 1: Kaplan Meier overall survival of all patients

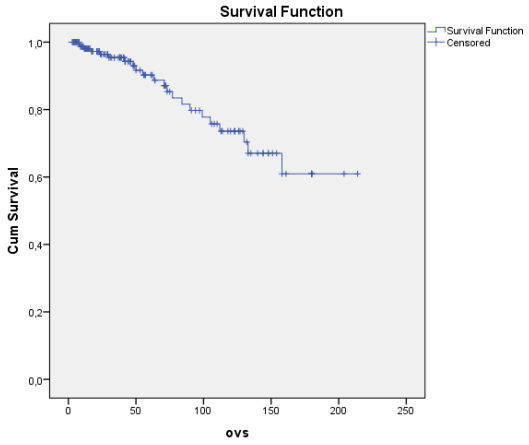
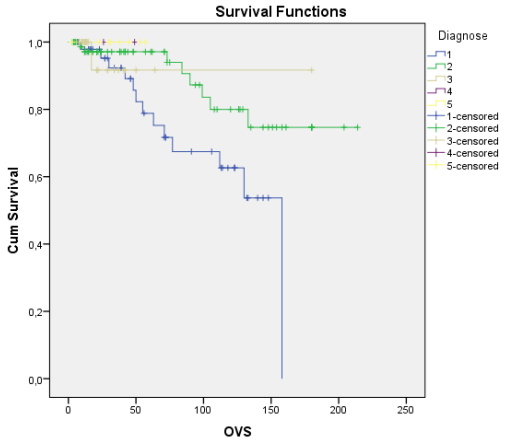


Figure 2: Kaplan Meier survival analysis of sarcoma types (P=0.1)



1: Leiomyosarcoma, 2: Carcinosarcoma, 3: Endometrial stromal sarcoma, 4: Undifferentiated sarcoma, 5: Adenosarcoma.

Figure 3: Kaplan Meier survival analysis of stages 1,2 and 3,4 (p<0.001)

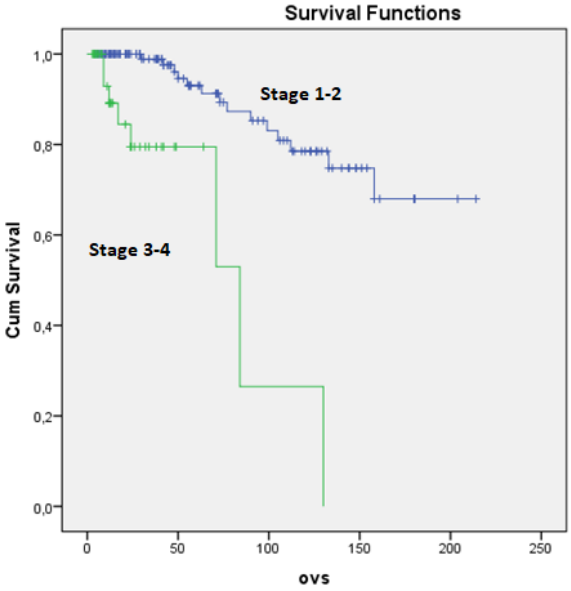
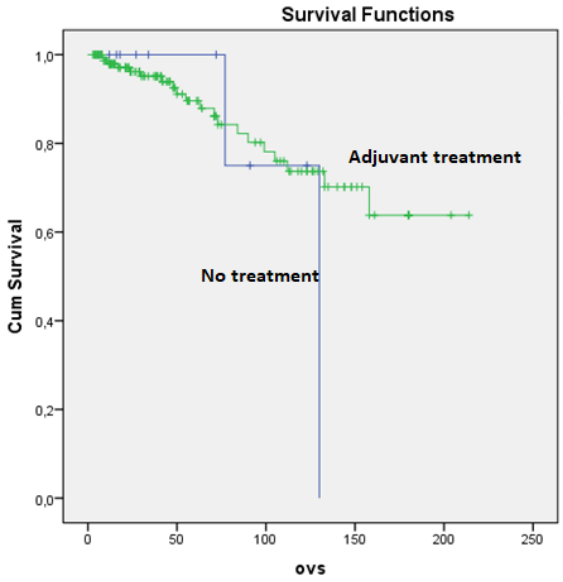


Figure 4: Kaplan Meier overall survival analysis of patients who received adjuvant therapy (P= 0.55)



Discussion

Uterine sarcomas are rare and aggressive gynecological tumors with poor prognosis. Our results demonstrated that CS is the most common type of sarcoma in our clinic. Compared to other groups of sarcomas, none of the sarcoma diagnosed patients had significantly worse overall survival. The rate of LMS and CS among all uterine sarcomas were reported as 40% and 40%, respectively [5]. In the present study, the rates of LMS and CS were 27.7% and 50.9%, respectively.

Leiomyosarcomas are highly aggressive tumors and rare entities with a poor and unfavorable prognosis. The recurrence rate ranges from 53% to 71% [3]. In this study, local recurrence and distant metastasis occurred in 2.1% and 18.8% of the patients, respectively. LMS may result from a sarcomatous transformation of a leiomyoma [6]. The basis of the therapy is total abdominal hysterectomy and debulking of any extrauterine tumor. For early stage leiomyosarcoma, the incidence of lymph node metastasis is rare, therefore lymphadenectomy is not recommended [7]. In the present study, 10.4% of patients underwent TAH BSO, P and LND and 29.2% patients underwent

TAH BSO, P, PA, and LND. Metastasis was not detected in any of the patients who underwent lymph node dissection.

The effect of adjuvant therapies on survival is controversial [8]. Several studies have found that radiation therapy improved local control but had no significant impact on OS [9]. In the present study, 47.9% of leiomyosarcoma diagnosed patients received only RT, 8.4% received only CT and 20.8% received both RT and CT. Among those who received RT, 2.1% had local recurrence. On the other hand, in this study, adjuvant treatment had no impact on OS.

Tumor size and mitotic index were reported as prognostic factors [3,10]. Stage is considered the most important prognostic factor for uterine sarcomas. In the present study, tumor size, age, and adjuvant treatments (RT, CT, or both) had no significant impact on OS and DFS in both univariate and multivariate cox regression analysis. However, for LMS patients, recurrence had a significant impact on survival in univariate and multivariate analyses.

Carcinosarcomas are rare tumors. They are considered a variant of high-risk endometrial adenocarcinoma [11] and arise from the endometrial tissue of the uterus. However, endometrial sampling may not be an accurate test for the diagnosis of uterine carcinosarcoma [12]. Carcinosarcomas mostly occur in elderly patients. Similarly, in our study, the median age was 58.2 (12.2) years. For surgical staging, total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH BSO), pelvic and para-aortic lymph node dissection, and pelvic lavage are required. In one study, the median survival with and without lymphadenectomy was 54 and 25 months [13]. Ferguson et al. reported that 10% of carcinomatous components were grade I, 10% were grade II, and 80% were grade III [14].

In our study, 88 (50.9%) patients had carcinosarcoma, twice as much as the number of LMS patients [48(27.7%)]. Like endometrial carcinomas, stage and the depth of the myometrial invasion are the most important prognostic factors. Serous and clear cell carcinoma components tend to metastasize more. In our study, recurrence was the only significant prognostic factor in multivariate analysis of CS patients.

Endometrial stromal sarcomas (ESS) are exceedingly rare tumors. The percentage of ESS is approximately 7–25% in all uterine sarcomas [15]. In the present study, 15.6% of all sarcoma patients were diagnosed with ESS. Endometrial stromal tumor (ESS) cells resemble endometrial stromal cells of the proliferative endometrium. ESS can be divided into 3 subgroups: Endometrial stromal nodule, low grade endometrial stromal sarcoma (LG-ESS), and high-grade endometrial sarcoma [16]. ESS typically develops in perimenopausal women with a mean age of 46 years (range: 18–83 years) [17]. In this study, the mean age was 62.8 (7.4) years. Abeler et al. [3] reported that prognosis of endometrial stromal sarcoma confined to the uterus was related to mitotic index and tumor cell necrosis. The risk of recurrence in LG-ESS is 10–20%, and late recurrences are characteristic of the disease [18]. LG-ESS have high levels of steroid receptors and these tumors can metastasize from the uterus to the ovaries. Five of our LG-ESS diagnosed patients received progestin therapy and local and distant metastases occurred in 2 (7.4%) and 4 (14.8%) patients, respectively. The reported pelvic lymph node metastasis in CS and ESS is about 15% [19]. However, in our study, 36% of ESS diagnosed patients had pelvic and 24% had paraaortic lymph node metastasis. ESS requires the same extended surgical staging as endometrial adenocarcinoma. We had eight patients with adenosarcoma.

This study is not free of bias. First, these results represent the experience of a single center and do not give us the opportunity for a head-to-head comparison with other centers. Second, experience and training of surgeons may differ globally and the outcomes may differ accordingly. Despite these potential biases, single center experience allowed us to define a more homogeneous surgical technique to compare the outcomes with respect to different patient characteristics.

In the literature, there is a little evidence that supports the use of adjuvant chemotherapy for sarcomas, except for CS. On the other hand, Terek et al. reported that adjuvant chemotherapy is a significant prognostic factor for survival in uterine sarcomas [20].

Limitations

The main limitation of this study is its retrospective design. Since we did not design an experimental prospective study, sample size calculation was not performed prior to analysis. Additionally, sarcomas are rare tumors and the design of a prospective study with a-priori sample size calculation was not feasible. Larger prospective series and meta-analysis evaluating global results are needed to further evaluate uterine sarcomas.

Conclusion

As in all cancers, early stage is an important prognostic factor for all sarcoma types. Tumor size, age and adjuvant treatments had no significant impact on survival. Although the data is limited about ESS, based on our results, ESS requires extended surgical staging as well as CS. However, further clinical studies are needed for the surgical and adjuvant treatment decisions of uterine sarcomas.

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Frequencies of glutathione S-transferase A1 rs3957357 polymorphism in a Turkish population

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Abstract

Background/Aim: Glutathione-S-transferases (GSTs), a major group of phase II enzymes, play a significant role in the detoxification and metabolism of endogenous and exogenous compounds. The objective of the survey was to identify the distribution of genotype and allele frequencies of *GSTA1* -69C>T (rs3957357) polymorphism in a healthy Turkish population and compare the determined frequencies with those in various populations.

Methods: Polymerase chain reaction and restriction fragment length polymorphism methods were used to analyze *GSTA1* -69C>T polymorphism in DNA samples of 105 healthy Turkish individuals.

Results: The distribution of *GSTA1* CC, CT, and TT genotype frequencies were 32.4%, 48.6% and 19.0%, respectively while the allele frequencies were 56.7% for C allele and 43.3% for T allele. The findings obtained were compared with the results of various populations. The frequencies of *GSTA1* -69C>T polymorphism were similar to those of the African American population and the populations with White ancestry, but significantly different from those reported for the populations with Asian ancestry.

Conclusion: To the best of our knowledge, this is the first study to present the frequencies of the *GSTA1* -69C>T polymorphism among Turkish individuals. The findings of the current study may provide a perspective for further studies exploring the role of *GSTA1* -69C>T polymorphism on predisposition to diverse illnesses such as cancer and may be used as a control group for such studies. In addition, this study might contribute to epidemiological and toxicogenetic investigations.

Keywords: Glutathione S-transferases, *GSTA1*, rs3957357, Polymorphism, Turkish population

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Ethics Committee Approval
The study was approved by the Ethics Committee of Mersin University (date: 02/09/2020, protocol no: 2020/615).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Introduction

Biotransformation of xenobiotics and endogenous compounds occurs through phase I and/or phase II enzymes. One of the main groups of phase II enzymes is glutathione S-transferases (GSTs). GSTs play a significant role in the detoxification and metabolism of endogenous and exogenous substances that include a wide range of medications, products of oxidative stress, carcinogens, environmental toxins by catalyzing the conjugation between electrophilic substances and reduced glutathione [1, 2]. Different GST isoenzymes have been identified in humans. Alpha (GSTA), theta (GSTT), pi (GSTP) and mu (GSTM) are the most characterized GST classes [3]. The GSTA class is the most plentiful GST enzyme in the human liver among all hGSTs and accounts for approximately sixty-five to eighty percent of their total liver concentration [4]. Besides, the GSTAs are expressed in the small intestine, adrenal glands, testicles and kidneys [1]. The GSTA isoenzymes conjugate compounds like the nitrogen mustard group of some anticancer drugs, α, ß-unsaturated aldehydes and some heterocyclic amines, steroid and thyroid hormones, penicillin, bile acids and bilirubin [2]. GSTAs exhibit high glutathione peroxidase activity and play a significant part in the protection of cells against exogenous and endogenous electrophilic compounds [5].

Inter-individual variations in the activities of GST enzymes might be caused by environmental effects such as exposure to toxins in the environment, lifestyle (use of medication, etc.) and diet, but genetic variations may also play a role [4]**.** Nearly all the GST family members have genetic polymorphisms that result in reduction of enzyme activity or a complete lack [3].

Several single nucleotide polymorphisms (SNPs) have been detected in the promoter region of the *GSTA1* gene. One of SNPs are *GSTA1* -69C>T (rs3957357) [6]. There are four functional polymorphisms in *GSTA1*, which are full linkage disequilibrium, and called *GSTA1*A* for -52G, -69C, -567T, -631T and *GSTA1*B* for -52A, -69T, -567G, -631G [7]. The base change C-69T leads to an Ear1 restriction enzyme site into the *GSTA1*B* variant [8]. The homozygous mutant genotype of the *GSTA1* -69C>T gene polymorphism is reported to have a lower enzymatic activity than the wild-type genotype [9]. *GSTA1* -69C>T polymorphism is reportedly related with various disorders such as gestational hypertension, leukemia, bladder cancer [10].

There have been many studies displaying that the distribution of GST polymorphisms differs among distinct regional, national and ethnic populations [11]. However, in the literature search, no studies were found on the *GSTA1* -69C>T polymorphism in Turkish population. Thus, the objective of the survey was to identify the distribution of the genotype and allele frequencies of the mentioned polymorphism in a healthy Turkish population, and compare the frequencies found with those of various populations.

Materials and methods

Samples

The DNA samples used for polymorphic analysis were obtained during the previous study approved by Mersin University Ethics Committee (22/10/2015, protocol no: 2015/317), and some of the DNA samples isolated were randomly contained to the present study. The present survey was also approved by the Ethics Committee of Mersin University (02/09/2020, protocol no: 2020/615). This study comprised the DNA samples of unrelated 105 Turkish healthy volunteers (age range: 18-65 years) and was conducted in accordance with the principles of the Good Clinical Practices and the Declaration of Helsinki.

Genotyping

Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods defined by Hezova et al. [9] with slight modifications were used for genotyping analysis of *GSTA1 -69C>T* polymorphism. *A* 400-bp fragment was amplified using the following primers: Forward: 5'-GCATCAGCTTGCCTTCA-3' and reverse: 5'-AAACGCTGTCACCGTCCTG-3'. The PCR reaction mixture contained 10x PCR buffer, 2.0 mM $MgCl_2$, 0.2 mM of each deoxynucleotide triphosphate, 20 pmol of each primer, 1.25 U of Taq DNA polymerase (Fermentas), approximately 300 ng DNA and last volume completed with distilled water to 30-µl. Amplification was for one cycle of 300 min at 94 ˚C, 30 cycles of 20 sec at 94 ˚C, 20 sec at 64 ˚C, 30 sec at 72 ˚C, and final 7 min extension at 72 ˚C. Negative control (NC), a DNA-free sample, was included in each PCR experiment and was used to determine whether the reagents used are contaminated with foreign DNA. PCR products (400-bp) were electrophoretically determined on a 2.0 % agarose gel containing ethidium bromide (EtBr, 500 µg/L) making the products visible. The PCR products were digested with FastDigest EarI (Eam1104I) (Thermo Fisher Scientific, USA) restriction enzyme and incubated at 37 °C for 15 min. The digested and undigested products were detected on 2.5% agarose gel visualized by EtBr. The wild-type genotype (CC) had no Eam1104I restriction enzyme site and was therefore 400 bp. On the other hand, the homozygous mutant genotype (TT) had Eam1104I restriction enzyme site and gave bands at 308 bp and 92 bp. The heterozygous genotype (CT) gave bands at 400 bp, 308 bp and 92 bp. Ten percent of the randomly selected samples were reanalyzed for confirmation. PCR-RFLP was conducted on a MiniAmp Plus Thermal Cycler (Thermo Fisher, USA).

Statistical analysis

Statistical data were analyzed using IBM SPSS 25.0 computer software for Windows. The frequencies of *GSTA1* -69C>T polymorphism were obtained by counting, and chi-square (X^2) test was used for assessment of Hardy–Weinberg equilibrium. The data obtained were compared with previously reported data of various populations. Distinctions in the allele and genotype frequencies between populations were tested by X^2 test. $P<0.05$ and $P<0.001$ were considered statistically significant.

Results

GSTA1 C-69T SNP was detected using PCR-RFLP technique in the DNA samples of unrelated 105 Turkish healthy individuals. Of the 105 individuals, 50 (48%) were male, and the remaining 55 (52%) were female. The distributions of the genotype frequencies obtained were consistent with Hardy-

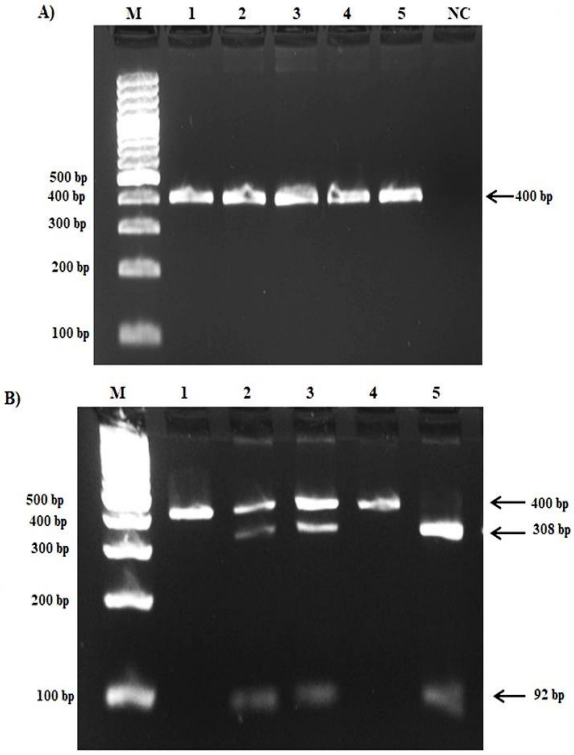
Weinberg equilibrium (X^2=0.013, P>0.05). The frequencies were 32.4% for the wild-type genotype (CC), 48.6% for the heterozygous genotype (CT) and 19.0% for the homozygous mutant genotype (TT). Thus, the frequencies of C and T alleles were 56.7% and 43.3%, respectively (Table 1).

Figure 1 shows agarose gel images of PCR and RFLP patterns of electrophoretically detected *GSTA1* -69C>T polymorphism.

Table 1: The frequencies of *GSTA1* -69C>T gene polymorphism in a healthy Turkish population

	Genotype				
	CC	CT	TT	TOTAL	
n (observed)	34	51	20	105	X^2: 0.013
Genotype frequencies, %	32.4	48.6	19.0	100	*df* =1; *P*>0.05
n (expected)	33.7	51.6	19.7	105	
	Allele				
Allele frequencies, %	C		T		
	56.7		43.3	100	

Figure 1: Electrophoresis examples of *GSTA1* -69C>T polymorphism identified using polymerase chain reaction (PCR) (A) and restriction fragment length polymorphism (RFLP) (B). For A (PCR) part; Lane M: 100 bp DNA ladder, Lane 1-5: PCR product (400 bp), NC: negative control. For B (RFLP) part; Lane M: 100 bp DNA Ladder, Lane 1,4: wild type genotype (400 bp), Lane 2,3: heterozygous genotype (400, 308, 92 bp), Lane 5: mutant genotype (308, 92 bp).



Discussion

The GSTs superfamily, one of the enzymatic families in phase II metabolism is highly polymorphic, and the polymorphic variations in the GSTs enzymes can influence their activities, therefore may lead to individual predisposition to a variety of diseases like cancer [2]. Due to genetic variants in GSTs, ethnic and inter-individual distinctions in the detoxification capacity of GSTs have been identified in diverse populations [12]. In this study, the frequencies of *GSTA1* -69C>T polymorphism were examined in a Turkish population. The distributions of frequencies of *GSTA1* CC, CT, and TT genotype were 32.4%, 48.6% and 19.0%, respectively, while the frequencies of C and T alleles were 56.7% and 43.3%, respectively.

The frequencies of genotype and allele of *GSTA1* -69C>T polymorphism have been reported in diverse populations. The findings obtained for the Turkish population were compared with the results reported for various populations [4, 6, 8, 9, 12-25] as depicted in Table 2. Accordingly, *GSTA1* -69T variant allele was more frequent in South Tunisians and Germans compared to other populations. In Asian ancestry, the frequencies of *GSTA1* -69T variant allele ranged from 10.5% to 16.0%. The allele and genotype frequencies of the Turkish population showed significant distinction when compared to those of Asian ancestry, including Chinese, Chinese Han, Asian (Northeast Thailand), Taiwanese, Japanese (*P<0.001*). In White ancestry, the frequencies of *GSTA1* -69T variant allele ranged from 35.1% to 48.4%. The frequency of *GSTA1* -69T variant allele in the Turkish population was very similar to those of White ancestry, including Serbian, Hispanic, Caucasian, Caucasian (USA), Danish, German, Italian, Polish, Caucasian (The Netherlands), Czech Central European, Eastern Slavs (Russia), Caucasian (Poland), South Tunisian (*P>0.05*). Moreover, no significant distinction was noted between the Turkish population and the American-African population with 35.7% allelic frequency (*P>0.05*).

Table 2: Comparison of the frequencies of *GSTA1 -69C >T* polymorphism in various populations

Ethnicity &Population	Healthy, control & patients etc.	Sample size	Genotype frequencies n (%)			Allele frequencies n (%)		Ref#
		n	CC	CT	TT	C	T	
WHITE								
Turkish	Healthy	105	34 (32.4)	51 (48.6)	20 (19.0)	119 (56.7)	91 (43.3)	Present study
Serbian	Healthy Control	66	23 (34.8)	36 (54.5)	7 (10.7)	82 (62.1)	50 (37.9)	[3]
Serbian	Control	122	49 (40.0)	57 (47.0)	16 (13.0)	155 (63.5)	89 (36.5)	[13]
Caucasian	Control	278	106 (38.0)	133 (48.0)	39 (14.0)	345 (62.0)	211 (38.0)	[8]
Caucasian (USA)	Control	81	24 (29.6)	44 (54.3)	13 (16.1)	92 (56.8)	70 (43.2)	[14]
Danish women	Control	396	123 (31.0)	210 (53.0)	63 (16.0)	456 (57.6)	336 (42.4)	[15]
German	Control	826	256 (31.0)	395 (47.8)	175 (21.2)	907 (54.9)	745 (45.1)	[16]
Caucasian (The Netherlands)	Healthy Control	411	168 (40.9)	184 (44.8)	59 (14.3)	520 (63.3)	302 (36.7)	[17]
Hispanic women	Control	53	19 (36.0)	27 (51.0)	7 (13.0)	65 (61.3)	41 (38.7)	[8]
Italian women	Control	137	46 (33.6)	65 (47.4)	26 (19.0)	157 (57.3)	117 (42.7)	[18]
Eastern Slavonic origin women (Russia)	Ovarian cancer	104	43 (41.3)	49 (47.1)	12 (11.6)	135 (64.9)	73 (35.1)	[19]
Polish	Healthy	160	54 (33.7)	74 (46.3)	32 (20.0)	182 (56.9)	138 (43.1)	[1]
Caucasian (Poland)	Control	365	137 (37.5)	165 (45.2)	63 (17.3)	439 (60.1)	291(39.9)	[6]
Czech Central European	Control	218	76 (34.9)	108 (49.5)	34 (15.6)	260 (59.6)	176 (40.4)	[9]
South Tunisian	Healthy	154	38 (24.7)	83 (53.9)	33 (21.4)	159 (51.6)	149 (48.4)	[12]
ASIAN								
Chinese*	Healthy	140	105 (75.0)	34 (24.3)	1 (0.7)	244 (87.1)	36 (12.9)	[4]
Chinese Han women*	Healthy Control	112	86 (76.8)	24 (21.4)	2 (1.8)	196 (87.5)	28 (12.5)	[20]
Asian (Northeast Thailand)*	Healthy Control	198	141 (71.2)	53 (26.8)	4 (2.0)	335 (84.6)	61 (15.4)	[21]
Taiwanese*	Non-diabetes mellitus	198	157 (79.3)	38 (19.2)	3 (1.5)	352 (88.9)	44 (11.1)	[22]
Taiwanese*	Control	274	214 (78.1)	56 (20.4)	4 (1.5)	484 (88.3)	64 (11.7)	[23]
Japanese *	Healthy	147	104 (70.8)	39 (26.5)	4 (2.7)	247 (84.0)	47 (16.0)	[24]
Japanese*	Healthy Control	294	238 (81.0)	50 (17.0)	6 (2.0)	526 (89.5)	62 (10.5)	[25]
BLACK								
African-American	Control	63	25 (39.7)	31 (49.2)	7 (11.1)	81 (64.3)	45 (35.7)	[14]

n: total number of subjects. Distinctions between the frequencies were studied using X^2, * P<0.001 at significance when compared to the results of the present study.

Genetic variations in the genes encoding enzymes that metabolize xenobiotics may alter the expression level of the protein product, thereby affecting an individual's susceptibility to various diseases and carcinogens and influencing the efficacy and toxicity of certain drugs [1]. As mentioned above, the frequencies of *GSTA1* C-69T polymorphism can be variable among distinct populations, which may lead to intra- and inter-population distinctions in xenobiotic-induced toxic effects.

In the study conducted by Sweeney et al. [26] on a total of 245 breast cancer patients, 198 of which were Caucasian and 47 of which were African American, *GSTA1* -69C>T polymorphism was related with survival after treatment with combination chemotherapy containing cyclophosphamide, and that a significantly decreased risk of dying was noted for subjects with *GSTA1* –69TT genotype. Khrunin et al. [19] declared that in 104 ovarian cancer patients of East Slavic origin, the allelic state of the *GSTA1* C-69T polymorphism was associated with overall survival and that the subjects carrying *GSTA1* -69TT genotype indicated better survival compared to the *GSTA1* -69CC carriers. Rossi et al. [27] reported that the *GSTA1* rs3957357 C>T polymorphism might be related with event-free survival (EFS) in patients with diffuse large B-cell lymphoma (DLBCL) and reported that patients with DLBCL carrying the CT/TT genotypes showed better EFS than patients with the CC genotype. Iorio et al. [18] explored the role of the *GSTA1* -69C>T SNP in genetic susceptibility to gestational hypertension (GH) in 195 case-control populations of Italian origin. It was notified that GH subjects had an importantly lower allele frequency of *GSTA1* -69T compared to control groups and that the subjects carrying at least one *GSTA1* -69T allele had a forty-five percent decrease in GH risk compared to those with *GSTA1* -69CC genotype (odds ratio [OR]=0.54, 95% confidence Interval [CI]=0.29–0.99; $P<0.05$). The *GSTA1* -69C>T polymorphism was significantly related with GH risk.

Contrary to the above, Akhdar et al. [28] examined the associations between the risk of hepatocellular carcinoma (HCC) development and the rs3957357C>T SNP in *GSTA1* among European individuals and reported that TT genotype was related with a 2 times increased risk of HCC occurrence (OR=2.1, $P=0.02$). In a meta-analysis study performed by Deng et al. [29], the variant genotype and allele of the *GSTA1* rs3957357 polymorphism was related with an incremental risk of cancer, particularly colorectal cancer, in Caucasian populations.

Liu et al. [10] investigated the potential relationships between schizophrenia (SCZ) and *GPX3* rs736775 and *GSTA1* rs3957357 polymorphisms in a case-control study of 648 healthy control and 617 schizophrenia patients from northern Han Chinese populations, and *GSTA1* rs3957357 polymorphism and the interplay between *GPX3* and *GSTA1* was reported to have impacts on SCZ risk.

Genetic polymorphisms may alter the activities of enzymes playing significant roles in the metabolism and detoxification of various xenobiotics that include carcinogens and drugs, and thus may lead to intra- and inter-population distinctions in predisposition to diverse diseases, xenobiotics toxicities, drug safety and efficacy [30].

Conclusion

To our knowledge, this is the first investigation to present the frequencies of the *GSTA1* -69C>T polymorphism among Turkish individuals. In the current study, the -69C>T polymorphism in the *GSTA1* gene is observed to be common among Turkish individuals. The frequencies of *GSTA1* -69C>T polymorphism were similar to those in the African American population and the populations with White ancestry, but significantly different from those reported for the populations with Asian ancestry. The findings of the current study may ensure a perspective for further studies exploring the role of *GSTA1* -69C>T polymorphism on predisposition to diverse illnesses such as cancer and may be used as a control group for such investigation. In addition, this study might contribute to epidemiological and toxicogenetic investigations as well.

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Comparison of intestinal metaplasia and Helicobacter pylori positivity in patients from different age groups with antral gastritis

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Ethics Committee Approval
The study was approved by the Institutional Board of Nisa Private Hospital (date: 01.04.2019). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Gastric carcinoma (GC) is the fourth most common cancer worldwide and the second most common cause of cancer death. Primary prevention for GC includes healthy diet, eradication of Helicobacter pylori (HP), chemoprevention and early diagnosis. For this reason, finding out the HP incidence in patients with suspected antral gastritis in various age groups can lead to forming a treatment strategy to prevent development of GC. The aim of this study is to find out the HP incidence in patients with a proven antral gastritis diagnosis in various age groups and form different treatment strategies.
Methods: This study included 1589 patients aged between 15-91 years who underwent diagnostic upper gastrointestinal endoscopy due to complaints of dyspepsia. The demographic characteristics, such as age and sex, and histopathological HP score (HPS) and IM score (IMS) were recorded. The patients were divided into three groups according to age: 15-29 years, 30-64 years, and 65 years and above.
Results: In the 15–29-year age group, IM positivity was significantly lower and HP positivity was significantly higher compared to other age groups ($P<0.01$). In the age group of 65 years and above, HP positivity was significantly lower than in the other groups ($P<0.01$). The incidence of IM was significantly higher and that of HP was significantly lower in male patients aged 65 years and older ($P<0.01$ for both). IM positivity was significantly higher in HP negative patients than in HP positive patients ($P=0.02$).
Conclusion: The most important risk factors for the development of IM are male gender and being aged 65 years and older. HP positivity is higher among the young population and IM prevalence is higher in advanced ages. There is no correlation between HP positivity and the presence of IM.

Keywords: Endoscopy, Gastrointestinal system, Intestinal metaplasia, Helicobacter pylori

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Introduction

Gastric carcinoma (GC) is the fourth most common cancer worldwide and the second most common cause of cancer death. Primary prevention for GC includes healthy diet, eradication of Helicobacter pylori (HP), chemoprevention and early diagnosis [1].

HP is a gram-negative bacterium found in the stomach and detected in 50% of population [2]. In 1994, HP was classified as a class I carcinogen by the International Agency for Research on Cancer [3]. The Maastricht III Guidelines recommend treating the H. pylori infections [4]. In chronic HP infections, a multistep process of atrophy, intestinal metaplasia (IM), and dysplasia develops, which leads to GC [2, 5]. Therefore, IM is considered a precancerous lesion for gastric carcinoma [6]. It is known that the most important risk factor for developing IM is HP [2, 7]. However, the effect of the presence of HP on the development of IM is still debated [2]. Studies on the frequency and the effects of HP infections may significantly contribute to early diagnosis and treatment of GC and survival [6].

In this study, the aim was to determine the frequency of and relationship between IM and HP in different age groups.

Materials and methods

Patients who underwent upper GI endoscopy between January 1, 2017 and March 22, 2019 were retrospectively evaluated. This study included 1589 patients aged between 15-91 years who underwent diagnostic upper gastrointestinal endoscopy due to complaints of dyspepsia. The demographic characteristics, such as age and sex, and histopathological scoring of HP score (HPS) and IM score (IMS) were recorded. The patients were divided into three groups according to age: 15-29 years, 30-64 years, and 65 years and above. Biopsies were obtained from antrum. The samples were histopathologically graded from 0 to 3 according to the severity of IMS and HPS. IMS and HPS were evaluated as 0=none, 1=mild, 2=moderate and 3=severe. In statistical analysis, IMS and HPS scores were evaluated as mild and moderate/severe.

The endoscopy and pathology results of 1842 patients who underwent upper GIS endoscopy for dyspeptic complaints were reviewed retrospectively. Among them, 1589 patients with endoscopic and histopathologic findings of antral gastritis were included. A total of 253 patients were excluded from the study based on the results of control gastroscopy, along with a 107-year-old patient who had a previous pathology of antral gastritis (gastric cancer, Maltoma, etc.), who had previously undergone HP eradication therapy and control gastroscopy. The presence and correlation of IM and HP were compared only in patients with antral gastritis. Therefore, only antrum biopsies were considered. This study was not planned primarily to reveal the incidence of HP.

Since the number of patients with IMS and HPS 3 was very low and did not indicate statistical significance, IMS / HPS: 3 patients were categorized as moderate / severe with 2 patients and statistically evaluated.

Endoscopy technique

All upper gastrointestinal mucosa, from oropharynx to second part of the duodenum, were examined under direct vision with Pentax EPK 100-p brand endoscopy device in the Endoscopy Unit after at least 8 hours of fasting and under sedo-anesthesia (propofol). Antral mucosal biopsy was performed in all patients.

Histopathological examination

Gastric mucosal biopsy specimens were fixed in 10% formaldehyde and followed by routine tissue follow-up. After being embedded in paraffin, 4-5-micron thick sections were removed from the specimens. They were stained with Hematoxylin-Eosin and histological examination was performed. The other sections were stained with modified Giemsa and HP was investigated. Histopathological examination was performed according to Sydney classification [8], and they were evaluated for inflammation, activation, intestinal metaplasia, atrophy, and Helicobacter pylori presence in 4 degrees (0: None, 1: Mild, 2: Moderate, 3: Severe).

Statistical analysis

IBM SPSS Statistics V23.0 package software was used to analyze the data. Central and prevalence criteria such as number, percentage, mean, median, range of distribution, standard deviation were used to present descriptive data. The conformity of numerical variables to normal distribution was evaluated with visual (histogram) and analytical (Shapiro Wilk test) tests. Pearson's Chi-square test was used to determine the differences between categorical variables and Spearman Correlation tests were used to determine those between numerical variables. A value of $P<0.05$ was considered statistically significant.

Results

This study included 1589 patients aged 15-91 years. There were 267 patients in the 15–29-year age group, 1088 patients in the 30-64-year age group and 234 patients in the 65-year and above age group. Of the patients, 38.21% were female and 61.79% were male. The mean age of patients was 46.23 years. IM and HP positivity rates were 8.62% and 34.61%, respectively.

In the 15–29-year age group, IM positivity was significantly lower and HP positivity was significantly higher in comparison with other age groups ($P<0.01$). In the group of 65 years and above, HP positivity was significantly lower than in the other groups ($P<0.01$). Comparison of the age groups of patients with IM and HP positivity is presented in Table 1.

Table 1: Comparison of age groups of patients with IM and HP positivity

	Age groups							
	15-29		30-64		65 and over			
	n	*%	n	*%	n	*%	X^2	*P*-value**
IM positivity								
Negative	259	97.0	989	90.9	204	87.2	16.3	<0.01
Positive	8	3.0	99	9.1	30	12.8		
HP positivity								
Negative	151	56.6	693	63.7	195	83.3	43.9	<0.01
Positive	116	43.4	395	36.3	39	16.7		

* Column percentage, ** Chi-square tests

No significant difference was found between the age groups in terms of IM and HP scores ($P>0.05$). The incidence of IM was significantly higher and that of HP was significantly lower in male patients aged 65 and above than other age groups ($P<0.01$ for both). While the frequency of HP was significantly

lower in female patients aged 65 and older (P<0.01), there was no significant difference in terms of IM frequency (P>0.05). Comparison of IM and HP positivity among age groups in male and female patients is shown in Tables 2 and 3.

Table 2: Comparison of IM and HP positivity among age groups in male patients

	Age groups							
	15-29		30-64		65 and over			
	n	*%	n	*%	n	*%	X^2	*P*-value**
IM positivity								
Negative	98	98.0	378	91.3	76	81.7	15.7	<0.01
Positive	2	2.0	36	8.7	17	18.3		
HP positivity								
Negative	48	48.0	251	60.6	76	81.7	23.9	<0.01
Positive	52	52.0	163	39.4	17	18.3		

* Column percentage, ** Chi-square tests

Table 3: Comparison of IM and HP positivity among age groups in female patients

	Age groups							
	15-29		30-64		65 and over			
	n	*%	n	*%	n	*%	X^2	*P*-value**
IM positivity								
Negative	161	96.4	611	90.7	128	90.8	6	>0.05
Positive	6	3.6	63	9.3	13	9.2		
HP positivity								
Negative	103	61.7	442	65.6	119	84.4	22.1	<0.01
Positive	64	38.3	232	34.4	22	15.6		

* Column percentage, ** Chi-square tests

In terms of gender, HP positivity was significantly higher among male patients compared to female patients (P=0.02), however, IM positivity was similar (P>0.05). Comparison of gender with IM and HP positivity in patients is shown in Table 4.

IM positivity was significantly higher in HP negative patients than in HP positive patients (P=0.02). Comparison of HP and intestinal metaplasia positivity in patients is shown in Table 5. There was no significant correlation between HPS and IMS (P>0.05).

Table 4: Comparison of gender with IM and HP positivity in patients

	Sex					
	Male		Female			
	n	*%	n	*%	X^2	*P*-value**
IM positivity						
Negative	552	90.9	900	91.6	0.2	0.62
Positive	55	9.1	82	8.4		
HP positivity						
Negative	375	61.8	664	67.6	5.6	0.02
Positive	232	38.2	318	32.4		

* Column percentage, ** Chi-square tests

Table 5: Comparison of HP and intestinal metaplasia positivity in patients

	IM positivity					
	Negative		Positive			
	n	*%	n	*%	X^2	*P*-value**
HP positivity						
Negative	937	90.2	102	9.8	5.4	0.02
Positive	515	93.6	35	6.4		

* Column percentage, ** Chi-square tests

Discussion

In some histopathological studies, chronic atrophic gastritis, IM, dysplasia, and carcinoma development period beginning with chronic active gastritis due to HP is reported as 16-24 years [9]. Therefore, early detection and treatment of HP presence are clinically important to prevent the development of GC. In our study, there was a significant difference in HP positivity in the 15-29-year age group compared to the other age groups, and all patients underwent HP eradication.

There are numerous studies showing regression in IM with HP eradication therapy, whereas some other studies report otherwise [2, 6, 10-14]. The results of these studies lead to debates about HP eradication. In a study conducted by Rokkas et al. [15], GC development was prevented if HP was eradicated in the case of atrophic and non-atrophic gastritis. On the other hand, once IM and dysplasia developed, eradication therapy did not prevent the development of GC. Hwang et al. [16] conducted a study on 598 patients with a 10-year follow-up period and showed that HP eradication caused regression in IM and atrophic gastritis. It was reported as a preventive strategy for the development of intestinal type GC. These results demonstrate the importance of early diagnosis and treatment of HP in preventing the development of GC. In our study, considering the high presence of HP among the younger population, we consider that detecting the presence of HP and its treatment are important, especially in patients with complaints of dyspepsia at younger ages.

IM is more commonly present in advanced ages. However, there are some studies showing that HP is more common in advanced ages, while in some other studies it is higher in the earlier ages. In a study conducted by Craanen et al. [9], HP positivity was more common in the elderly population, while Kesici [2] reported that it was more common in the younger population. In our study, HP positivity was significantly higher especially in earlier ages and gradually decreased in advanced ages. In studies conducted by Craanen et al. [9] and Kesici [2], IM presence was more common in advanced ages. In our study, the presence of IM increased with age, and it was significantly higher in the group aged 65 years and older, which is consistent with the results of these studies.

In the literature, the rates of IM vary considerably. This may be because patients in different studies have different age and gender ratios. In their study conducted on 3301 patients in Turkey, Ozdil et al. [17] reported the HP positivity as 71.3% and IM presence as 17.8%. In our study, the HP positivity and IM rates were 34.61% and 8.62%, respectively. The rate of IM was 19.8% in a study by Ajdarkosh et al. [18] and 11.5% in a study by Kesici [2]. In the study of Jiang et al. [19] on 28745 patients in the Chinese population, the most important risk factors for the development of IM were 40-70-year age range, male gender, gastric ulcer, bile reflux, HP infection and severe chronic inflammation. In our study, similar to the results of this study, the most important risk factor for developing IM was being male and being aged 65 years and above. In a study by Ozdil et al. [17], HP infection decreased, and the prevalence of IM increased with age. In our study, in line with these results, HP positivity decreased with age and the presence of IM increased with it.

While some studies in the literature have reported a significant relationship between HP positivity and IM presence, some other studies have not identified a significant relationship. In a study by Uemura et al. [20], a significant relationship was found between HP positivity and development of IM, whereas Topal et al. [21] and Kesici [2] reported otherwise. In our study, no significant relationship was found between HP positivity and the presence of IM. However, the presence of IM in HP negative patients was significantly higher than in HP positive patients. The lack of correlation between concurrent HP and IM presence in our study did not indicate that HP is not a risk factor for development of IM. Although HP is highly prevalent in the young population, the lack of correlation in concurrent investigations should be considered a possible outcome since development of IM takes a long period of time. Due to the low HP positivity rate in advanced ages, long-term exposure to HP

and the lack of timely eradication treatment, the fact that there is no correlation between IM and HP depending on high IM development can be considered a possible result.

Conclusion

The most important risk factor for the development of IM is male gender and being aged 65 years and above. HP positivity is higher in young population and IM prevalence is higher in advanced ages, and there is no correlation between HP positivity and the presence of IM. By taking the results of this study and other studies in the literature into account and considering that cancer develops within 16-24 years in the presence of HP, since HP positivity is more common in patients with complaints of dyspepsia, especially in the 15-29 age group, it is believed that early detection and eradication of HP play an essential role to prevent the development of cancer in this group. However, due to the multifactorial nature of cancer development, we believe that more studies are needed to reveal the relationship between HP and IM. Multi-center studies are needed to reveal the incidence.

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Antimicrobial effect of local anesthetics on Helicobacter pylori

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Ethics Committee Approval
No ethics committee approval was obtained for this study because of its in vitro design.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Helicobacter pylori (HP) is a gram-negative bacillus, with a prevalence of 50% throughout the world. HP infection is considered the strongest etiological factor for gastric cancer (GC). Therefore, early diagnosis and treatment of HP can be considered as the primary prevention strategy for the development of GC. This study aimed to reveal the antimicrobial effect of commonly used local anesthetics (LAs) on HP. The literature review in English has revealed no study on this subject.

Methods: This *in vitro* laboratory study was conducted in a University laboratory between 25 October 2019 and 1 November 2019. In the study, antimicrobial effect of 1 mL sterile saline, 20 mg/mL lidocaine, 1 mg/mL adrenaline, 10 mg/mL prilocaine, 50 mg/mL bupivacaine, and 20 mg+0.0125 mg/mL lidocaine plus adrenaline against *H. pylori* strain NCTC 11637 obtained from National Collection of Type Cultures (NCTC) were tested *in vitro*. The groups were designated as follows: Group C (Control), Group B (Bupivacaine), Group L (Lidocaine), Group A (Adrenaline), Group P (Prilocaine), and Group LA (Lidocaine plus adrenaline). HP strain NCTC 11637 was cultured in Mueller Hinton agar (Oxoid, UK) supplemented with 5% sheep blood plates at 37°C under microaerophilic conditions (5% oxygen, 10% carbon dioxide, and 85% nitrogen gas combination) for 72 hours.

Results: Antimicrobial activity was observed in Group L and Group LA. No antimicrobial action against HP was observed in other groups. The comparison of groups in terms of inhibition zone diameters showed that there was a statistically significant inhibiting effect in Group L and Group LA compared to Group C (P=0.002 and P<0.001, respectively).

Conclusion: Among the LAs used in the present study, lidocaine and lidocaine + adrenaline had antimicrobial action against HP whereas bupivacaine and prilocaine had no statistically significant effect. Therefore, we believe that lidocaine can be used in the eradication therapy of HP. If the findings obtained from the present study are supported by clinical trials, lidocaine can help break the increasing resistance mechanisms in the treatment of HP or can be used in its treatment, which may help to improve treatment success and reduce treatment costs.

Keywords: Helicobacter pylori, Antimicrobial, Lidocaine, Adrenaline, Bupivacaine, Prilocaine

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Introduction

Helicobacter pylori (HP) is a gram-negative bacillus, with a prevalence of 50% throughout the world [1]. HP infection is considered the strongest etiological factor for gastric cancer (GC) [2]. In various studies, gastritis from a chronic active form to chronic atrophic form, intestinal metaplasia (IM), dysplasia, and gastric cancer (GC) due to HP have been reported to develop within 16–24 years [3]. Therefore, early diagnosis and treatment of HP can be considered as the primary prevention strategy for the development of GC.

The traditional treatment of HP is based on the combination of proton pump inhibitors (PPI) with dual antibiotics [1]. However, the development of drug resistance is reported after repeated treatments [4]. Eradication therapy of HP becomes more difficult due to increased antimicrobial resistance, leading to an increase in treatment costs [5]. Therefore, there is a need for alternative or supportive therapies that reduce antimicrobial resistance, facilitate treatment, and reduce costs.

The primary aim of this study was to reveal the antimicrobial effect of commonly used local anesthetics (LAs) on HP. The literature review in English has shown no study on this subject.

Materials and methods

Determination of *in vitro* antimicrobial effect

In the study, antimicrobial effect of 1 mL sterile saline, 20 mg/mL lidocaine, 1 mg/mL adrenaline, 10 mg/mL prilocaine, 50 mg/mL bupivacaine, and 20 mg+0.0125 mg/mL lidocaine plus adrenaline against *H. pylori* strain NCTC 11637 obtained from National Collection of Type Cultures (NCTC) were tested in an *in vitro* environment. The groups were designated as follows: Group C (Control), Group B (Bupivacaine), Group L (Lidocaine), Group A (Adrenaline), Group P (Prilocaine), and Group LA (Lidocaine+adrenaline). *H. pylori* strain NCTC 11637 was cultured onto Mueller Hinton agar (Oxoid, UK) supplemented with 5% sheep blood plates at 37°C under microaerophilic conditions (5% oxygen, 10% carbon dioxide, and 85% nitrogen gas combination) for 72 hours. Colonies from these plates were suspended in sterile saline and a 2 McFarland turbidity standards suspension of each isolate was prepared. Each labeled Mueller-Hinton agar (Oxoid, UK) containing 5% sheep blood plate was uniformly seeded with a test organism by means of a sterile swab rolled in the suspension and streaked on the plate surface. *In vitro* antimicrobial activity of 1 mL sterile saline, 20 mg/mL Lidocaine, 1 mg/mL adrenaline, 10 mg/mL prilocaine, 50 mg/mL bupivacaine, and 20 mg/mL Lidocaine plus Adrenaline were evaluated by modified disc diffusion method with determination of inhibition zones. Each sterile disc (Merck, Germany) was impregnated with the anesthetics and dried. After dried, they were placed and incubated on Mueller-Hinton Agar containing 5% sheep blood for 72 hours at 37°C under microaerophilic conditions. The zone of inhibition was measured at the 72nd hour. Each experiment was repeated ten times **[6].**

Determination of minimum inhibitory concentration (MIC) and minimal bactericidal concentration (MBC)

The broth microdilution method was used to determine the MIC values on brain heart infusion broth (BHIB) (Oxoid, UK) supplemented with 10% horse serum and 0.25% yeast extract using 96 well microplates (Hachem et al., 1996). The anesthetic agents were prepared by dilution in BHIB containing 10% horse serum and 0.25% yeast extract and 100, 80, 60, 50, 40, 20, 10, 5, 2.5, 1.25, 0.625, 0.312, 0.156, and 0.078 mg/mL concentrations of lidocaine, lidocaine plus adrenaline, prilocaine, bupivacaine, and adrenaline were tested. Anesthetics were added to the wells of a 96-well microplate containing HP strain NCTC 11637. Each test was repeated two times for each microplate. Microplates were incubated at 37°C under microaerophilic conditions for 72 hours (3 days). The OD600 (wavelength of 600 nm) was measured after 72-hour incubation by using Epoch spectrophotometer (BioTek Inst. Inc. Vermont, USA). Wells without anesthetic agents were used as growth control and wells with BHIB containing 10% horse serum and 0.25% yeast extract alone served as negative control. Amoxicillin and Clarithromycin were also tested for control (twofold serial dilution 16-0.002 mg/L).

To determine the MBC, each well exhibiting no visible growth (viability) after 72 hours was tested for viable organisms by subculturing 10 µL samples of each well onto Mueller-Hinton Agar containing 5% sheep blood. The plates were incubated at 37°C under microaerophilic conditions to observe the growth of any colony after 72 hours.

Statistical analysis

Descriptive statistics were used to define continuous variables (mean, standard deviation, minimum, median, and maximum). Two continuous independent variables not following normal distribution were compared using the Mann–Whitney U test whereas Kruskal–Wallis test was used for the comparison of more than two continuous independent variables not following normal distribution. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013.

Results

Mean inhibition zone diameters of all groups are shown in Table 1.

Table 1: Mean inhibition zone diameters of groups

	Mean (SD)	Mean (min-max)
Control	0(0)	0(0-0)
Lidocaine	1.2(0.8)	1(0-2)
Lidocaine+Adrenaline	1.9(0.7)	2(1-3)
Bupivacaine	0(0)	0(0-0)
Prilocaine	0(0)	0(0-0)
Adrenalin	0(0)	0(0-0)

Kruskal Wallis test, P<0.001

Antimicrobial activity was observed in Group L and Group LA whereas no antimicrobial activity was observed against *H. pylori* in other groups. The comparison of groups in terms of inhibition zone diameters showed that there was a statistically significant inhibiting effect in Group L and Group LA compared to Group C (P=0.002 and P<0.001, respectively). No statistically significant difference was observed between Group L and Group LA (P=0.074).

Table 3: Distribution of MIC values and the effect of different concentrations of anesthetic agents against H.pylori NCTC 11637 strains

Lidocaine (mg/mL)	0.078	0.156	0.313	0.625	1.25	2.50	5	10	20	40	50	60	80	100
H. pylori NCTC 11637	+	+	+	+	+	+	+	+	+	+	+	+	-*	-
Lidocaine+adrenaline (mg/mL)	0.078	0.156	0.313	0.625	1.25	2.50	5	10	20	40	50	60	80	100
H. pylori NCTC 11637	+	+	+	+	+	+	+	+	+	+	+	-*	-	-
Bupivacaine (mg/mL)	0.078	0.156	0.313	0.625	1.25	2.50	5	10	20	40	50	60	80	100
H. pylori NCTC 11637	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prilocaine (mg/mL)	0.078	0.156	0.313	0.625	1.25	2.50	5	10	20	40	50	60	80	100
H. pylori NCTC 11637	+	+	+	+	+	+	+	+	+	+	+	+	+	-*
Adrenaline (mg/mL)	0.078	0.156	0.313	0.625	1.25	2.50	5	10	20	40	50	60	80	100
H. pylori NCTC 11637	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Amoxicillin (mg/L)	0.002	0.004	0.008	0.016	0.032	0.064	0.128	0.256	1	1	2	4	8	16
H. pylori NCTC 11637	+	+	+	-*	-	-	-	-	-	-	-	-	-	-
Clarithromycin (mg/L)	0.002	0.004	0.008	0.016	0.032	0.064	0.128	0.256	1	1	2	4	8	16
H. pylori NCTC 11637	+	+	-*	-	-	-	-	-	-	-	-	-	-	-

*MIC values

A significant difference was observed between Group C and Group B, Group P, and Group A (P=1.00). Table 2 shows the comparison of inhibition zone diameters of the groups. The MIC values in all groups are shown in Table 3 in comparison with Amoxicillin and Clarithromycin. The MIC and MBC values in all groups are shown in Table 4 in comparison with amoxicillin and Clarithromycin.

Table 2: Comparison of inhibition zone diameters between groups

	P-value
Control vs Lidocaine	0.002
Control vs Lidocaine+Adrenaline	<0.001
Lidocaine vs Lidocaine+Adrenaline	0.074
Control vs Bupivacaine	1.00
Control vs Prilocaine	1.00
Control vs Adrenalin	1.00

*Mann Whitney u test

Table 4: MIC and MBC values anesthetic agents, amoxicillin and clarithromycin against *H.pylori NCTC 11637*

H. pylori NCTC 11637	MIC	MBC
Lidocaine (mg/mL)	80.00	-
Lidocaine+adrenaline (mg/mL)	60.00	-
Bupivacaine (mg/mL)	-	-
Prilocaine (mg/mL)	100.00	-
Adrenaline (mg/mL)	-	-
Amoxicillin (mg/L)	0.016	2
Clarithromycin (mg/L)	0.008	4

MIC: Minimum inhibitor concentration, MBC: Minimum bactericidal concentration

Discussion

HP is a major public health problem affecting about 52.1–58% of the worldwide population [5] as gastric and extragastric diseases are reported in the HP-associated broad spectrum. It has been reported to particularly cause peptic ulcer disease, gastritis, gastric atrophy, GC, gastric mucosa-associated lymphoid tissue lymphoma, idiopathic thrombocytopenic purpura, iron deficiency anemia, colorectal cancer, esophageal adenocarcinoma, metabolic syndrome, Alzheimer's disease, or glaucoma [2, 5, 7, 8]. Histopathological studies have reported that gastritis from a chronic active form to chronic atrophic form, IM, dysplasia, and GC due to HP develop within 16 to 24 years [3]. Therefore, early identification and eradication therapy of HP have become more important. However, antibiotic resistance in HP has been increasing in many parts of the world [2, 7]. Increased antimicrobial resistance leads to the search for new treatment strategies [5]. Considering the existence of major *H. pylori*-associated diseases, the importance of eradication therapy is understood. The present study has shown the antimicrobial effect of commonly used LAs on HP.

Among the LAs used in the present study, lidocaine and lidocaine plus adrenaline were found to have an antimicrobial action against HP whereas bupivacaine and prilocaine did not. There has been no significant difference between lidocaine and lidocaine plus adrenaline in terms of antimicrobial effect, however, MIC levels have been lower in the lidocaine plus adrenaline group, suggesting that lidocaine plus adrenaline combination may have a clinically significant contribution to reducing the risk of dose-related adverse effects. The uncertainty regarding its clinical use increases since this is the first study in English literature and an *in vitro* study. However, considering the increase in HP antimicrobial resistance, it is understood that there is a need for new treatment options due to the difficulty in treatment and increased costs. Therefore, we believe that demonstrating the contribution of lidocaine to HP treatment through clinical trials is of great importance.

Various antibiotic-resistance mechanisms have been described for HP. One of them is the reduction of bacterial membrane permeability [9]. In the literature, LAs have been reported to inhibit the growth of live bacteria, to reduce the membrane-dependent enzymatic activity of living cells, to cause lysis in protoplasts, to change the membrane permeability, and to cause ultrastructural alterations [10, 11]. Considering these effects of LAs, their antimicrobial effects on HP can be utilized and the mechanism of action on membrane permeability can contribute to the elimination of mechanisms of antibiotic resistance in HP.

Limitations

Its in vitro design is the limitation of the present study. Findings of this study should be supported by clinical trials.

Conclusion

HP infection is considered the strongest etiological factor for GC. Therefore, eradication therapy of HP can be preferred as the primary treatment strategy in the prevention of GC. Considering the existence of other major HP-related diseases, eradication therapy is of great importance. However, HP antibiotic resistance has been increasing in many parts of the world. One of the various antibiotic-resistance mechanisms in *H. pylori* is the reduction of bacterial membrane permeability. Due to the mechanism of action of LAs on membrane permeability, they can contribute to the elimination of mechanisms of antibiotic resistance in HP. Among the LAs used in the present study, lidocaine and lidocaine plus adrenaline have an antimicrobial effect on HP whereas bupivacaine and prilocaine have no statistically significant effect. Therefore, lidocaine is thought to be used in the eradication therapy of HP.

The findings obtained from the present study should be supported by clinical trials. Thus, lidocaine can be used to break the increasing resistance mechanisms in HP or be used in the

treatment of HP, which may help to improve treatment success and reduce treatment costs.

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Clinical biomarkers to predict preoperative lymph node metastasis in endometrial cancer

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Ethics Committee Approval
Canakkale Onsekiz Mart University Clinical Research Ethics Committee (date: 10.02.2021, number: 02-22)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Although the evaluation of preoperative lymph node metastasis is very important for the appropriate approach of the surgeon, it cannot be determined precisely. We aimed to investigate preoperative systemic inflammatory markers and the value of CA 125 in the prediction of lymph node metastasis (LNM) in epithelial endometrial carcinoma.
Methods: In our retrospective cohort study, 327 patients were pathologically diagnosed with epithelial endometrial carcinoma and underwent surgical staging including lymphadenectomy. We investigated preoperative serum CA 125, neutrophil/lymphocyte (NLR) and thrombocyte/lymphocyte (PLR) values and their relationship with LNM. ROC analysis was performed to these variables for prediction of LNM.
Results: There was a significant difference between histological type (P=0.021), myometrial invasion (P<0.001), lymphovascular space invasion (LVSI) (P<0.001), and peritoneal cytology (P=0.001) in those with and without LNM. Among the NLR, PLR and CA 125 values, only CA 125 was significantly higher in the LN positive group compared to the LN negative group (P=0.516, P=0.408 and P=0.001, respectively). The optimal CA 125 cut-off value in the preoperative diagnosis of LNM was ≥39.0 U/ml. The diagnostic sensitivity, specificity, PPV, NPV, and accuracy values of CA 125 were 77%, 82%, 48%, 94%, and 81%, respectively.
Conclusion: While preoperative CA 125 value was a significant predictor for LNM in epithelial endometrial cancers, we did not detect this relationship in NLR, PLR and systemic inflammatory markers.

Keywords: Endometrial cancer, Systemic inflammatory markers, Serum CA 125 level, Lymph node metastasis

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Introduction

Endometrial cancer (EC) is the most common gynecological malignancy and the 6th most common cause of all female cancers in developed countries. Obesity and the increasing frequency of the elderly population gradually increase the prevalence of this cancer [1].

Endometrial cancer is often diagnosed at an early stage and has a good prognosis. However, lymph node metastasis (LNM) is observed in 10% of patients in the clinical early stage [2].

With prospective studies, it has been shown that lymph node dissection does not benefit overall and recurrence-free survival in patients with clinical early-stage endometrial cancer and is furthermore associated with surgical morbidity (prolonged operation time, deep vein thrombosis, leg edema) at a frequency of 15-20% [2-5]. On the other hand, pelvic or paraaortic LNM is associated with a poor prognosis, and detection of LNM is important for appropriate adjuvant therapy [6]. Although most gynecological oncologists do not consider pelvic/paraaortic lymphadenectomy as a standard procedure in patients with a low risk of lymph node involvement, it is also a fact that in most presumed early-stage patients, the surgeon is caught between overtreatment or under treatment as a therapeutic challenge [7]. Preoperative assessment of the risk of lymph node metastasis by the clinician would therefore be an appropriate approach.

Although tumor grade, histology and myometrial depth are considered the strong determinant criteria of LNM [8-10], there is no biochemical marker or radiological sign which can precisely predict lymph node metastasis preoperatively. In histological grade, a result discrepancy of up to 30% can be observed in preoperative and permanent pathology reports [11]. Additionally, access to magnetic resonance (MRI), computerized tomography (CT), and positron emission tomography (PET/CT) from radiological imaging are difficult and costly, and their value in lymph node involvement is limited [12]. The systemic inflammatory response is stimulated by the proliferation, metastasis, and angiogenesis of cancer cells [13]. Inflammation and immune response play a significant role in the progression of cancer. While neutrophil, thrombocyte and CRP levels increase due to the immune response, the lymphocyte count decreases. Interleukin-6 has been shown to cause thrombocytosis by increasing hepatic thrombopoietin synthesis [14]. Many inflammatory response markers, such as CRP, neutrophil/lymphocyte ratio (NLR), thrombocyte/lymphocyte ratio (PLR), have been investigated as prognostic factors in different cancer types [15, 16].

We aimed to investigate the values of NLR and PLR, which are the routinely examined hemocytometric measurements in preoperative evaluation, and CA125, which we commonly use in the diagnosis and follow-up of gynecological malignancies, in the prediction of lymph node metastasis in endometrial cancer.

Materials and methods

Our retrospective study reviewed the medical records of 327 patients who were diagnosed with endometrial adenocarcinoma between February 2010 and February 2019 and underwent surgical staging with pelvic lymph node dissection (PLND) ± paraaortic lymph node dissection (PALND). Our study was approved by the clinical research ethics committee of Çanakkale Onsekiz Mart University and conducted in accordance with the Helsinki Declaration principles (10.02.2021 approval date and 02-22 number).

Preoperative complete blood count and CA 125 measurement were performed one week before at the latest. NLR was defined as the ratio of absolute neutrophil count to absolute lymphocyte count, whereas PLR was defined as the ratio of absolute thrombocyte number to absolute lymphocyte count. Quantitative measurement of CA125 concentration was conducted with the Abbott Architect 2000i Analyzer (Abbott Diagnostics, Abbott Park, IL).

Patients who were not diagnosed with epithelial endometrial carcinoma, who did not undergo pelvic lymphadenectomy, those who had any acute or chronic inflammatory disease, received preoperative chemotherapy or had other synchronous malignancies were excluded from the study.

Surgical procedure

First, peritoneal cytology samples were obtained with median laparotomy or laparoscopy, and all intra-abdominal organs and peritoneal surfaces were examined. Biopsies were taken from suspicious areas, and total hysterectomy and retroperitoneal lymphadenectomy were then performed. For pelvic lymphadenectomy, the external iliac artery and vein were mobilized; the obturator nerve was then protected, and the external iliac vessels, internal iliac, and lymphatic tissue were excised from the obturator fossa. In paraaortic lymphadenectomy, precaval, aortocaval and paraaortic lymphatic tissues were dissected up to the level of the left renal vein. The endometrial cancer 2009 FIGO staging system was used in surgical staging.

Statistical analysis

Categorical variables were expressed as frequencies and percentages (%) whereas continuous variables were expressed as mean (SD), and median and interquartile range (IQR) due to non-normality. The Shapiro–Wilk test was used to assess the normality assumption of continuous variables. Differences between two independent groups for continuous variables were evaluated by Student's t-test and Mann–Whitney U test accordingly. The differences in proportions between the groups were compared using Chi-Square or Fisher Exact tests as appropriate. ROC analysis was used to calculate the areas under the receiving operator curves (AUC) and 95% confidence intervals for study parameters to predict LNM (positive). Sensitivity, specificity, PPV, NPV and accuracy were calculated. All statistical analyses were conducted using SPSS 19.0 for Windows Version 19.0 software (IBM Corp., Armonk, NY, USA) and *P*-values of less than 0.05 were considered to indicate statistical significance.

Results

With the implementation of our exclusion criteria, we reached 327 patients who underwent surgical staging for endometrial cancer. While only pelvic lymphadenectomy was performed in 69 of our 327 patients (21.1%), pelvic and paraaortic lymphadenectomy were performed in 258 patients (78.9%). No patients underwent paraaortic lymphadenectomy without pelvic lymphadenectomy.

LNM was detected in 54 of our 327 patients (16.5%). There was a significant relationship between histological type, myometrial invasion, LVSI, peritoneal cytology and the presence of LNM. Age and pathological characteristics of our study population are given in Table 1.

Among NLR, PLR and CA 125, only CA 125 was found to have a significant relationship with LNM (P=0.001, Table 2).

Table 1: Patient characteristics according to lymph node status

Characteristics		n	LNM (negative) n=273	LNM (positive) n=54	*P*-value
Age		327	61.63 (9.20)" (31-86)	61.22 (8.57)" (45-80)	*0.762
Grade	1	244	204 83.60%	40 16.40%	0.615
	2	56	45 80.40%	11 19.60%	
	3	27	24 88.90%	3 11.10%	
Type	Endometroid	225	195 86.70%	30 13.30%	0.021
	Non-endometroid	102	78 76.50%	24 23.50%	
Tumor size(cm)	<2	43	39 90.70%	4 9.30%	0.166
	≥2	276	227 82.20%	49 17.80%	
MI	<50 %	207	191 92.30%	16 7.70%	<0.001
	≥50 %	120	82 68.30%	38 31.70%	
LVSI	no	210	191 91.00%	19 9.00%	<0.001
	yes	112	77 68.80%	35 31.30%	
Peritoneal cytology	negative	287	243 84.70%	44 15.30%	0.001
	positive	9	4 44.40%	5 55.60%	

*Student t test, mean (SD), n: number; LNM: lymph node metastasis; MI: myometrial invasion; LVSI: Lymphovascular space invasion

Table 2: Comparing median of study variables according to their association with LNM

Biomarker	n1/n2	LNM (negative)	LNM (positive)	*P*-value
CA 125	184/39	17.9 (11.42 – 30.7) U/ml	51.45 (40.4-128.4) U/ml	0.001
NLR	272/53	2.12 (1.67 -2.95)	2.43(1.61-3.35)	0.516
PLR	272/53	125.23 (96.91-159.81)	149.89 (97.38-171.50)	0.408

Mann Whitney U-test, median (interquartile range), n:number, LNM: lymph node metastasis, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio.

ROC analysis was performed to compare the predictive diagnostic performances of our variable values. CA 125 significantly predicted the LNM positivity rate (ROC AUC = 0.80, P<0.001), while NLR and PLR did not (AUC=0.60, P=0.052 and AUC=0.59, P=0.086, respectively). Our cutoff value for CA 125 was 39 U/ ml. Diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy values of CA 125, which were significant and superior to others, were 77%, 82%, 48%, 94% and 81%, respectively (Figure 1, Table 3).

Figure 1: Receiver operating characteristics curves for serum CA 125, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio for lymph node metastasis.

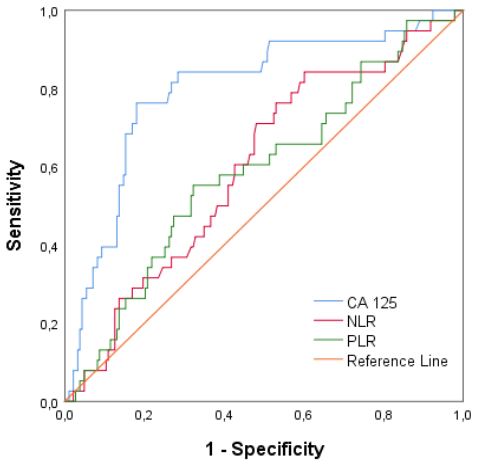

Table 3: Area under curve (AUC) and cut-off values in the receiver operating characteristic curve and sensitivity, specificity of CA 125, NLR and PLR to predict LNM

	Cut-off	AUC	%95 CI	*P*-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
CA 125	39.00	0.80	0.715-0.878	<0.001	0.77	0.82	0.48	0.94	0.81
NLR	2.03	0.60	0.505-0.695	0.052	0.64	0.46	0.19	0.87	0.48
PLR	149.35	0.59	0.489-0.688	0.086	0.45	0.68	0.22	0.87	0.65

NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

Discussion

Our objective is to avoid unnecessary lymphadenectomies by accurately predicting metastatic or nonmetastatic lymph nodes in EC preoperatively. We know that the known LNM risk factors (grade, mycobacterial invasion, lymphovascular invasion, cervical involvement, positive peritoneal cytology) can only be determined after surgery [2]. While preoperative and permanent mismatches can be seen at high rates for histological grade, the sensitivity and specificity of the pelvic MRI that we use in the evaluation of myometrial invasion can vary between 63-100% and 56-100% [17, 18]. The sensitivity and specificity of MRI for detecting LNM is 45% and 80.8%, respectively [19]. Therefore, many studies have focused on non-invasive, highly accurate and sensitive methods in the preoperative detection of possible LNM.

A systemic host response occurs against malignant tumors that alters the tumor's microenvironment. Leukocytosis and neutrophilia are the most common systemic changes. Lymphocytopenia associated with increased leukocytes is a response of systemic inflammation and the immune system [20]. Inflammatory cytokines released by tumor and adenosine diphosphate (ADP) also stimulate megakaryocytes and increase thrombocyte count and aggregation. Thrombocytosis reflects systemic inflammation and induces tumor invasion and metastasis [21]. Based on this theory, the prognostic value of many systemic inflammatory markers (WBC, CRP, neutrophil/lymphocyte ratio, thrombocyte/lymphocyte ratio, fibrinogen, etc.) has been demonstrated in various malignancies [22, 23].

NLR and CRP increase and thrombocytosis predict survival in epithelial ovarian tumors [24, 25,26]. Although the correlation of preoperative thrombocyte count with cervical involvement in endometrial cancer and grade 3 histology has been demonstrated in numerous studies [27, 28], the predictive effect of systemic inflammatory markers in the detection of LNM in endometrial cancers has been evaluated in very few.

While Casper et al. [29] stated that preoperative leukocytosis and thrombocytosis increased the risk of LNM at a low-moderate degree in their meta-analysis, Tuomi et al.[30] stated that thrombocytosis could be used at a moderate impact degree in the preoperative scoring system in the detection of LNM in advanced ECs. Suh et al. [31] found that NLR, PLR and CA 125 values were significantly higher in the LNM positive group compared to the negative group in 319 patients with endometrioid type endometrial carcinoma who underwent surgical staging and that SIR markers were not, however, more effective markers for detecting LNM than serum CA 125. Although we found the negative predictive effect of both NLR and PLR to be high in our study, we could not find a significant relationship between the median or cut off values in terms of detecting LNM.

Several guidelines, including the consensus statement of the European Society for Medical Oncology and the European

Society of Gynecologic Oncology, describe the search for lymphadenopathy mediated by CA 125 antigen measurement and imaging methods in endometrial cancers as part of preoperative research [5,32].

Elevated Serum CA 125 levels are an indicator of lymph node involvement and poor prognosis in EC [33].

In a study in which all patients were surgically staged, as in our study, preoperative CA 125 had 77.8% sensitivity and 81% specificity in determining LNM [34]. Our results were 77% and 82%, respectively, very close to these values. Chung et al. [35] found that the CA 125 value had a low sensitivity of 61.5% in predicting LNM but emphasized that it was still an important independent predictor. When Todo et al. [36] combined the CA 125 value with commonly used preoperative pathological findings (histology, grade, myometrium invasion), they found a false negative rate of 3.6% in detecting LNM.

In our study, while tumor histology, myometrial invasion, LVSI, abdominal cytology and preoperative CA125 value were significant predictors for LNM, we did not find this relationship in NLR and PLR systemic inflammatory markers.

Limitations

Our limitations include the retrospective nature of the study and that other inflammatory markers such as CRP and fibrinogen were not included due to insufficient data. The exclusion of patients who did not undergo lymphadenectomy increases the reliability of our study.

As our knowledge of the sentinel lymph node (SNL) increases, the morbidity associated with surgery will decrease and a more appropriate staging will be possible. Today, sufficient expert surgeons and large oncological centers are needed for the SNL procedure, which is costly.

Conclusion

CA 125 value was an effective marker for lymph node metastasis in endometrial cancer. Contrary to many studies mentioned in the literature, we did not find the NLR and PLR values to be significant in the prediction of lymph node metastasis. More studies involving combined risk scoring systems with high sensitivity rates are needed.

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The effect of preprocedural serum albumin to fibrinogen ratio on arteriovenous fistula maturation

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Abstract

Background/Aim: Inflammation and inflammatory parameters are known to have unfavorable effects both on the surgical success and survival. The reference point of the present study are the results of an investigation of the effects of blood proteins such as albumin and fibrinogen, which affect blood viscosity, and other hematological parameters, on the success of arteriovenous fistula operations.

Methods: This retrospective cohort study includes the data of 135 patients who underwent arteriovenous fistula surgery by the same surgeon in the same center. The patients were divided into two groups, as those with an active fistula 8–12 weeks after surgery and those with a dysfunctional fistula. After applying the exclusion criteria, the remaining data were compared using appropriate statistical methods to evaluate the influence on fistula maturation rates.

Results: A statistical analysis performed after the evaluation of the fitness of the data to a normal distribution revealed fistula maturation to be associated with fibrinogen ($P<0.001$), albumin ($P<0.001$), fibrinogen-to-albumin ratio (FAR) ($P<0.001$) and neutrophil-to-lymphocyte ratio (NLR) ($P=0.002$). It was further noted that C-reactive protein (CRP) ($P<0.001$), CRP-to-albumin ratio (CAR) ($P<0.001$), neutrophil count ($P=0.003$) and lymphocyte count ($P=0.03$) all played a role in this process. A receiver operating characteristic (ROC) curve analysis revealed the cut-off values for fibrinogen ($P<0.001$, AUC: 0.930), CRP ($P<0.001$, AUC: 0.892), FAR ($P<0.001$, AUC: 0.988), CAR ($P<0.001$, AUC: 0.916), neutrophil count ($P=0.011$, AUC: 0.661) and albumin ($P<0.001$, AUC: 0.946) in terms of fistula maturation.

Conclusion: The present study reveals that low albumin and high fibrinogen levels negatively affect AVF maturation. As reported previously in literature, and supported by the present study, high CRP levels may be associated with early AVF dysfunction.

Keywords: Arteriovenous fistula, Albumin, Fibrinogen, AV fistula, NLR, Neutrophil to lymphocyte ratio

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Ethics Committee Approval
Ethical Committee of Evliya Celebi Training and Research Hospital, 55719891/604.02.94
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Introduction

Hemodialysis catheters (HDCs) and autologous arteriovenous fistulas (AVFs) are the most popular methods for the delivery of hemodialysis to patients with end-stage renal failure (ESRF). Among these, HDC is not the first choice, given the risk of infection, stenosis in the central veins and intracardiac thrombus. The creation of an AVF is the approach to vascular access recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative, as well as the European Society of Vascular Surgery: 2018 Vascular Access Clinical Practice guidelines, due to its high patency rates, low morbidity and mortality, and high patient comfort [1]. Among the leading disadvantages of AVFs, however, is the maturation period, and furthermore, an appropriate-diameter venous system and an intact arterial system are required for the creation of a successful AVF. Studies have found that the primary reason for early AVF failures are venous pathologies [2]. The long maturation period, the potential for early AVF dysfunction and the resulting need to insert an HDC can be counted among the disadvantages of AVFs [3].

The idea that hematological parameters may be involved in the AVF maturation process, affecting AVF patency, and the physical characteristics of vascular structures, have led to various studies in this field. High CRP levels and a high NLR have been identified as poor prognostic markers in many diseases [4-6].

Despite the number of studies of inflammatory markers, the reference point of the present study is the lack of studies examining the hematological parameters [7] that constitute the gross mass of the blood and that affect blood viscosity, such as albumin and fibrinogen. The present study hypothesizes that hemoconcentration may be associated with early AVF dysfunction, and focuses particularly on albumin and fibrinogen, while reproducing previously reported findings for CRP and NLR.

Materials and methods

Study design and patient selection

After making the required application to the local ethics committee (Evliya Celebi Training and Research Hospital, 55719891/604.02.94), the data of patients who underwent AVF creation between 2015 and 2019 were reviewed, and those who underwent successful radiocephalic (Brescia-Cimino) AVF creation by the same surgeon were included in the study. Patients who underwent fistula creations using approaches other than the Brescia-Cimino technique, those with missing hematological parameters, those receiving steroids and those with evidence of an active infection were excluded from the study. Due to the retrospective nature of the study, there was no need to obtain informed consent from the patients.

Patients who are to undergo fistula creation operations in the study center are admitted on the operation day. Blood samples are collected on the same day as the operation and analyzed in the hospital's laboratory. The study data derives from the blood samples drawn on operation day.

The patients were discharged after the AVF operation, and after being weighed, they were placed on a 5-day course of enoxaparin sodium therapy at half the recommended dose for patients without ESRD (0.5 mg/kg, 2x1). At the time of the outpatient control visit (6–12 weeks after surgery), the patients were divided into two groups depending on the maturation of the fistula: Patent fistula (Group 1) and fistula failure (Group 2). The parameters used to determine the maturation of AVF were the presence of a thrill sensation and audible bruit extending along the adequate length, a superficialized and easily compressible vein, a minimum 600 mL/min AVF flow rate, and an at least 6 mm internal diameter and a maximal 6 mm depth from the skin to the outflow vein upon Doppler ultrasound measurement [8]. No follow-up data in the late term was examined, as the focus of the present study was on early outcomes. In patients with subclavian vein HDC, care was taken not to open the AVF from the same side.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.). The initial analysis ascertained whether the variables differed across the study groups, and the outliers of each variable were excluded. In the comparison of mean values, it was found that:

i) The dependent variable between the groups was continuous,

ii) The dependent variable showed a normal distribution in the two groups. It was therefore decided to perform a t test, for which the homogeneity of variance was assumed. A correction was made to the SD value if the variances were not homogeneous.

After the correction was made:

- a Chi-square test was performed if assumption "i" was not met; in other words, if the dependent variable was continuous (binary data).

- A non-parametric Mann-Whitney U-test was used if the assumption "ii" was not met.

Control for outliers was made only for continuous variables, and the missing values were deleted in a pairwise manner in all analyses (not the entire unit, but only the pairs). A *P*-value of less than 0.05 was considered statistically significant.

ROC curves were drawn to calculate the AUC and cut-off values of the fibrinogen, albumin, FAR, CRP, CAR, neutrophil count, and lymphocyte count for AVF maturation.

Results

A demographic analysis revealed 60 patients (44%) to be female, and an overall mean age of 56.48 (13.6) years.

At the 6–12-week outpatient control visit, the fistula was dysfunctional in 29 patients (22%) (Group 2). The characteristics of the patients are presented in Table 1. It was concluded that high CRP, fibrinogen, neutrophil count, and lymphocyte count in blood samples collected prior to the procedure were associated with AVF dysfunction, while other parameters, including triglyceride, HDL, LDL, gender, age, or the presence of DM, HT, COPD, smoking and history of MI were not. Albumin values were significantly lower in Group 2 (Tables 1 and 2).

A logistic regression analysis was performed to evaluate the effects of fibrinogen, albumin, CRP, FAR and CAR on the dependent variable of fistula function, in which significant differences were observed between the groups, and were found to be of diagnostic significance.

The ROC curve analysis revealed the cut-off values for fibrinogen (α=0.01, AUC=0.930 and P<0.001, cut off: 451), CRP

(α=0.01, AUC=0.892 and *P*<0.001, cut-off: 7.20), FAR (α=0.01, AUC=0.988 and *P*<0.001, cut-off: 147), CAR (α=0.01, AUC=0.916 and *P*<0.001, cut-off: 2.494), neutrophil (α=0.01, AUC=0.661 and *P*=0.011) and lymphocyte (α=0.01, AUC=0.603 and *P*=0.100) count, which had an inverse relationship with AVF maturation (Figure 1), and albumin (α=0.01, AUC=0.946 and *P*<0.001, cut-off: 3,15) and NLR (α=0.01, AUC=0.634 and *P*=0.048), which had a direct relationship with AVF maturation (Figure 2).

Table 1: The characteristics of the patients

Variables	Successful AVF (n=106)	Unsuccessful AVF (n=29)	*P*-value
Age, mean (SD)	59.2(19.6)	61.8 (16.3)	0.487%
Gender			
Female	48 (46%)	12 (42%)	0.776*
Male	58 (54%)	17 (58%)	
Median weight (kg)	72(4.4)	74(3.7)	0.436&
BMI (kg/m^2)	22.4(2.4)	22.9 (3.2)	0.223&
DM (n, %)	44 (42%)	14 (48%)	0,456*
HT (n, %)	22 (21%)	6 (20%)	0.958*
COPD (n, %)	24 (22%)	7 (24%)	0.865*
Smoking (now or recent)	50 (47%)	15 (51%)	0.664*
MI History (n, %)	9 (8%)	3 (10%)	0.720*
BUN (mg/dL)	114(28)	109 (30)	0.198&
Creatinine (mg/dL)	4.4(1.9)	4.2(2.1)	0.107&

&Student t test, * X^2 Test, % Mann Whitney U Test

Table 2:Hematologicparameters of the patients

	Successful AVF (n=106)	Unsuccessful AVF (n=29)	*P*-value
Albumin (g/dL)	3.65(0.5)	2.8(0.7)	<0.001&
Fibrinogen (mg/dL)	322.6 (92.2)	533.7 (165.2)	<0.001&
CRP (mg/dL)	3.8 (1.7)	15.2 (4.4)	<0.001%
Total protein (g/dL)	6.9(0.2)	6.7(0.5)	0.359&
Triglyceride (mg/dL)	159.7 (75.8)	150.1 (80.2)	0.120%
Total Cholesterol (mg/dL)	177.2(39.5)	182.2 (41.1)	0.549%
LDL Cholesterol (mg/dL)	120.5 (22.4)	125.9(30.4)	0.111%
HDL Cholesterol (mg/dL)	33.9(9.2)	32.1 (8.9)	0.914%
Neutrophil (10^3 /uL)	5.36(0.35)	6.1(1.26)	0.003%
Lymphocyte (10^3 /uL)	1.49(0.19)	1.65(0.35)	0.030%
CAR	1,69 (2.5)	0.38 (0,6)	<0.001%
FAR	90.81(26.27)	211.57(86.44)	<0.001&
NLR	3.653 (0.82)	3.289(0.39)	0.002&

& Student t Test, % Mann Whitney U Test

Figure 1: ROC curve analysis for hematological parameters which show inverse relationship with AVF maturation

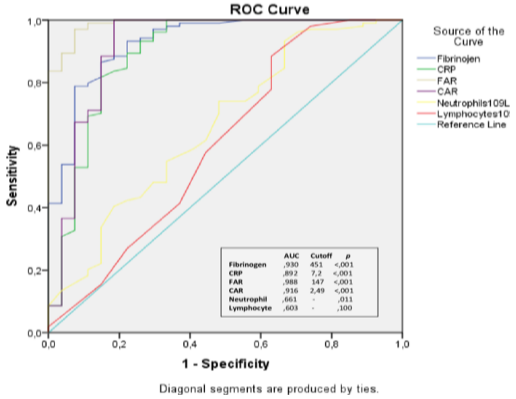
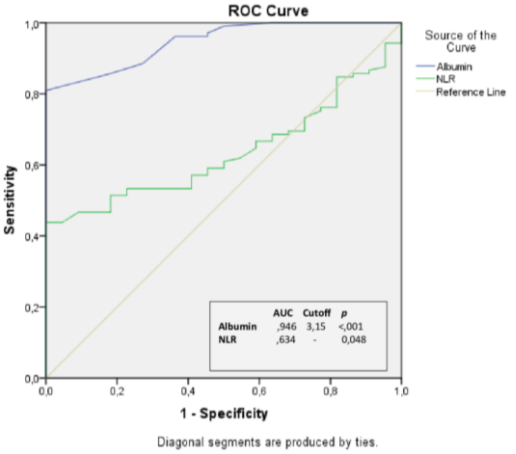


Figure 2: ROC curve analysis for hematological parameters which show direct relationship with AVF maturation



A multiple linear regression analysis was carried out and the outliers were controlled for before proceeding with the logistic regression analysis. Accordingly, the FAR and CAR were excluded from the logistic regression analysis, as they had the highest level of correlation with other parameters. A logistic regression analysis was conducted after the assumptions were met. The dependent variable of the test was taken as "Functional Fistula - 0" and "Dysfunctional Fistula - 1". Accordingly, the accuracy rate of the prediction was 79.5.

An Omnibus test revealed a significant difference between the two blocks (Block 0 and Block 1) (Chi-square = 121.423, SD = 3, *P*<0.001, *P*<α). Hosmer and Lemeshow tests identified no significant difference between the predicted values and the observed values, with a *P*-value of 0.998 (Chi-square = 1.028, SD = 8 (α = 0.05, *P*>α). In other words, the model can be suggested to reflect the actual condition.

The Nagelkerke R2 value revealed that the independent variables explain 94% of the variation in the "fistula dysfunction" dependent variable. Values greater than 30% are considered acceptable, and thus the model can be suggested as having a high prediction ability.

Table 3 presents the results of a Wald Test, in which a variable with a value of less than 0.05 (or 0.1) is considered significant. Accordingly, the fibrinogen variable was significant, with a value of 5%, while the fibrinogen, albumin and CRP variables were significant with a significance level of 10%.

Table 3: Evaluation of independent variables

	Wald	*P*-value
Fibrinogen	6.620	0.010*
Albumin	3.639	0.056&
CRP	3.154	0.076&
Constant	0.720	0.396

* α=0.05, &α=0.10

Discussion

Tunneled catheters can save lives in cases where the vascular structures are unsuitable for AVF creation, although autologous AVF is the preferred approach to vascular access for dialysis purposes, as catheter insertion is not superior to AVF when considering the above-stated complications and the long-term patency of vascular access [9].

AVF may seem to be less harmful than a catheter, although there may be some undesired effects due to abnormal blood circulation. According to the results of a systematic review, the most common complications and pathological conditions associated with AVF are venous aneurysms, ischemic steal syndromes, infection, venous and arterial thrombosis, venous hypertension, pulmonary hypertension, hyperdynamic heart failure, and hematoma due to recurrent cannulation [10]. As can be understood from these results, AVF creation is unfortunately not a risk-free approach. There is a lack of data in literature regarding the patency rate of AVFs in the early period, with a wide range of early primary patency rates (between 24 and 92%) reported [11,12], while early dysfunction rates ranging between 5% and 62% have been reported [10].

This wide range of patency rates reported in literature may be explained by the lack of a thorough preoperative examination of the vascular structure by Doppler USG. The fact that both the vein and the artery to be used in fistula creation must have a minimum diameter of 2.0 mm is an important detail that

may be overlooked [13]. Inadequacies in the vascular anatomy may be determined beforehand through an appropriate ultrasonographic examination, and the most suitable interventions may be selected accordingly. In our clinic, not all patients underwent preoperative Doppler USG examinations during the study period, although no radiocephalic fistulas were created in patients deemed to have small caliber cephalic veins at the forearm level upon visual inspection, with the operation being performed at the brachial level in such patients. Even though the surgeon's familiarity with anatomic structures can lead to a correct decision upon inspection, the method may fail due to the lack of quantitative measurements. This can be regarded as a limitation of the present study, in which the early patency rate was 78.5%.

It was anticipated in the present study, which is based on preoperative blood samples, that hematological changes due to additional postoperative pathologies may affect the study outcomes. There have been many studies in literature linking preoperative NLR with the course and outcome of operations [14]. In one study comparing preoperative and postoperative NLR values, the AVF patency rate was higher in patients with high preoperative but low postoperative NLR values, suggesting that low preoperative and postoperative NLR values may indicate early fistula failure [1]. The present study focused only on postoperative NLR values but found NLR values to be lower in patients with early fistula dysfunction, and the difference between the groups was statistically significant. The ROC curve analysis identified higher NLR values in Group 1.

When the parameters constituting the NLR measurement are evaluated separately, both the neutrophil and lymphocyte counts were significantly higher in Group 2 than in Group 1, and the NLR was higher in Group 1, suggesting the lymphocyte count to be more predictive of AVF dysfunction than neutrophil count. The main finding related to lymphocytes is that the count is elevated in the presence of infection, and particularly in viral infections, autoimmune disorders, malignancies and chronic diseases. The unfavorable effect of lymphocytes, as well as the cytokines released from lymphocytes, on the success of surgical procedures may be considered an area of interest in further studies.

CRP levels change in the presence of infections, with high levels decreasing the success of surgical procedures. A common finding of studies in literature is that elevated CRP levels are associated with negative outcomes in various surgical procedures and medical therapies [15,16]. In the present study, CRP was higher in Group 2 than in Group 1. In a ROC curve analysis, high CRP values were recorded in Group 2, with a cut-off value of 7.20 for CRP. The presence of an active infection certainly required the postponement of surgery. Considering the findings of the present study, the postponement of operations is a rational option in patients with high CRP values, being indicative of an active infection, although the patient may be asymptomatic. In this regard, a high CAR – measured based on CRP values – has been shown to be associated with increased mortality and morbidity in literature [16]. In the ROC curve analysis, the patients in Group 2 had a high CAR with a cut-off level of 2.49. The high CAR values in Group 2 were expected, considering the association between high CRP values and increased mortality and morbidity.

Dyslipidemia values were similar in the two groups and showed no statistically significant difference. Despite the proven negative effect of hyperlipidemia on the vascular system, the lack of a significant difference between the groups in the present study in this regard can be attributed to the study design being limited to early postoperative results. A study evaluating AVF stenosis over a period of 5 years revealed LDL to be associated with stenosis [17], indicating an association between LDL and stenosis in the long term, but with no effect on early fistula stenosis.

There have been many studies reporting increases in blood viscosity to be an independent risk factor [18, 19]. Parameters such as dyslipidemia, DM, smoking, hematocrit level, erythrocyte deformability and fibrinogen all affect blood viscosity [20]. In the present study, fibrinogen levels were higher in Group 2 than in Group 1, and the between-group difference was statistically significant. A ROC curve analysis revealed high fibrinogen levels in Group 2 with a cut-off level of 451, which is a finding that is consistent with earlier studies in literature. Avoiding the activation of fibrinogen, which is involved in the thrombosis pathway, through the use of antiaggregant and anticoagulant medications may indirectly increase the success of surgical interventions.

Albumin was selected as the key actor in the present study, in that it constitutes more than half of plasma serum concentration. Blood concentrations of albumin were decreased in malnutrition and infection. Depending on the plasma concentrations, albumin possesses antiaggregant, anticoagulant, anti-inflammatory and anti-oxidant properties, based on its osmotic effect [21]. Low albumin levels are known to cause cardiovascular diseases, ischemic stroke, and venous thromboembolism [22]. Considering its functions and key effects, it comes as no surprise that changes in albumin values significantly affect prognosis. In the present study, albumin values were significantly lower in Group 2. A ROC curve analysis showed a cut-off value of 3.15 for albumin, and the values were significantly lower in Group 2. Furthermore, the results of a logistic regression analysis suggested that low albumin levels can be regarded as a cause of early AFV dysfunction. Studies have suggested that patients without malnutrition or high blood protein and albumin levels are resistant to vascular access failure, which is consistent with the findings of the present study [23]. Similarly, high FAR values were found in Group 2, with a cut-off value of 147.

Limitation

The limitations of this study include its retrospective and single-center design, and small sample size. AVF maturation and patency rates may be better predicted through an examination of the parameters that provide more details of blood viscosity.

Conclusion

NLR has been the subject of many studies, but since we are unable to influence them, how useful it is to know these values is debatable. The present study has shown albumin levels to affect AVF maturation, and low albumin levels are associated with an increased risk of AVF dysfunction. Blood albumin levels can easily be increased with proper nutrition and intravenous replacement, and more AV fistula patency rates can be gained, which gives us the chance to influence the AVF maturation process, unlike with NLR.

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Views of Turkish healthcare professionals and their hesitations about the COVID-19 vaccine

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Ethics Committee Approval
This study was approved by the Health Sciences University Adana City Training and Research Hospital Clinical Research Ethics Committee on December 16, 2020 (1168). In addition, an application was made to the Ministry of Health Scientific Research Platform, which was also approved (consent number 2020-12-09T18_02_36).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Views of health sector workers on the safety and efficacy of a vaccine, which forms the basis of a vaccination program, can affect both the public perception of the vaccine and its implementation in the community. Accordingly, this study aimed to acknowledge potential hesitations of healthcare specialists and their views on the acceptability of a vaccine before initiating a vaccine policy program.
Methods: A total of 442 healthcare professionals participated in this study by answering a 24-question survey online from their social media accounts. We analyzed the data and present the descriptive statistics with mean and standard deviation values. We performed *t*-test analysis and analysis of variance to examine physicians' attitudes toward vaccines and the coronavirus disease 2019 (COVID-19) infection, based on their demographic, and other characteristics. Tamhane and Sidak paired comparison tests were conducted to determine differences in groups after variance analysis.
Results: Of the healthcare professionals, 55.9% agreed that the COVID-19 vaccine would end the pandemic. A total of 72.6% of healthcare workers reported that they were planning to get vaccinated with the free COVID-19 vaccine, which is to be distributed by the Ministry. The biggest drawback of the vaccination was its unknown long-term side effects. We noted a difference in the attitude toward vaccines in those older than 41 years and younger than 30 years of age. We also found a significant and positive relationship between the attitudes of the participants toward the measures taken regarding the COVID-19 infection and their attitudes toward the vaccine.
Conclusion: Hesitation about a vaccine during a pandemic is a major obstacle to implementing vaccination campaigns. To continue the benefits of vaccination programs, understanding and addressing these hesitations held by healthcare professionals are crucial to the successful implementation of a vaccination program.

Keywords: COVID-19 vaccines, Healthcare workers, Vaccine hesitation

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Introduction

The new coronavirus disease 2019 (COVID-19) is a viral infection first identified on January 13, 2020, because of research conducted on a group of patients who developed respiratory symptoms in Wuhan Province, China, in late December. The first case was reported in Turkey on March 11, 2020 [1]. Since then, more than 80 million patients with COVID-19 have been affected worldwide by this pandemic. In Turkey, more than 2 million patients have been diagnosed with COVID-19, and about 20,000 have lost their lives [2].

The first aim of health services and health personnel is to ensure that people continue to lead healthy lives. Vaccination is the most effective method of providing protection from infectious diseases. Although technical infrastructure and healthcare workers are the most important criteria in vaccination studies, it has become important that healthcare providers have sufficient knowledge about vaccines and are informed about the necessity of vaccination through in-service training provided by the Ministry of Health [3].

The COVID-19 pandemic has generated a heavy burden on healthcare worldwide and has no specific antiviral therapy. As immunization is one of the most successful and cost-effective health interventions for preventing infectious diseases, vaccines against COVID-19 are considered of paramount importance in the prevention and control of COVID-19 [4]. The immunity of the community depends on achieving a total vaccination rate ranging from 80% to 95% of community members. With these vaccination rates, we can ensure that we protect not only the vaccinated individuals of the society but also the unvaccinated individuals, as well. Therefore, vaccines administered to an individual are related to the health status of all members of society [5]. Although remarkable progress has been made in this area, significant challenges remain regarding future vaccination against COVID-19, one of which is the uncertainty about the public acceptance of COVID-19 vaccination. Vaccine acceptance reflects the general perception of disease risk, vaccine attitudes, and demand in the general population and it is critical to the success of immunization programs to achieve high vaccination coverage rates for emerging infectious diseases [4].

Hesitation about a vaccine constitutes a threat to public health [6]. Although vaccination has reduced the global burden of disease and death, public confidence in vaccines might be affected by various concerns. Therefore, vaccine hesitation can lead to delays in implementing or even the rejection of vaccines, which can sometimes contribute to outbreaks. Maintaining confidence in vaccination depends on the interaction between patients and healthcare professionals. The need for and acceptance of vaccination by healthcare professionals is an important factor associated with public adoption, compliance with vaccination schedules, and reduced vaccine hesitancy. Moreover, vaccinated healthcare professionals also have a significant influence on patients' decision to vaccinate [7].

Health professionals' intention to use the vaccine and recommend it to their patients depends on their knowledge and attitude about it. Healthcare workers with a negative attitude toward vaccines, reluctance, or hesitation have been reported to convey their hostile attitude toward the vaccine to patients and are less likely to recommend receiving the vaccine. Moreover, vaccine hesitation observed in the general population has been associated with the level of vaccine hesitation among health professionals. In addition, the quality of educational information on vaccines by healthcare professionals has been useful in improving patients' acceptance of the vaccine, reducing reluctance, and guiding informed decisions about vaccination [7].

The media are promoting the vaccines that will be applied to control the COVID-19 pandemic. We see that there is speculation about the side effects and different production technologies of the COVID-19 vaccines, whose phase 3 studies have just been completed.

This results in insufficient community-based trust. The aim of our study was to understand the hesitations regarding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine, which will be administered first to healthcare workers and patients deemed to be at risk in Turkey and determine methods to eliminate these reservations. Therefore, we conducted a survey among healthcare professionals to determine whether they have any hesitation regarding the vaccination program and their views on administering the SARS-CoV-2 vaccine.

Materials and methods

This study was approved by the Health Sciences University Adana City Training and Research Hospital Clinical Research Ethics Committee on December 16, 2020 (1168). In addition, an application was made to the Ministry of Health Scientific Research Platform, which was also approved (consent number 2020-12-09T18_02_36).

Between October 16, 2020 and December 29, 2020, we identified academic physicians (professors, associate professors), specialist physicians, family physicians, midwives, nurses, health technicians, health officers, and pharmacists working in public and private institution hospitals in various provinces. We planned to include healthcare workers between the ages of 20–72 years who agreed to participate voluntarily in the study. The participants received a link to the questionnaire through their e-mails, social media accounts, and social media groups in the institutions where they worked in the provinces and districts. The questionnaires were answered online. Except for healthcare professionals, we included no community members in the research group.

No personal identification information was requested from the participants. Before using SurveyMonkey services, you must have a SurveyMonkey account. The Survey Creator can only enter this account with a password. We do not share information or data with third parties outside of SurveyMonkey. All response data at the individual level is controlled by the Survey Creator. The responsibility belongs only to the physician responsible for conducting the survey and the study. The organization SurveyMonkey provided the confidentiality principles for the preparation and use of the survey (SurveyMonkey, © 1999–2020). Before completing the questionnaire, SurveyMonkey tested the usability, and technical functionality of the electronic questionnaire. After participants completed the questionnaire, we analyzed the results of all the answers and exported them into an Excel file format. SurveyMonkey participates in and has approved compliance with the European Union–United States Privacy Shield Framework and the Swiss–United States Privacy Shield.

The full data set and complete answers to the questionnaire are available at https://tr.surveymonkey.com/results/SM-WMPYRYHZ7/. We did not provide any nonmonetary incentives, monetary rewards, or offers to submit survey results.

Our survey consisted of six pages and twenty-four questions, and the average response time was 5 minutes, 55 seconds. The average number of questions per page was four, and the average number of options per question was six. The software program used for the survey restricted participants from moving to other questions without first answering the previous question. Participants did not skip any of the questions in our questionnaire; all questions were answered. As we were looking for significant data, we preferred closed-ended questions. Closed-ended questions are designed to create measurable data, and the precision of the questions can be determined. The simple coding of these types of questions made it easy to prove the statistical significance of the survey results. In addition, the message learned through closed-ended questions allowed the respondents to be arranged based on the preferences they chose. We detected a survey achievement rate of 100%, because of its short and understandable structure. The questionnaire was administered in the Turkish language for it be understood by all healthcare professionals and to be answered within a brief time. Demographic variables included age, gender, marital status, with who shared their household, position in the health sector, working hours, department in which the respondent worked, the institution in which the respondent worked, respondent's province, and the environment in which the respondent was in contact with COVID-19. Questions on opinions regarding the sufficiency of the SARS-CoV-2 infection prevention practices and perspectives on the SARS-CoV-2 vaccine were in the last nine questions of the survey.

Research on all healthcare workers employed in both public and private hospitals in Turkey was made by the Turkey Health Statistics Yearbook 2018 Newsletter. The number of healthcare workers (N = 642,184) was determined based on the data of the Ministry of Health. Using a simple random sampling method, we calculated that at least n= 384 healthcare workers with a 5% acceptable error margin and a 95% confidence level could provide the representation power of the universe.

We obtained data from 442 healthcare workers in this study. We found that this sample size would provide a sampling power of 0.92 and an effect size level of 0.40, which enabled sufficient power and a sufficient effect size level, respectively. The inclusion of 442 healthcare workers in this study constitutes a sufficient sample size to obtain meaningful results.

Statistical analysis

For the data analyses, we present the descriptive statistics with means and standard deviations. We performed *t*-test analysis and analysis of variance tests to examine the physicians' attitudes toward vaccines and the COVID-19 infection, based on their demographic, and other characteristics. To determine differences among groups after variance analysis, we conducted Tamhane and Sidak paired comparison tests. *P* values of less than 0.05 were considered statistically significant. We used SPSS 20.0 to analyze the results. The research population-sample size, power level, and effect size calculations were determined using G * Power Version 3.1.7.

Results

We presented the statistical results of the questions we asked in our research questionnaire from Table 1 to Table 12. Each table has its own explanation.

Table 1: General characteristics of healthcare professionals

Characteristic		n	%
Age, years	20–30	44	10.0%
	31–40	106	24.0%
	41–50	168	38.0%
	51–60	100	22.6%
	≥61	24	5.4%
Gender	Male	148	33.5%
	Female	294	66.5%
Marital status	Married	343	77.6%
	Single	99	22.4%
Position in the healthcare industry	General practitioner–family physician	63	14.3%
	Assistant doctor	17	3.8%
	Specialist doctor	154	34.8%
	Associate professor	20	4.5%
	Professor doctor	29	6.6%
	Midwife–nurse	122	27.6%
	Other healthcare professionals	37	8.4%
Institution	University hospital	35	7.9%
	Education and research hospital	134	30.3%
	Public hospital	64	14.5%
	Private health institutions	67	15.2%
	Family health center	142	32.1%

Table 2: Unit worked during the pandemic period

Unit Worked during the Pandemic Period*	n	%
Policlinic	248	56.1%
Operating room	158	35.7%
Inpatient service	135	30.5%
COVID-19 inpatient service	82	18.6%
Delivery room	115	26.0%
Emergency service	74	16.7%
Pandemic area emergency service	51	11.5%
Laboratory	14	3.2%

*Respondents may work in more than one unit.

Table 3: Level of contact with patients with COVID-19

Contact Level	n	%
I have direct contact with patients diagnosed with COVID-19	172	38.9%
I have been in contact with symptomatic patients diagnosed with possible COVID-19	159	36.0%
I am in contact with patients who do not show symptoms of COVID-19	213	48.2%
I am in contact with all patients with or without COVID-19 symptoms	302	68.3%
I am in contact with patients who have recovered from COVID-19 infection	242	54.8%
The healthcare worker I worked with, with whom I was in contact, was diagnosed with COVID-19	261	59.0%
I had COVID-19 infection, recovered, and continue to work	65	14.7%

Table 4: Other characteristics of healthcare professionals

		n	%
Weekly working hours	20–30	32	7.2%
	31–40	37	8.4%
	41–50	266	60.2%
	≥51	107	24.2%
Who do you live with?	Alone	47	10.6%
	Nuclear family	328	74.2%
	Extended family	67	15.2%
Have you changed where you live or stay because of COVID-19 infection and being in contact with patients?	No	347	78.5%
	Yes	95	21.5%
Do you think that society is aware of COVID-19 and complies with the decisions taken?	Yes	8	1.8%
	No	352	79.6%
	Partially	82	18.6%
When do you expect the pandemic process to return to normal?	6 months	29	6.6%
	7–12 months	119	26.9%
	1–2 months	219	49.5%
	>2–3 years	13	2.9%
	I do not know	62	14.0%

Table 5: Preferred vaccine if vaccinated

Vaccine Preference	n	%
Oxford-Astra Zeneca (England)	30	6.8%
Moderna (USA)	15	3.4%
Pfizer-BioNTech (USA+Germany)	201	45.5%
Gamaleya (Sputnik 5) (Russia)	3	0.7%
Sinovac (China)	105	23.8%
Koçak Farma (Turkey)	60	13.6%

Table 6: Concerns about vaccination

Concerns about Vaccination	n	%
The biggest drawback in vaccine administration is that I have no information about the long-term side effects	355	80.3%
I am worried that the side effects of vaccines will affect me; I am afraid it will affect my workforce and social life	126	28.5%
I think the supervisory bodies that approve vaccines are biased and do not trust these organizations	86	19.5%
Which country's vaccine is more reliable, I have no idea	77	17.4%
There is a lot of speculation in the media about whether to do it	50	11.3%
I think that the aluminum content in preparing vaccines causes precancerous formations, and I have no idea how safe this dose is	47	10.6%
It has a claim to play with our DNA	28	6.3%
I have no idea about the vaccine and its feasibility	21	4.8%
I think it is the sheath theory of implanting traceable microchips in the bodies of millions of people with the "vaccine microchip" claimed in the media	14	3.2%
I think it is unnecessary to administer the vaccine because of the high recovery rate and high antibody rates without vaccination	13	2.9%
The claim that vaccines contain some tissues of human and animal embryos	6	1.4%
I heard that some vaccine ingredients contain pig gelatin	5	1.1%
I have heard that some vaccines have been developed in chicken egg and chick embryos; I do not think it is animal friendly	2	0.5%

Table 7: Vaccine opinions and preferred vaccine

If you decide to have a paid vaccine instead of the SARS-CoV-2 vaccine of the Sinovac company, which will be distributed free by the Ministry, which company would you prefer?	n	%
Absolutely will not get vaccinated	44	10.0%
The price does not matter; I am hesitant about the vaccine	89	20.1%
Moderna (USA)	16	3.6%
Pfizer-BioNTech (USA + Germany)	203	45.9%
Oxford-Astra Zeneca (England)	35	7.9%
Gamaleya (Sputnik 5) (Russia)	3	0.7%
Sinovac (CoronaVac) (China)	44	10.0%
Domestic vaccine	8	1.8%

Table 8: Attitudes toward the COVID-19 infection and vaccine

	Mean (SD)**
Do you agree with the idea that with the onset of the COVID-19 process, hands are washed more than usual?	4.13 (1.03)
Do you agree with the idea that the use of masks and disinfectants with COVID-19 prevents the spread of the virus?	4.41 (0.71)
Do you agree with the idea that the COVID-19 vaccine will end the pandemic?	3.61 (1.00)
When the COVID-19 vaccine is given to healthcare workers free by the Ministry of Health, would you consider having the vaccine at your institution?	4.04 (1.06)
If the vaccine administration is controlled by the HES* code individually, do you agree with the idea that unvaccinated people in the society will not stay if it becomes compulsory to be shown during travel, in shopping malls, entertainment venues, banks, and government institutions?	3.66 (1.13)

*HES is a code that allows a person to share with organizations and individuals whether they carry any risk in terms of the COVID-19 disease in their operations, such as transportation or visiting within controlled social life. The HES codes shared can be queried through the application or through the services provided to the institutions. **Mean: Average Score, SD: Standard Deviation

Participants stated that during the COVID-19 outbreak, as healthcare workers, they washed their hands more than before and their level of compliance with the measures taken was high. However, we determined that the participants' confidence towards vaccination were above average. Moreover, the increase of vaccination confidence with various practices were not high (3.6 of 5). We also observed that the healthcare personnel were not highly confident in the vaccines, and according to the perceptions of health personnel, nor was the public.

Factors Affecting Attitude Levels

Table 9 shows the difference in the attitudes of the participants toward the measures taken against COVID-19 based on the participants' ages. We found less trusting attitudes among individuals aged between 20 and 30 years (P=0.03). However, we found a difference in the attitudes of the participants towards the vaccine according to their ages, which was attributed to a difference in the attitude of individuals older than 41 years (P=0.01).

We also observed that the attitudes of participants toward measures taken against the COVID-19 infection did not differ based on gender (P=0.93). However, more trusting vaccination attitudes of male individuals (P=0.04) resulted in a difference based on gender. Attitudes of the participants toward the measures taken regarding the COVID-19 infection did not differ based on their marital status (P=0.93), while attitudes toward the vaccine did. Married individuals had more positive attitudes (P=0.04).

The attitude of the participants toward the measures taken regarding the COVID-19 infection differed with their positions in the health sector, and the difference was because of the less positive attitude of the resident physicians (P=0.01). The differences in the attitudes of the participants toward the vaccine were found to result from their positions in the health sector. Resident physicians, nurses, and other healthcare personnel had more negative attitudes, while associate professors and professors were more positive regarding the subject (P=0.01).

We found no difference in the attitudes of the participants toward the measures taken regarding the COVID-19 infection based on their institutions (P=0.13). However, we observed that the attitudes differed according to the participants' institutions, which was attributed to higher vaccine confidence of healthcare professionals working at universities (P=0.01).

Table 9: Participants' attitudes toward the COVID-19 infection and vaccine according to their characteristics

Specifications		Attitude toward measures taken regarding COVID-19 (Mask, disinfection) Mean (SD)**	*P*-value	Attitude toward the COVID-19 Vaccine (Propensity to Trust and Adopt) Mean (SD)**	*P*-value
Age, years	20–30	3.88 (0.72)	0.03*	3.42 (0.84)	0.01*
	31–40	4.02 (0.57)		3.55 (0.86)	
	41–50	4.10 (0.62)		3.88 (0.75)	
	51–60	4.08 (0.55)		3.96 (0.69)	
	61 and over	4.10 (0.49)		3.94 (0.69)	
Gender	Male	4.05 (0.61)	0,93	3.94 (0.70)	0.04*
	Female	4.04 (0.65)		3.69 (0.83)	
Marital Status	Married	4.06 (0.61)	0,22	3,88 (0.78)	0.04*
	Single	4.02 (0.57)		3.68 (0.839	
Position in the healthcare industry	General practitioner–family physician	4.18 (0.50)	0.,01*	3.93 (0.68)	0.01*
	Resident	3.66 (0.50)		3.67 (0.66)	
	Specialist	4.07 (0.57)		3.94 (0.62)	
	Associate professor	4.17 (0.87)		4.38 (0.49)	
	Professor doctor	4.08 (0.51)		4.15 (0.75)	
	Nurse–midwife	3.99 (0.62)		3.39 (0.91)	
	Other healthcare professionals	3.96 (0.69)		3.57 (0.90)	
Institution	University hospital	4.04 (0.62)	0.13	4.1 (0.66)	0.01*
	Training and research hospital	4.05 (0.59)		3.73 (0.73)	
	Public hospital	4.01 (0.67)		3.69 (0.94)	
	Private health institutions	4.02 (0.66)		3.78 (0.81)	
	Family health center	4.10 (0.55)		3.71 (0.82)	

**Mean: Average Score, SD: Standard Deviation

Table 10 shows that the participants' attitudes toward measures taken and vaccination for the COVID-19 infection did not differ based on with whom the participants lived ($p > 0.05$).

We also noted that the attitudes of the participants toward precautions taken and vaccination for the COVID-19 infection were not different based on changes in their accommodation during the COVID-19 infection process (P>0.05).

The participants' attitudes towards measures taken regarding the COVID-19 infection were different according to when they predicted the pandemic would end, with individuals who stated that it would end in ≤12 months having more positive attitudes (P=0.03). The same was true among individuals' attitudes towards vaccination, as those who thought the pandemic would end between 2 and 3 years had more negative attitudes (P=0.01).

The attitudes of participants toward measures taken regarding the COVID-19 infection differed based on their working hours, with individuals who worked 51 hours and more having more negative attitudes (P=0.03). The same was true for attitudes towards the vaccine; healthcare professionals who worked between 20 and 30 hours per week had more positive attitudes (P=0.01).

Table 10: Participants' attitudes toward the COVID-19 infection and vaccine according to their characteristics

		Attitude toward measures taken regarding COVID-19 (Mask, Disinfection)		Attitude toward the COVID-19 Vaccine (Propensity to Trust and Adopt)	
		Mean (SD)**	*P*-value	Mean (SD)**	*P*-value
Who lives with you?	Alone	4.02 (0.49)	0.06	3.89 (0.73)	0.10
	Nuclear Family	4.09 (0.55)		3.79 (0.78)	
	Extended Family	3.93 (0.82)		3.63 (0.91)	
Have you changed where you live or stay for COVID-19 infection and being in contact with patients?	Hayır	4.10 (0.57)	0.16	3.84 (0.62)	0.09
	Evet	4.02 (0.66)		3.76 (0.89)	
When do you expect the pandemic process to return to normal?	6 months	4.22 (0.61)	0.03*	3.87 (0.83)	0.01*
	7–12 months	4.23 (0.49)		4.03 (0.67)	
	1–2 years	3.94 (0.66)		3.65 (0.82)	
	>2–3 years	4. 00 (0.53)		3.36 (1.05)	
	I do not know	4.04 (0.46)		3.77 (0.74)	
Weekly working hours	20–30	4. 21 (0.46)	0.02*	4.05 (0.61)	0.01*
	31–40	4.20 (0.49)		3.84 (0.64)	
	41–50	4.05 (0.45)		3.74 (0.82)	
	≥51	3.94 (0.51)		3.74 (0.81)	

Table 11 shows that the attitudes of participants toward the vaccine differed based on their preferred vaccine brand. This difference was attributed to the high confidence of the healthcare personnel in vaccination who preferred the Sinovac company vaccine and the low vaccination attitude of those who preferred the vaccine of Gamaleya (Sputnik 5) (P=0.01).

Table 11: Attitudes toward vaccination by brand of vaccine

Vaccine Brand to be Made	Attitude Regarding COVID Vaccine (Trusting and Adopting)	
	Mean (SD)**	*P*-value
Oxford-Astra Zeneca (England)	3.78 (0.76)	0.01*
Moderna (USA)	3.67 (0.69)	
Pfizer-BioNTech (USA+Germany)	3.76 (0.83)	
Gamaleya (Sputnik 5) (Russia)	2.89 (1.02)	
Sinovac (China)	4.13 (0.58)	
Koçak Farma (Turkey)	3.41 (0.82)	

Table 12 shows a significant and positive relationship between the attitudes of the participants toward the measures taken regarding the COVID-19 infection and their attitudes toward the vaccine (r = 0.49, P=0.01).

We found a significant and positive relationship between the confidence levels of participants in the Sinovac company vaccine manufactured in China, which will be applied to healthcare workers by our Ministry of Health, and their attitude toward the vaccines (r = 0.77, P=0.01).

We found a significantly negative correlation between the number of shifts of the participants and their attitudes toward vaccination (r = −0.26, P=0.01).

We also noted that participants' attitudes toward the measures taken against the COVID-19 infection and their level of confidence in the vaccine of the Sinovac company produced in China were more positive, and individuals with a high number of shifts had a lower attitude toward the vaccine.

Table 12: Variables affecting participants' attitude toward vaccination

		Attitude toward the COVID Vaccine (Trusting and Adopting)
Attitude toward the measures taken for COVID-19 (Mask, Disinfection)	r	0.49
	P	0.01
Trust in the CoronaVac vaccine of Sinovac company, which will be applied to healthcare professionals by our Ministry	r	0.77
	P	0.01
Number of shifts per month	r	−0.26
	P	0.01

Discussion

The primary goal of health services and staff is to ensure that individuals continue to lead healthy lives. Vaccination is the most effective method of providing protection from infectious diseases [3]. Healthcare professionals who follow scientific innovations and whose knowledge is most sought after to protect public health serve as ambassadors of evidence-based medical interventions and are critical in promoting the adoption of vaccines. Healthcare experts are in the vanguard of the pandemic response fields with a serious risk of occupational SARS-CoV-2 exposure and transmission [8,9]. Healthcare specialists are still considered to be trusted and dynamic national representatives for social health issues [8]. In this context, there is a need to address concerns and raise awareness among healthcare professionals to increase the acceptance of the COVID-19 vaccine [7]. Otherwise, there is a risk of mass rejection of the COVID-19 vaccine by the general population when the vaccine becomes available [7].

Healthcare employees who accept the COVID-19 vaccine and have a confident perspective are more prone to be vaccinated. These data are essential, as the World Health Organization identified vaccine reluctance as one of the ten greatest hazards to overall health in 2019 [10]. In particular, healthcare professionals who work in primary healthcare should convey the message that vaccines are safe and that vaccination is necessary to prevent the epidemic in the community. As a safe and effective COVID-19 vaccine appears to be the only solution for this pandemic, it is imperative that healthcare professionals maintain a positive attitude toward vaccination [11].

The success of vaccination strategies is based on societies' perceptions of the benefits or risks of vaccines and the associated trust in vaccination [12]. In a systematic analysis of 145 articles published in European Union countries, the authors found that the biggest concern in society regarding vaccination was vaccine safety, which often led individuals to conclude that the risks of vaccines outweigh the benefits [13]. In our study, 355 respondents (80.3%) indicated that the biggest drawback in

vaccination was the lack of information on its long-term side effects.

In our research, although the participants accepted the safety, effectiveness, and value of vaccination for public health studies, 28% stated that they were worried about the serious side effects of vaccines, which had an influence on their workforce and social life [8]. Such reservations may cause doubts about the perceived safety of vaccines.

In our survey, we observed that the confidence of residents, nurses, and other health personnel in vaccination were low. Public health officials should take steps to raise the awareness among this important group of professionals, who interact with the public and are often responsible for the direct administration of vaccines during the vaccination phase.

As seen in our results, we found that older age was associated with an increased desire to be vaccinated against COVID-19. This finding is not surprising, as healthcare professionals are familiar with the fact that advanced age is one of the strongest risk factors for COVID-19 mortality. Therefore, it makes sense for elderly healthcare professionals to be given priority in receiving the COVID-19 vaccine in their institutions [10].

Studies have found that an individual's perceived risk of the COVID-19 infection is associated with an increased acceptance of vaccination against COVID-19 among healthcare professionals. Some state that healthcare workers may be reluctant to receive the COVID-19 vaccine if they believe that it does not provide individual protection [14]. In our study, we observed a significant and positive relationship between the attitudes of the participants toward the measures taken regarding the COVID-19 infection and toward the vaccine. However, we also found that the vaccination attitudes of healthcare workers were not at top levels, and, in parallel with the perception of healthcare professionals, the attitudes of the public toward vaccination are also not at the desired level. It is important to broadcast informative public service announcements in the media regarding this issue and eliminate concerns.

Based on the results of our survey, to eliminate vaccination hesitation, there is a need to increase the awareness of vaccination and provide informative, in-service training among residents, nurses, and health officials who are single and aged between 20 and 30 years. Sustaining the gains achieved because of efforts to protect and improve human health is possible only with political determination and social participation. Vaccine hesitation, vaccine rejection, and antivaccination studies, which have developed in recent years in our country and worldwide, damage the progress obtained thus far in the avoidance of virulent epidemics [15, 16].

Limitations

There are several limitations to this study. First, subjects were recruited and surveyed online rather than face to face, which could lead to bias in the discrete choice experiment study. Another limitation is the fact that the work was cross-sectional and shows only a picture of the community response. We also asked participants to report their intention to receive the COVID-19 vaccine when the current vaccine production begins in the future. A significant number of study participants (12.67%) reported "I have no idea" regarding their intention to obtain the COVID-19 vaccine. Their actual intention may differ when the vaccine is available. This can lead to potential bias when reporting their responses.

Another limitation is that using an internet-based online survey program has become one of the most popular and common ways of collecting data. Preparing the questions to be answered online is the most important part of the questionnaire form. Choosing the right question among dozens of question types ensures high quality data and makes a statistical analysis of data accurate and dependable. However, using such internet-based non-standard survey preparation programs can create bias on research.

Conclusion

We identify healthcare workers as priority recipients of the COVID-19 vaccine worldwide, because they represent a group at high risk for the transmission of the SARS-CoV-2 infection. In addition, healthcare professionals serve as trusted community workers in public health issues, and their role in promoting the adoption of the COVID-19 vaccine is critical. Hence, reluctance about the SARS-CoV-2 vaccine among healthcare specialists must be eradicated to improve the public's attitude toward the COVID-19 vaccine. Vaccine hesitation in a pandemic is a major obstacle to implementing vaccination campaigns. To continue the benefits of vaccination programs and implement the vaccination successfully, it is crucial to understand and address the vaccine hesitations among healthcare professionals.

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Comparison of third generation long Gamma nail and femur intramedullary nail for the treatment of femoral subtrochanteric fractures

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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Internal fixation is the current gold standard procedure in treatment of subtrochanteric femur fractures. One of the most common causes of morbidity after subtrochanteric femoral fracture treatment is mechanical complications, such as implant failure. The aim of this study is to share our experience and compare the radiological and functional results of two different fixation implants in patients with subtrochanteric fractures.

Methods: A cohort of 57 patients with a subtrochanteric fracture operated using a third generation Gamma nail (G3LN) or an anterograde intramedullary nail (AIMN) were prospectively followed up. Twenty-eight underwent fracture fixation with the Gamma nail while the other twenty-nine were operated using a conventional AIMN. All patients were followed up until union or, in case of a revision, healing and recovery. Their radiological findings were retrospectively analyzed, and the functional results were assessed using a Harris Hip Score.

Results: Data regarding demographic properties such as sex, trauma mechanism and smoking were similar for the subgroups ($P<0.05$ for each). Blood loss amount, surgery time, hospital stay and follow up time were also similar between the two groups ($P>0.05$ for each). Compared to the AIMN group, whose reduction was mostly acceptable (48.28%), the majority of G3LN patients (57.14%) had an anatomical reduction on early follow up. Most fractures, regardless of the implant used, needed an open reduction. Both implants showed similar union time and had similar final HHS scores. None of the complication rates reached statistical significance between the two groups ($P>0.05$ for each).

Conclusion: Both third-generation Gamma Nail implant and anterograde intramedullary nailing are viable means of fixation for subtrochanteric hip fractures. They lead to similar and few complications while providing a rigid and secure fixation. These findings lead us to believe that good reduction and adherence to the principles of internal fixation rather than implants used are the key to success in the treatment of subtrochanteric fractures.

Keywords: Subtrochanteric femur fracture, Gamma nail, Antegrade intramedullary nail

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Introduction

The subtrochanteric region has traditionally been defined as the femoral region 5 cm distal to the lesser trochanter and located between the lesser trochanter and the femoral isthmus [1]. Fractures of this region consist of approximately 5-20% of all proximal femoral fractures and show a bimodal age distribution [2]. High-speed trauma is usually the cause in young and healthy individuals while simple falls and minor trauma are responsible for these kind of fractures in the aging population [1].

Intraoperative reduction of these fractures has always been tricky given that the posteromedial compressing forces and the anterolateral tensile forces combined with a variety of strong muscle attachments tend to pull the fracture fragments apart and have been deemed by many scholars as risk factors for non-union, malunion, varus malreduction and implant failure [1]. Many extramedullary fixation tools like sliding hip screws [3], dynamic condylar screws [4] and locked compression plates [5] have been used to address subtrochanteric fractures. Compared to extramedullary fixation systems, intramedullary nails are less invasive, lead to less blood loss intraoperatively, have lower rates of infection and non-union and give the patient the possibility of a quicker recovery by allowing early postoperative weight bearing [1]. Intramedullary nails are also biomechanically preferable to extramedullary devices due to shorter lever arms for the counter torque of bending moments [6]. Despite these advantages, fracture reduction tends to be more difficult when using intramedullary devices [1].

The aim of this study is to compare the radiological and clinical results of two different intramedullary devices widely used in the fixation of subtrochanteric fractures.

Materials and methods

Data regarding all consecutive patients visiting the Level 1 trauma center of Ankara Atatürk Education and Training Hospital between May 2014 and September 2018 with a subtrochanteric fracture were retrospectively gathered and analyzed for this study.

Exclusion criteria were pathological fractures, open fractures, being under 18 years of age, polytrauma, multiple fractures and having a preoperative American Society of Anesthesiologists (ASA) score higher than IV.

To be included in our study, patients had to be operated with either a third-generation Gamma Long Nail (G3LN) (Stryker Trauma Gmbh, Schonkirchen, Germany) or an anterograde intramedullary nail implant (AIMN). While the Gamma Nail implant type was constant in one group, two different implants, acting on the same fixation principles were used for the anterograde intramedullary fixation (AFN, Synthes, Solothurn, Switzerland; Zimed Turkey)

The Gamma Nail system consists of a lag screw and a rod to overcome problems in sliding-screw fixations. Although it has shown superior efficacy in the fixation of intertrochanteric and subtrochanteric fractures, its clinical application has been associated with several complications, including breakage of the lag screw and fracture of the femora distal to the intramedullary device [7]. The AIMN is designed with a proximal lateral bend specifically to facilitate insertion through the greater trochanter. This theoretically reduces the potential complications of varus malalignment. Two separate screws can be placed through the femoral neck and compared to the Gamma system they provide lower fracture site compression but greater rotational stability and greater load sharing [8]. Anti-rotation function of the long gamma nail is obtained by inserting a blocking bolt into the proximal canal of the nail [9]. We routinely used fully reamed AIMN implants while the G3LN implants only required reaming of the proximal intertrochanteric region to facilitate insertion.

All fractures were classified using the Seinsheimer classification which has been widely accepted as one of the most practical classification systems for this condition [10]. It consists of five types (I–V), based on the number of fractured bone pieces, location, and shape of the fracture line.

Data relative to the surgery duration time, blood loss, hospital stay, open or closed reduction and cerclage cable usage were also taken of note. Fracture union was defined as painless weightbearing associated with a radiological bridging callus formation on at least three cortices on two orthogonal projections [11] while nonunion was defined as lack of cortical bridging after 6 months on at least three cortices with persistent pain at the fracture site during weight bearing [12]. Malunion was defined as less than 50% contact between proximal and distal fragments.

Surgical technique

The surgeries were performed by three experienced surgeons familiar with both implants. Patients were placed supine on a radiolucent surgical trauma table. Approximately 30 minutes before the skin incision, they were administered an intravenous prophylactic antibiotic dose of 2 grams of Cefazoline. Traction was applied depending on the fracture pattern and a closed reduction was attempted. If not possible, a minimal skin incision was performed at the fracture site and an anatomical, or sometimes acceptable, reduction was obtained with the usage of clamps and sometimes cerclage cables. Then another small incision was performed 5 cm cranial to the greater trochanter and the entry point was chosen by radiographic confirmation. The entry point in all patients was slightly medial to the tip of the greater trochanter to avoid a varus malreduction. A guiding wire was then placed into the intramedullary cavity. Then according to the surgeon's judgement, a Gamma 3 Long Nail (sizes between 260-480mm) or an AIMN was inserted and locked proximally and distally. Care was taken to insert the G3LN's lag screw and the AIMN's inferior screw close to the inferior border of the femoral neck on the anteroposterior (AP) view and centrally on the lateral view as described by Jiang et al [9]. Compression was applied depending on the fracture pattern. The tip-apex distance (TAD) of the G3LN's lag screw and the AIMN's inferior (and longer) screw had to be <25mm [13, 14] so that cut-out and Z-effect complications could be minimized. Neck-shaft angle was measured on the final AP view and was later used as a reference to assess for cut-out, Z effect and other varus related complications. After radiological confirmation, a drainage bag was placed and the wound was closed.

Postoperative management

Assisted active and passive hip and knee range of motion was started the day after surgery and foot-touch weightbearing was allowed. Weightbearing amount was increased in the following weeks depending on patient compliance and reduction

quality. Throughout the follow up period strengthening exercises were shown and recommended to the patients. All patients were given a thromboembolism prophylaxis of enoxaparin for 6 weeks.

Method of assessment

Patients were followed up monthly and evaluated clinically on each visit for pain, stiffness, infection, and deep venous thrombosis (DVT) signs and weightbearing amount. Radiologically they were assessed for healing signs, reduction loss, implant breakage and additional fractures. Reduction quality was noted and analyzed on the radiographs taken on early follow up (1-2 months) using Baumgartner et al.'s classification of good, acceptable and poor [13]. TAD was measured according to Li et al [14]. Two independent radiologists unfamiliar with the patients evaluated all the radiological data for this study.

All patients were monthly followed until complete union was achieved. They were then scheduled for yearly check-up visits. Those who experienced complications were treated accordingly and followed up until remission with yearly visits thereafter. All complications were noted and compared between the two groups. All revisions were managed at our center by the primary operating surgeons and their teams.

Patients were evaluated for hip pain and lower limb shortening and were analyzed at every visit with a Harris Hip Score (HHS). The data compared here consists of the HHS of their last visit at the clinic.

All patients gave their informed consent for this study and the local ethical committee approved the study design (Ankara City Hospital, Educational Board of Medical Specialization Committee – Date 26/03/2020 - Document nr. 72300690 – 799).

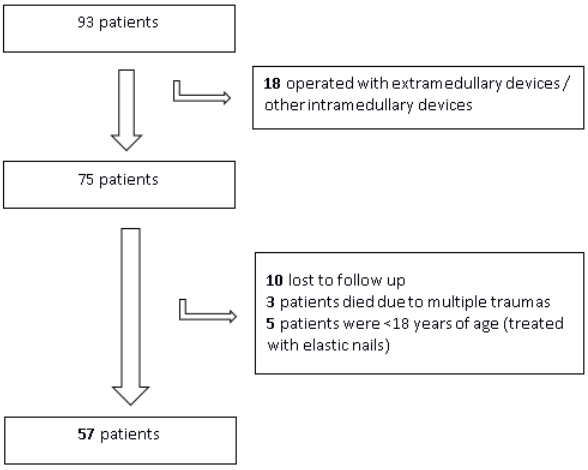
Statistical analysis

Statistical significance level was determined as P <0.05. Statistical analyses were performed using Statistical Package for Social Sciences - IBM Statistics 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) and Microsoft Excel 2016. The relevance of the distribution of continuous variables such as age, blood loss, surgery time, hospital stay was evaluated using the Shapiro-Wilk test and graphical methods. Variables matching normal distribution were mean (standard deviation) and non-matching variables are summarized by median (min; max). Number and percentage [n (%)] statistics were used to summarize categorical variables such as gender, ASA, side, trauma. Mann Whitney U test was used for non-normal continuous variables and independent samples t test was used for normal continuous variables to compare inter-group differences. Chi-square test was used to compare categorical variables and Likelihood ratio, Fisher exact test, Continuity correction, Pearson Chi-square test results were reported as appropriate.

Results

Ninety-three patients with a subtrochanteric fracture were operated at our center, out of which eighteen were operated with an either extramedullary device or an intramedullary device not compatible with our study. Ten were lost to follow up and three patients had died shortly after surgery at the ICU due to the severity of the sustained multiple traumas. Five other patients were excluded for not meeting the inclusion criteria. Fifty-seven patients treated with intramedullary devices were included in this study (Figure 1). Twenty-eight were operated with a G3LN while twenty-nine were operated with an AIMN.

Figure 1: Patient selection according to the inclusion and exclusion criteria for the current study.



Patients' mean age was 51.54 (19.74) years in G3LN, and 51.24 (19.13) years in the AIMN group, which were similar (P=0.955). A slight majority of patients operated with G3LN were male (60.71%) while 55.17% of patients operated with an AIMN were female. Both implants were mostly used of the right side since most the fractures occurred on this side. No significant differences on demographic properties such as sex, trauma mechanism and smoking were observed (P>0.05). We found statistical significance in between subgroups regarding ASA and the Seinsheimer classification (P<0.05). All demographic data are shown on Table 1.

Table 1: Patients' demographic findings

Demographics	G3LN [n=28] Mean (SD) n (%)	AIMN [n=29] Mean (SD) n (%)	Test χ^2	Statistics *P*-value
Age	51.54 (19.74)	51.24 (19.13)	t=0.057	0.955
Sex			–	0.175[+]
Female	11 (39.29)	16 (55.17)		
Male	17 (60.71)	13 (44.83)		
Side				
Right	22 (78.57)	22 (75.86)		
Left	6 (21.43)	7 (24.14)		
Trauma				
FFH	6 (21.43)	9 (31.03)	0.273	0.601[#]
HST	10 (35.71)	9 (31.03)	0.009	0.925[#]
FI	2 (7.14)	2 (6.90)	–	0.681[+]
FSL	10 (35.71)	9 (31.03)	0.009	0.925[#]
ASA				
1	1 (3.57)	3 (10.34)	–	0.319[+]
2	7 (25.00)	16 (55.17)	4.2018	0.040[#]
3	20 (71.43)	10 (34.48)	6.388	0.011[#]
Seinsheimer				
2	12 (42.86)	4 (13.79)	4.607	0.032[#]
3	7 (25.00)	13 (44.83)	1.665	0.197[#]
4	3 (10.71)	11 (37.93)	4.321	0.038[#]
5	6 (21.43)	1 (3.45)	–	0.046[+]
Smoking			0.024	0.877[#]
No	17 (60.71)	16 (55.17)		
Yes	11 (39.29)	13 (44.83)		

+: Fisher, #: Continuity Correction Chi-Square test results. G3LN: Third generation Gamma long nail, AIMN: antegrade intramedullary nail, ASA: American Society of Anesthesiologists score, HST: High Speed Trauma, FFH: Fall from Hight, FSL: Fall on Same Level, FI: Firearm Injury.

Blood loss amount, surgery time, hospital stay and follow up time were also similar between the two groups (P>0.05). The majority of G3LN patients (57.14%) had an anatomical reduction on early follow up and this reached statistical significance compared to the AIMN group whose reduction was mostly acceptable (48.28%). Most fractures, regardless of the implant used, needed an open reduction. Two cerclage cables were mostly used during fixation and very few fractures needed none (10 in total). All other surgery results are shown in Table 2.

Table 2: Surgery results of the patients

Surgery variables	G3LN [n=28] Mean (SD) Median (min - max)	AIMN [n=29] Mean (SD) Median (min - max)	Test t, Z	Statistics *P*-value
Blood Loss [cc]	396.79 (161.87)	413.10 (118.93)	0.435	0.665
Surgery Time [min]	85.00 (40 - 185)	85.00 (55 - 110)	0.008	0.944
Hospital Stay [day]	3.00 (2 - 6)	3.00 (2 - 10)	0.842	0.400
Follow-up Time [months]	33.50 (14 - 65)	41.00 (14 - 64)	0.743	0.458
	n (%)	n (%)	χ^2	*P*-value
Reduction				
Anatomical	16 (57.14)	8 (27.59)	3.965	0.046#
Acceptable	9 (32.14)	14 (48.28)	0.943	0.331#
Poor	3 (10.71)	7 (24.14)	–	0.163+
Open/Close			0.542	0.462#
Close	7 (25.00)	4 (13.79)		
Open	21 (75.00)	25 (86.21)		
Cerclage				
0	6 (21.43)	4 (13.79)	–	0.342+
1	9 (32.14)	2 (6.90)	4.322	0.038#
2	10 (35.71)	18 (62.07)	2.975	0.085#
3	3 (10.71)	5 (17.24)	–	0.373+

+: Fisher, #: Continuity Correction Chi-Square test results.

Table 3 shows the complications and the revision data regarding both surgical implants. Both implants showed similar union time and had similar final HHSs. No shaft fractures, infections, malunions and pulmonary thromboembolisms (PTE) were detected, and no surgery-related deaths occurred. Four patients receiving a G3LN were revised in total while five were revised in the AIMN group. None of the complication rates reached statistical significance between the two groups. All data is shown in Table 3.

Table 3: Complications

Complications	G3LN [n=28] Median (min - max)	AIMN [n=29] Median (min - max)	Test Statistics *P*-value
Time to union [weeks]	20.00 (16 - 51)	25.00 (16 - 48)	0.240
NSA decrease [degree]	3.00 (0 - 10)	4.00 (0 - 12)	0.081
HHS Score	85.65 (51.5 - 96.2)	88.40 (66 - 96)	0.487
	n (%)	n (%)	p
Cut Out	1 (3.57)	3 (10.34)	0.319
Shaft Fracture	0 (0.00)	0 (0.00)	N/A
Non-union	2 (7.14)	1 (3.45)	0.487
Infection	0 (0.00)	0 (0.00)	N/A
Malunion	0 (0.00)	0 (0.00)	N/A
AVN	1 (3.57)	1 (3.45)	0.746
Hip Pain	3 (10.71)	3 (10.34)	0.648
HO	1 (3.57)	1 (3.45)	0.746
DVT	1 (3.57)	1 (3.45)	0.746
PTE	0 (0.00)	0 (0.00)	N/A
LLS>1.5 cm [SIAS-MM]	2 (7.14)	1 (3.45)	0.487
Reoperation	4 (14.29)	5 (17.24)	0.523
Death	0 (0.00)	0 (0.00)	N/A
Revised into			
THA	2 (50.00)	4 (80.00)	0.405
IMN	0 (0.00)	1 (20.00)	0.556
DCS	2 (50.00)	0 (0.00)	0.167

* Fisher Exact Chi-Square test results. NSA: Neck shaft angle. HHS: Harris Hip Score. AVVN: Avascular necrosis. HO: Heterotopic ossification. DVT: Deep vein thrombosis. PTE: Pulmonary thromboembolism. LLS: Lower Limb Shortening. SIAS: Superior anterior iliac spine. MM: Medial malleolus. THA: Total hip arthroplasty. IMN: Intramedullary nail. DCS: Dynamic compression screw.

Discussion

This study compared the results of two biomechanically strong intramedullary devices used in the treatment of subtrochanteric fractures and shared our experience with the studied devices. It showed that both the AIMN (Figure 2) and the Gamma 3 Long Nail (Figure 3) lead to acceptable healing rates with satisfactory clinical results.

Figure 2: A 35-year-old patient with a Seinsheimer type 2 subtrochanteric femur fracture on her arrival after a high-speed trauma (a). The fracture was reduced and an AIMN implant was chosen to stabilize the fracture and no cerclage cables were required. Her early follow up radiographs (3rd month postop) already show healing signs (b, c). The fracture site is completely healed at 9 months and the patient has returned to her daily activities (d, e).

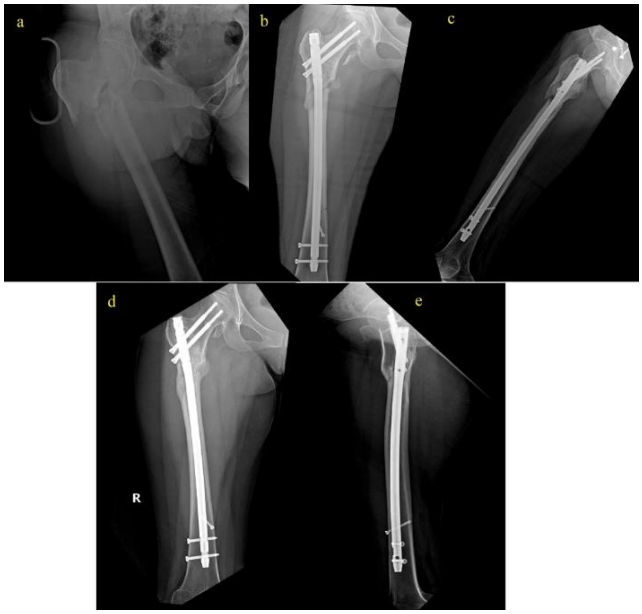
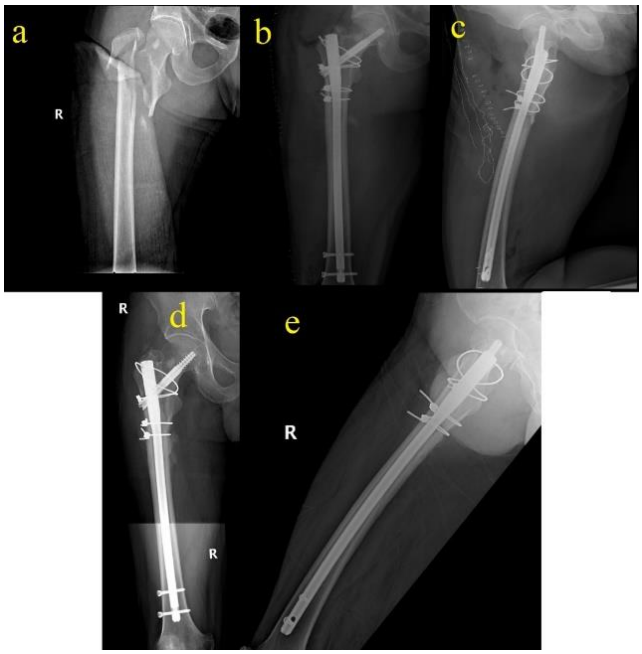


Figure 3: A 44-year-old male patient fell from a tree and presented to the emergency department with a Seinsheimer type 5 subtrochanteric femur fracture (a). His fracture was anatomically reduced using 3 cerclage cables and a Gamma Long nail was chosen as a fixation tool (b, c). At 7 months the patient is fully active and the fracture has healed without complications (d, e).



Subtrochanteric fractures fixation has always been a challenging procedure even for experienced surgeons. The massive forces acting on the fracture tend to pull the proximal fragments in flexion, abduction and external rotation making it difficult to align them anatomically without an open reduction [1]. Moreover, the discontinuity of the posteromedial wall of the proximal femur, a quite common feature of subtrochanteric fractures, leads to a varus malalignment if not addressed properly during surgery [15]. These studies suggest prior reduction with or without cerclage cables/wires before nail insertion. We followed the same procedure in this study.

Intramedullary implants have become the treatment of choice and almost a gold standard for these challenging fractures [1]. Extramedullary devices need extensive tissue/fracture site exposure, can lead to higher blood loss and higher tissue injury [16], have higher re-operation rates [17] and are biomechanically

inferior due to their longer lever arm [6]. Our center routinely uses intramedullary fixation in the treatment of these kind of fractures, which this study reflects. Despite this, a dynamic compression screw (DCS) system has been described as a successful means to address non-unions in subtrochanteric fractures by Lotzien et al [18]. Two patients from this study were firstly operated with a G3LN and developed a nonunion. Revision was performed using a DCS implant and both healed uneventfully, showing that despite their disadvantages, extramedullary devices can achieve satisfactory results when used properly.

Extensive studies have shown the G3LN implant to be an excellent choice in the treatment of subtrochanteric fractures [1]. Few studies have been performed on the usage of AIMN implants on subtrochanteric fractures maybe due to their limited ability to compress the fracture sites [1], their higher affinity for the Z and reverse Z effect [9] and concern that full reaming could lead to greater blood loss and longer operating time [19]. In our study we found the cut-out rate of the dual screw implant to be of 10.34% which is comparable to what previous studies have found [9]. They were all revised into a total hip replacement. No statistical significance was reached on either of the mentioned complications showing that with proper reduction AIMN implants can achieve acceptable results.

Cerclage cable/wire usage has often been attributed to delayed union or non-union due to concerns that it might disrupt blood supply to an already delicate region [20]. This theory had little histological basis [21] and has always been controversial. In his study of 52 subtrochanteric fractures, Kilinc et al. [16], like many others in the literature [1, 2], achieved good reduction and satisfying results with the usage of cerclage wire with no negative effect on fracture healing.

Cut-out and hip pain were our most frequent complications in our study. One elderly patient treated with a G3LN and three patients (1 elderly, 2 relatively young) operated with AIMN failed through a cut-out. Both elderly patients failed to comply with weightbearing recommendations. One of the AIMN patients experienced a loss in reduction during follow up leading to a subsequent Z-effect while the other patient had a fall on the same hip. The Z and the reverse Z effects are among the most frequent and most stressed complications for AIMN mentioned in the literature and varies from 7.1 to 13% [8]. Cut out for proximal hip nail on the other hand varies from 0 – 16% [22]. The results of our study were similar to those reported in the literature with a 3.55% cut out on the G3LN and 10.34% on the AIMN.

Two patients developed avascular necrosis (AVN) associated with hip pain and were treated before advancing to a cut out. One of the patients had a history of rheumatoid arthritis while the other developed Bell's palsy shortly after surgery. They both used corticosteroids, which we believe contributed to the development of the AVN. Each of them had been treated with a different implant and we believe the complication was not implant related but rather, the result of an increase in intracapsular pressure due to trauma. Decompression has shown some promising results in these patients [23]. They were both treated with a hip replacement.

Harris Hip Score (HHS) was used for the examination of functional results [24]. Patients treated with both implants showed good results during follow up with many of them returning to preoperative activities. Only two patients operated with a G3LN implant developed a lower limb shortening of more than 1.5 cm. They were both treated with dynamic insoles and were recommended for physical rehabilitation. Heterotopic ossification (HO) is another complication mentioned in the literature [7]. While Hayashi et al [25] mention gender, surgical approach, ethnicity and fracture site as risk factors associated with HO, they found that severe HO was associated with longer time between time of acute hip fracture and surgery. In our study, two patients, one from each group, developed mild HO during follow up. They were both treated with nonsteroidal anti-inflammatory drugs and physical therapy.

Limitations

Despite its overall positive results, our study has several limitations. This was a retrospective study, and analysis is prone to bias. We tried to tackle this bias by having the data gathered prospectively during the years. Second, observer errors may be present, especially in the radiological measurements. We tried to limit this by having two independent radiologists evaluate the findings. Third, a higher number of patients would have increased the strength of the statistical analysis. Out of the initial ninety-three patients, only fifty-seven were eligible for the study and the results should be interpreted accordingly. On the other hand, our study had a homogeneous patient population regarding age, gender and trauma mechanism and the results shown here could be generalized to the overall population.

Conclusion

Both third-generation Gamma Nail implant and anterograde intramedullary nailing are viable means of fixation for subtrochanteric hip fractures. They lead to similar and few complications while providing a rigid and secure fixation. These findings lead us to believe that good reduction and adherence to the principles of internal fixation rather than implants used are the key to success in the treatment of subtrochanteric fractures.

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The effect of edaravone on a rat fracture model complicated with ischemia

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Abstract

Background/Aim: Ischemia is a common issue in fracture healing due to vascular injury, compartment syndrome, and long-term tourniquet use. With ischemia-reperfusion injury, normal tissue repair can become complicated. In our study, we aimed to investigate the effect of edaravone on fracture union in a rat fracture model complicated with ischemia.

Methods: We conducted our study on forty-four rats divided into four study groups and a control group, as follows: Group 1- Fracture, Group 2- Fracture-ischemia, Group 3- Fracture-ischemia-edaravone, Group 4- Fracture-edaravone, and Group 5- Control group. The control group comprised the contralateral intact tibia of the rats in Group 1 that were not complicated with ischemia and were not given edaravone treatment. The effects of edaravone on fracture healing were evaluated histologically, radiologically, and biomechanically.

Results: There were no differences between the groups in terms of biomechanical and radiological indices, except for hardness values in the control subjects (Group 5), which were significantly higher than those of the other groups ($P<0.05$ for all). Similarly, in terms of histological evaluations of fracture healing between groups, group 3 has better improvement fracture healing scores than group 2 ($P=0.042$), and Group 4 has better improvement fracture healing scores than group 1 ($P=0.049$).

Conclusion: These findings suggest that the administration of edaravone, independent of ischemia, had positive results on histopathological fracture healing.

Keywords: Fracture healing, Edaravone, Ischemia-reperfusion injury, Antioxidant agents, Rat fracture model

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Introduction

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, $C_{10}H_{10}N_2O$, MCI-186) is a strong synthetic free oxygen radical (FOR) scavenger that inhibits lipid peroxidation. In addition, edaravone exerts positive effects on cerebral ischemia and stroke models by suppressing hydroxyl and superoxide anion levels [1]. Molecules and mechanisms implicated in ischemia-reperfusion injury include endothelial damage, FORs, polymorph nuclear leukocytes, and complement system activation. FORs are short-lived molecules, containing unstable electrons that negatively interact with cell components, notably cell lipids. Lipid peroxidation is triggered by FORs and includes multiple unsaturated fatty acids that can cause tissue damage. Reactions proceed until terminated by antioxidants or the end of the lipid chain is reached. The basic approach to deactivating FORs is by using antioxidants.

Due to long-term tourniquet use, vascular injury, and compartment syndrome, the circulation of a fracture can be impacted. With reperfusion, blood circulation is not only provided, but also damaged because ischemia is also attempted to be remedied [2]. Reperfusion of ischemic tissue causes tissue damage through a series of cellular reactions. Ischemia-reperfusion injury produces increased toxic metabolites when compared with ischemic damage alone [3].

Numerous studies have examined the effects of FORs and other antioxidant molecules in healing fractures. Although some studies have focused on the antioxidant effects of edaravone on muscles and the skeletal system, no studies have focused on the healing process of edaravone in an ischemia-reperfusion injury fracture model.

In the current study, we assessed edaravone as a FOR scavenger in fracture healing, and evaluated its effects in terms of radiological, biomechanical, and histopathological outputs.

Materials and methods

Following permission from the Tokat Gaziosmanpaşa University Experimental Animals Ethics Committee (2016 HADYEK-01), 44 Wistar-albino rats (aged 10-14 weeks and weighting 250 (30) g) were divided into four experimental groups, with eleven in each group. Rats were kept in separate cages, away from air flow, at a standard temperature 23(2) °C and received periodical lighting for 14 hours daily. Feeds were filled to 50 g per rat every other day, and water containers were renewed to 50 ml per rat every other day.

The groups were designated as follows: Group 1: Fracture only, Group 2: Fracture-ischemia, Group 3: Fracture-ischemia-edaravone, Group 4: Fracture-edaravone, and Group 5: Control group. The control group comprised the intact tibia of the Group 1 (fracture group) rats (Table 1).

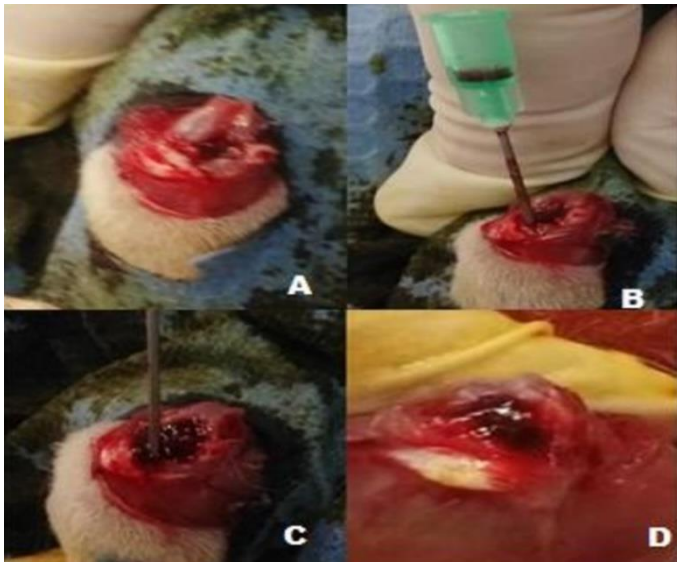
Table 1: Methods applied according to working groups

Group Number	Fracture application	Edaravone application	Ischemia application
Group 1	+	-	-
Group 2	+	-	+
Group 3	+	+	+
Group 4	+	+	-
Group 5	-	-	-

For prophylaxis, 20 mg/kg cefazolin sodium (Cezol®, Deva Saba Inc, İstanbul, Turkey) was administered intraperitoneally 30 min before surgery, which was repeated at the 8th postoperative hour. General anesthesia was achieved with 90 mg/kg of intraperitoneal ketamine hydrochloride (HCL) (Ketalar®, Pfizer, Inc., Istanbul, Turkey) and 10 mg/kg of Xylasine (Rompun®, Bayer Healthcare AG, Leverkusen, Germany). The lower right extremities were aseptically shaved and prepared. Then, the femoral artery was dissected from the nerve distal to the inguinal ligament. A microvascular clamp was used as described by Skjeldal et al. [3] to prevent femoral artery blood leakage. After clamping, loss of pulsation and volume in the distal femoral artery were evaluated macroscopically. Whether adequate ischemia occurred in rats with appropriate clamping was also observed macroscopically at the 30th minute of clamping. Adequate ischemia was considered to have occurred if loss of capillary refill, pallor and coldness occurred in the limb. Arterial clamping was applied for 5 hours at 24°C - and the rats were fixed in supine position. During this period, the incision line was closed with a wet sponge to prevent the tissues from drying. No qualitative method was used to evaluate the effects of the ischemia procedure. The process was terminated after 5 hours.

First, intramedullary fixation was applied to all rats, except the control group. The patella was everted laterally by entering through the right knee joint, with a 1 cm medial parapatellar incision. The tibia was cavitated using a 21-gauge needle (Beybi®, Inc., İstanbul, Turkey) over the tuberosity tibia, and a 0.8 mm stainless steel Kirschner wire was inserted into the tibia intramedullary. After bending and cutting the wire and reducing the patella, the incision layers were closed (Figure 1).

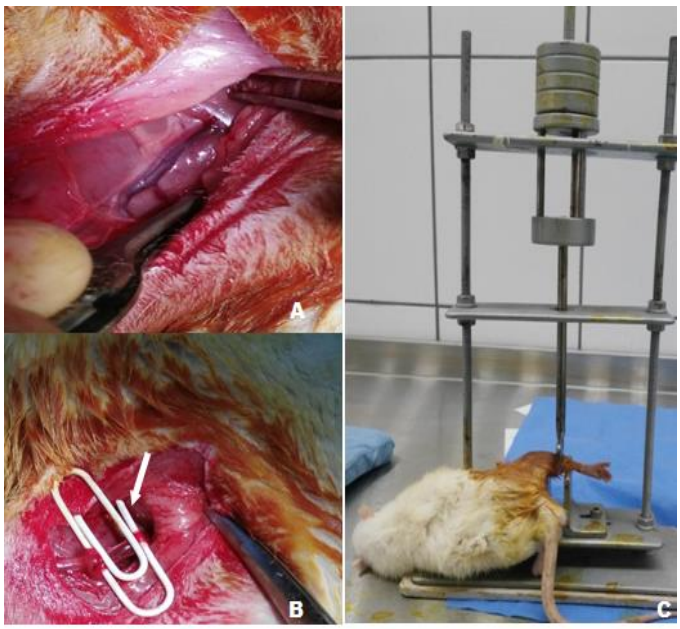
Figure 1: Intramedullary fixation technique; A) Medial parapatellar incision, B) Tibia cavitated through a number 21 needle, C) 0.8 mm stainless steel wire inserted intramedullary, D) Bending and cutting of K wire



Then, the closed tibial fracture model was realized in all tibias, except the control group, by exerting equal weight to the midline of tibias. Following the fracture, femoral artery clamping was performed on rats in the ischemia groups (Groups 2 and 3; Figure 2).

Edaravone (Mitsubishi Tanabe Pharma Corporation®, Tokyo, Japan) was provided in a powdered form. The powder was dissolved in 1N sodium hydroxide (NaOH) and titrated to pH 7.4 with 1N HCL. The final concentration was adjusted to 0.3 mg/ml. The intraperitoneal dose was determined as 3 mg/kg/day, which was repeated for seven days. Drug administration was performed under deep anesthesia.

Figure 2: Ischemia and fracture model A: Femoral artery and vein dissection (white arrow), B: Vascular clamping (white arrow), C: Mid-diaphysis fracture creation

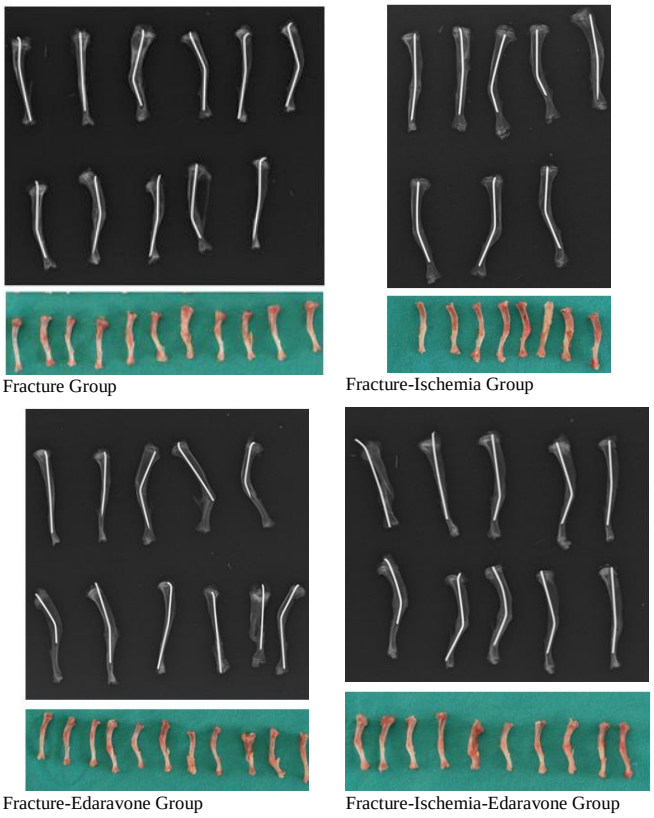


Edaravone was administered to Groups 3 and 4, prior to ischemia, at 3 mg/kg/day over seven days. Hourly observation was performed for 4 hours after intraperitoneal drug administration. Urine and feces were checked for hydration levels for 12 hours. Skin lesion, tumor appearance, and incision controls were performed hourly for the first 4 hours. After 5 hours of ischemia, the procedure was terminated by clamp removal. Femoral artery blood flow was generated. Afterwards, the groin incision was closed. During and after ischemia, rats were kept in a supine position at 24°C. The groin area was closed with a wet sponge to prevent local tissue dehydration. A 4 ml 0.9% Sodium chloride (NaCl) isotonic solution was administered to rats with ischemia for the same reason. Each day, two doses of 200 mg/kg paracetamol were also administered to control pain. During the study, three rats in Group 2 and one rat in Group 1 died; therefore, the study was completed with the following rat numbers per group: Group 1: n = 10; Group 2: n = 8; Group 3: n = 11; and Group 4: n = 11.

Animals were euthanized by cervical dislocation at the end of the 8th week of the experiment. Tibias were collected and cleaned from soft tissue. Radiologic evaluation was performed first, provided with the graphs of the samples by author (MA) unaware of the group number to avoid selection bias. Fracture areas were assessed according to the Lane and Sandhu radiological scoring system [4], which assesses new bone constitution and bone union degree (Figure 3).

After radiological analysis, tibias were stored at -20°C for biomechanical analyses. One day after radiological evaluation, tibias were thawed at room temperature. Three-point bending tests were applied to all specimens using a compression distraction device (Hounsfield H50KM, Surrey, England). Tibia samples were placed into the biomechanical test device after the intramedullary wire was removed. A stable 10 mm/mn pressure was applied to the fracture-healing section to create re-fracture. Breaking force and hardness (N/mm) were recorded separately. All biomechanical tests were performed by one author (SA) unaware of the group number to avoid the selection bias.

Figure 3: Morphological and radiologic view of groups at the end of the 8th week



After the biomechanical evaluation, the tibias were stored in saline until the decalcification process. Morse's Solution (10% sodium citrate, 20% formic acid) was used for decalcification. After decalcification was complete, the tissues were neutralized by sodium sulfate for 12 hours. 5-µm wide paraffin incisions were prepared and stained with hematoxylin-eosin. Samples were assessed by light microscopy. For each sample, five slides were analyzed, and fracture healing was evaluated histologically. A histologist with at least 10 years of experience evaluated the slides. Histological assessments were conducted according to Huddleston et al. [5], in terms of fibrosis, cartilage, immature bone tissue, and mature bone tissue rates.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 19 (IBM, Somers, NY, USA). Descriptive analyses were conducted to provide general group specifications. Continuous variable data were presented as mean and standard deviation. Differences between groups were assessed by one-way analysis of variance. Multi-comparisons were performed between variables using post hoc and Tukey honestly significant difference tests. A *P*-value <0.05 was considered statistically significant.

Results

In the histopathological analyses performed, a significant difference was observed between the groups (Table 2) (Figure 4).

When groups were evaluated mutually to determine histological differences between groups, the histopathological bone healing in Group 3 was significantly better than Group 2 ($P<0.05$), and that of Group 4 was significantly better than Group 1 ($P<0.05$; Table 3).

Table 2: Histological grade distribution by groups

Grade	Groups				Total	*P*-value
	Group 1	Group 2	Group 3	Group 4		
2	1(100)(10)	0(0)(0)	0(0)(0)	0(0)(0)	1(100)(2,6)	0.018
3	1(100)(10)	0(0)(0)	0(0)(0)	0(0)(0)	1(100)(2.6)	
4	0(0)(0)	0(0)(0)	1(100)(10)	0(0)(0)	1(100)(2.6)	
5	3(60)(30)	2(40)(25)	0(0)(0)	0(0)(0)	5(100)(12.8)	
6	2(33.3)(20)	0(0)(0)	4(66.7)(40)	0(0)(0)	6(100)(15.4)	
7	3(18.8)(30)	6(37.5)(75)	3(18.8)(30)	4(25)(36.4)	16(100)(41)	
8	0(0)(0)	0(0)(0)	2(50)(20)	2(50)(18.2)	4(100)(10.3)	
9	0(0)(0)	0(0)(0)	0(0)(0)	4(100)(36.4)	4(100)(10.3)	
10	0(0)(0)	0(0)(0)	0(0)(0)	1(100)(9.1)	1(100)(2.6)	
Total	10(25.6)(100)	8(20.5)(100)	10(25.6)(100)	11(28.2)(100)	39(100)(100)	

Data were presented as n (Row%) (Column%). Chi-square test was used.

Figure 4: Histopathological views of fracture healing according to Huddlestone Classification A) Group 4 (HE, X20) B): Group 3 (HE, X20) C) Group 3 (HE, X20) *: lamellar bone union tissue

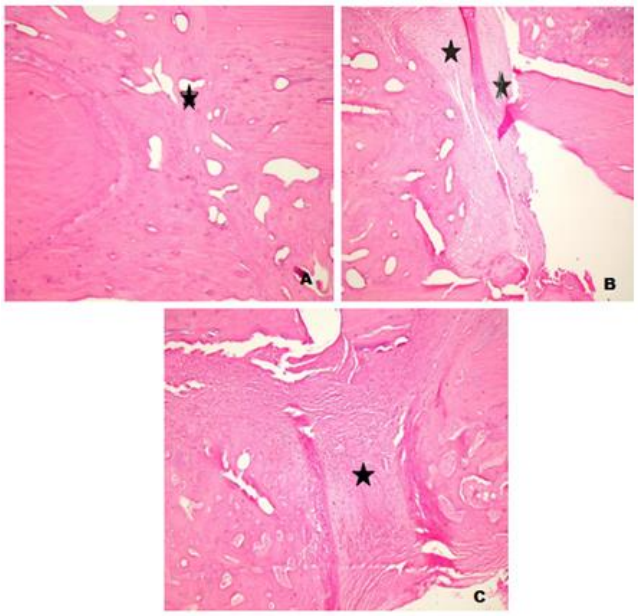


Table 3: Distribution in Comparison Bone Healing Histological Levels of Groups

	Group 1	Group2	Group 3	Group 4
Group 1		0.283	0.193	**0.049**
Group 2			**0.042**	0.057
Group 3				0.072
Group 4				

No side effects were observed after intraperitoneal injection of edaravone according to the above-mentioned criteria.

Four animals died during the experiment. Considering the distribution of dead animals by groups, three animals were in the fracture and ischemia group, one animal was in the isolated fracture group and one animal was in the fracture + edaravone group. Therefore, deaths were not thought to be related to drug administration.

Radiological union was observed in all groups. When bone formation in the fracture site was evaluated according to the Lane and Sandhu radiological scoring system, no significant differences were observed between the groups.

Based on the analysis of biomechanical data, no significant differences were observed between the groups once the control group, comprising rats with a robust tibia, was excluded (Table 4).

Table 4: Correlation between quantitative variables by groups

Group			Breaking force	Hardness (N/mm)	Radiology
Control Group 5	Breaking force	r	1	-0,516	.[a]
		p		0,104	.
		n	11	11	0
	Hardness (N/mm)	r	-0.516	1	.[a]
		p	0.104		.
		n	11	11	0
	Radiology	r	.[a]	.[a]	.[a]
		p	.	.	
		n	0	0	0
Group 1	Breaking force	r	1	0.697*	0.268
		p		**0.025**	0.455
		n	10	10	10
	Hardness (N/mm)	r	0.697*	1	0.296
		p	**0.025**		0.407
		N	10	10	10
	Radiology	r	0.268	0.296	1
		p	0.455	0.407	
		n	10	10	10
Group 2	Breaking force	r	1	0.429	-0.058
		p		0.289	0.891
		n	8	8	8
	Hardness (N/mm)	r	0.429	1	0.217
		p	0.289		0.606
		n	8	8	8
	Radiology	r	-0.058	0.217	1
		p	0.891	0.606	
		n	8	8	8
Group 3	Breaking force	r	1	-0.134	0.112
		p		0.712	0.757
		n	10	10	10
	Hardness (N/mm)	r	-0.134	1	-0.634*
		p	0.712		0.049
		n	10	10	10
	Radiology	r	0.112	-0.634*	1
		p	0.757	**0.049**	
		n	10	10	10
Group 4	Breaking force	r	1	-0.236	0.298
		p		0.486	0.373
		n	11	11	11
	Hardness (N/mm)	r	-0.236	1	-0.336
		p	0.486		0.313
		n	11	11	11
	Radiology	r	0.298	-0.336	1
		p	0.373	0.313	
		n	11	11	11

Discussion

The main finding of our study is that the use of edaravone in the rat fracture model contributes to healing at the histopathological level. This effect occurs both in the presence and absence of ischemia.

Ischemia has potential side effects for fracture healing. After a high energy-fracture, vascular injury, or compartment syndrome, reperfusion generally follows this process. Ischemia negatively affects fracture healing [6-8]. The ischemic period is a well-known part of fracture healing process, after which arterial vasodilation and reperfusion occurs. In our study, edaravone may have affected fracture healing by countering the negative effects of FORs. The fact that this effect was observed in the non-ischemia groups may be due to local ischemia in fracture hematoma at the histopathological level. However, since we did not measure FORs at the fracture hematoma level or in the systemic circulation, it is not possible to reach this conclusion with the results of our study.

Ischemia causes tissue damage, whereas reperfusion causes reperfusion damage, which is a pathophysiological incident [9]. Reperfusion promotes the accumulation of neutrophils in tissues and increases the activity of xanthine oxidase in endothelial cells, thereby accelerating FOR production. Extreme levels of FORs negatively affect fracture metabolism. Cells are exposed to oxidative stress, which results in tissue damage [10, 11]. In the ischemia-reperfusion model of Çetinus et

al. [7], levels of FORs in tibia fractures were higher during the inflammation period of the bone union process.

Several studies have demonstrated that FOR levels increase after ischemia-reperfusion, adversely effecting fracture healing. In our study, histopathological differences, especially between Groups 2 and 3, were observed due to the elimination of the negative effects of FORs. However, the significant differences in histopathological fracture healing between Groups 1-4 without ischemia suggested that the effects of edaravone on fracture healing should be independent of ischemia-reperfusion injury.

Antioxidant molecules help to prevent the negative effects of FORs on bone and fracture metabolism. We used edaravone, which has been used in Japan since 2001 for the treatment of ischemic stroke, as it exhibits FOR scavenging [12-14]. We observed differences at histopathological level, independent of ischemia. Our study differs from similar studies by the fact that biomechanical or radiological evaluation results were similar, but histopathological evaluation results were not.

Edaravone is a molecule that has previously shown efficacy in many animal models. The studies that have been carried out primarily consist of organ damage and ischemic damage models. These animal studies are associated with ischemic stroke [15], myocardial ischemia [16], lung injury [17], and atherosclerosis [18] animal models. To the best of our knowledge, ours is the first animal study to investigate the effects of edaravone on fracture healing.

Edaravone inhibits FORs by inhibiting dependent and independent lipid peroxidation [19]. The side effects of edaravone on the muscles and skeletal system have been previously studied, including the protective effects in osteoarthritis and in skeletal muscles, preventive effects in ischemia-reperfusion damage and muscle atrophy, and positive effects in osteonecrosis [20-23].

Our study suggests that the effects of edaravone may not only be related to ischemia-reperfusion injury but may also have different cytoprotective effects.

Ischemia exerts negative effects on fracture healing in complicated bone fractures following reperfusion. The group exposed to edaravone after reperfusion had better fracture healing in terms of histopathological outcomes. Therefore, edaravone could be beneficial for fractures involving ischemia-reperfusion incidents. However, edaravone may be effective on fracture healing not complicated by ischemia.

Limitations

Our study has several limitations. First limitation was lack of measurements for tissue necrosis scales and FOR levels and the fact that the rats were euthanized at the 8th week of the study period instead of at two different times. The second limitation was lack of standardized ischemia severity assessment. Although we clamped the femoral artery with the same tool for 5 hours in all ischemia applications, differences in the ischemia responses in the tissues may have occurred. In our model of macroscopic interruption of the major arterial circulation, we hope that these differences did not cause any significant changes. Third limitation was an insufficient number of study subjects. It may have been possible to determine significant differences between groups with the inclusion of more rats in the study.

Conclusions

Negative effects of ischemia on fractures complicated by vascular injury and compartment syndrome may be overcome by edaravone. The use of these kinds of molecular scavengers can be extended by conducting larger studies that examine the effects on fracture healing in isolated fractures.

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Effect of labiaplasty on women's sexual and psychological life

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Ethics Committee Approval
İstanbul Gelişim University, 20-05-2020, 2020-14-15. Written informed consent was obtained from all participants and those whose images were presented in the study.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The number of labiaplasties has increased in recent years, in accordance with the growing importance given to the female body. The main factors for labial surgery include emotional and physical discomfort, aesthetic concerns, and sexual disorders.
Methods: We designed this prospective cross-sectional study to evaluate women's sexual function and quality of life before and 3 months after labiaplasty. A total of thirty-four women with labium minus hypertrophy (LMH) and asymmetry were included in the study. Women with malignancies, psychological disorders, other gynecologic disorders, menopausal status, vulvar disorders, a history of vaginal or labial surgery, and those who were sexually inactive were excluded. We evaluated the Female Sexual Function Index (FSFI) and Beck Depression Inventory (BDI) scores before and 3 months after labiaplasty.
Results: The mean total FSFI score of the patients after the surgery (24.91 (2.74)) was higher than before the surgery (24.14 (3.06)) (P=0.001). Postoperative desire, arousal, lubrication, orgasm, satisfaction, and pain scores of the patients in FSFI were significantly higher (P=0.023, P=0.026, P=0.015, P=0.05, P=0.022 and P=0,004, respectively), while mean BDI scores were significantly lower (8.79 (4.51) vs. 10.90 (4.90)), P=0.037).
Conclusion: Labiaplasty is a comfortable, safe method with a short recovery period, satisfactory aesthetic results, and low complication rates. By using the radiofrequency with the trimming method, the sexual and quality of lives of the patients improve, along with their self-confidence and body image.

Keywords: Labiaplasty, Sexual life, FSFI, BDI

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Introduction

The number of labiaplasties has increased in recent years in accordance with the growing importance given to the female body [1]. Genital aesthetic procedures have become important for women's sexual, psychological, and emotional lives [2]. The main indications for labial surgery are emotional, physical discomfort, aesthetic concerns, and sexual disorders. Labium minus hypertrophy causes problems during physical exercise, discomfort in tight clothes, and pain during sexual intercourse. Although the etiology remains incompletely elucidated, pregnancies, vaginal births, chronic irritation, and increased elasticity of the labial skin with age are among the reasons. We know that labiaplasty procedures positively affect women's sexual and quality of lives and increase their self-confidence. Hence, we designed this study to evaluate patients before and 3 months after labiaplasty with Female Sexual Function Index (FSFI) and Beck Depression Inventory (BDI). The purpose of our study is to assess how labiaplasty affects women sexually and psychologically.

Materials and methods

This single-center, prospective cross-sectional study was approved by İstanbul Gelişim University Ethics Committee (Date: 20-05-2020; No:2020-14-15) and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants. A total of thirty-four sexually active women between the ages of 18 and 50 years who had grade 2-3-4 labium minus hypertrophy and were admitted to the gynecology unit with labium minus hypertrophy (LMH) and asymmetry were included in the study. Labium minus hypertrophy was assessed according to Franco's classification, as follows: <2 cm protrusion of labium minus over labium majus indicates grade 1, 2-4 cm protrusion indicates grade 2, 4-6 cm protrusion indicates grade 3, and >6cm protrusion indicates grade 4 labium minus hypertrophy. We excluded women with malignancies, psychological disorders, other gynecologic disorders, menopausal status, vulvar disorders, a history of vaginal or labial surgery, and those who were sexually inactive. The FSFI and BDI scores of patients before and 3 months after labiaplasty were evaluated.

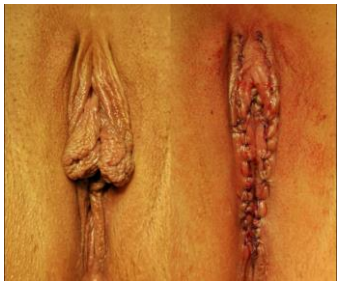
FSFI is a self-report inventory consisting of nineteen questions which is used for assessing female sexual function in six domains: Desire, arousal, lubrication, orgasm, satisfaction, pain. The questions comprise four items for arousal and lubrication, three items for orgasm, satisfaction, pain, and two items for desire. Items are scored on a five-point scale. BDI is a 21-question self-report multiple-choice inventory designed to assess the severity of depression, in which items are scored between 0-3 points.

To prevent bias, all patients who met the criteria within the designated period were included in the study group. None of the patients withdrew, which eliminated withdrawal bias. The researchers did not see the test results of the patients, which were instantly sent to the statistics team. Only validated and standardized scales were used to reduce the risk of bias.

Surgery technique

General anesthesia was administered before the procedure. All patients were operated in the lithotomy position by the same surgeon. Preoperative photographs were taken. The incision lines were marked on the internal aspect of the right labium minus, which was placed on the left labium minus to mirror the line. Then, the external aspects of the labium minora were marked. With a radiofrequency needle electrode (Surgitron, Ellman®, USA) using 4.0 MHz radio wave, an incision was made at an angle of 45º in the sagittal plane on the inner and outer surfaces of labium minora, and the hypertrophied tissue was removed in the form of an apple slice. After a wedge-shaped piece was removed from the labium minora longitudinally, the remaining two surfaces of the labium were sutured together with 5/0 rapid absorbable vicryl sutures. Radiofrequency incisions preserve the slim form of the labium and achieve tissue hemostasis. Patients were discharged on the same day. Follow-up appointments were scheduled after 7 days, 1 and 3 months. The postoperative FSFI and BDI tests were administered, and photographs were taken at the 3-month visit (Figure 1).

Figure 1: Grade 3 labium minus hypertrophy in a 35-year-old woman (before and after surgery, Informed consent for the photograph was obtained from the patient).



Statistical analysis

The power of the study and sample size were calculated with G Power 3.1.9.4 power based on the data of a reference study with FSFI and BDI scores [3]. The calculated sample size was thirty-two. We recruited thirty-four participants, which yielded a power of 95% with a type-1 error of 5%. The clinical features of the group were analyzed with the Statistical Package for Social Sciences (SPSS) for Windows, version 22 (SPSS Inc. IL, USA). The normality of data distribution was evaluated with the Kolmogorov-Smirnov test. Reliabilities of the FSFI and BDI tests were calculated with Cronbach's Alpha test. Data were presented as mean (SD) for continuous variables. The differences between the groups were analyzed with the paired t-test for normally distributed variables, and Mann Whitney U test for non-normally distributed variables. A *P* value of <0.05 was considered statistically significant.

Results

The mean age of the participants was 30.7 (7.68) years (Range: 18-50 years). Among the patients, sixteen (47.05%) were single. Half of the patients were nulligravid. Forty-one percent had graduated from university. Fifteen patients (44.1%) suffered from aesthetic concerns, 20.5 % (n=7) from dyspareunia, 11.7% (n=4) from reduced sexual pleasure, 5.88% (n=2) from poor hygiene, and 17.6% (n=6) from emotional discomfort (Table 1).

Table 2 shows the mean FSFI and BDI subscale scores. Postoperatively, the mean FSFI scores of the patients were significantly higher (24.91 (2.74) vs. 24.14 (3.06), *P*=0.001), while mean BDI scores were significantly lower (8.79 (4.51) vs. 10.90 (4.90), *P*=0.037) compared to the preoperative period. In terms of subscales, FSFI desire, arousal, lubrication, orgasm, satisfaction, and pain scores of the patients were all significantly

higher 3 months after surgery (*P*=0.023, *P*=0.026, *P*=0.015, *P*=0.05, *P*=0.022 and *P*=0,004, respectively).

Hematoma was observed in only one patient after the surgery, which was successfully managed with cold compression. The satisfaction rate of the patients was 93.75 % (30/32).

Table 1: Demographic characteristics of patients

		(n=34)
Age		30.7 (7.68)
Parity	0	17 (50%)
	1	7 (20.58%)
	2	6 (17.64%)
	≥3	4 (11.76%)
Education	Elementary School	2 (5.88%)
	Secondary School	5 (14.70%)
	High School	7 (20.58%)
	University	14 (41.17%)
	Post-Graduate	4 (11.76%)
	Doctorate	2 (5.88%)
Patient complaints	Aesthetic concerns	15 (44.11%)
	Dyspareunia	7 (20.58%)
	Emotional discomfort	6 (17.64%)
	Reduced sexual pleasure	4 (11.76%)
	Poor hygiene	2 (5.88%)

Table 2: Mean FSFI with subscale scores and BDI scores

	Before surgery	After surgery	*P*-value
Desire	3.59 (0.77)	3.76 (0.81)	0.023
Arousal	4.32 (0.63)	4.45 (0.52)	0.026
Lubrication	4.3 (0.51)	4.44 (0.48)	0.015
Orgasm	4.23 (1.06)	4.34 (0.98)	0.005
Satisfaction	4.48 (0.89)	4.6 (0.8)	0.022
Pain	3.2 (1,24)	3.3 (1.24)	0.004
FSFI total score	24.14 (3.06)	24.91 (2.74)	0.001
BDI total score	10.90 (4.90)	8.79 (4.51)	0,037

Discussion

In the recent years, societal norms, evolving concept of beauty, and social media have affected women's awareness of their own bodies. Labiaplasty procedures have increased by 29.7% between 2015-2019 [4]. This is a prospective study that aimed to evaluate the sexual and psychological effects of labiaplasty on females.

Enlarged labia minora can cause unaesthetic appearance, irritation, difficulty wearing tight clothes, hygienic and sexual problems. A classification system was described by Franco in 1993 to determine the severity of labial hypertrophy in four stages [5]. A hypertrophic tissue of less than 2 cm is considered Stage I, between 2-4 cm, Stage II, between 4-6 cm, Stage III and that more than 6 cm is considered stage IV. We used Franco classification and included patients with grade 2-3-4 labial hypertrophy in our study. Labiaplasty procedure was defined by Hodgkinson in 1983 [6]. Many labiaplasty techniques have been described in the following years, such as those by Giraldo and Munhoz [7, 8]. The main methods for of labiaplasty include trimming technique and wedge excision. The trimming technique has a short operation time and can create light-colored labia minors. The disadvantages are longitudinal scar and irregular labial shapes. The wedge technique's advantage is that the natural labial tissue of patients is used, and its disadvantages include longer operation time, wound dehiscence, and dark-colored labia minora [8]. All methods can be performed by scissors, knife radiofrequency, and laser. The laser has been used in gynecology for over 40 years [9]. Many studies used CO2 laser and radiofrequency for labiaplasty and observed very few complications [9, 10]. The advantages of radiofrequency include limited thermal damage of only one micron and accelerated wound healing. Smarrito et al. [11] observed hematomas in only 3 of 231 patients, while 4.71% of patients had dehiscence. In another study, Smarrito observed only five patients with wound dehiscence, and no hematomas, necrosis, or sexual dysfunction after surgery [12]. Alter et al. reported 4% complications and 93% improved self-esteem [13]. Pardo et al. described only a few complications of laser with hemostatic advantages [14]. We used the trim technique with radiofrequency for labiaplasty in this study and observed a 3.12% complication rate. We managed it with cold compression and the patient did not require a revision.

Labial minus hypertrophy can be associated with sexual problems, impairment of couple relations, and lower self-esteem. In this study, we investigated the differences in patient's sexual and psychological lives. The impact of labiaplasty on sexual life was assessed with Turkish FSFI which was developed by Aygin and Aslan [15]. The psychological effect was evaluated with the Turkish BDI questionnaire developed by Ulusoy [16]. FSFI is a self-report questionnaire of 19 items that comprises six domains: Satisfaction, desire, arousal, lubrication, pain, and orgasm. BDI is a 21-question self-report multiple-choice inventory. Items are scored between 0-3 points and designed to assess the depth of depression. According to a meta-analysis, the prevalence of female sexual dysfunction in premenopausal women is 40.9% [17]. Sir et al. [18] compared sexual dysfunction rates among women with labium minor hypertrophy (LMH) who did not undergo labiaplasty and healthy individuals and found that the LMH group had lower sexual function scores (24.18 (3.24) vs. 27.53 (4.43)). FSFI subsets of the LMH group, such as lubrication, orgasm, satisfaction, and pain, were significantly lower. They found that 86 percent of LMH patients had sexual problems. Our study's primary finding is that the lives of women who had labiaplasty improved both sexually and psychologically. The mean total FSFI score of the patients increased and BDI scores decreased significantly postoperatively. All FSFI subscales scores, especially pain and orgasm, showed statistically significant improvements after surgery. We can explain this with repair of functional discomfort with radiofrequency and improvement of emotional discomfort. We believe that improvement of sexual functions was also due to increased self-confidence, along with the physiological effect of surgery.

The strengths of the study include the fact that we could compare variables before and after the surgery, its retrospective nature, the performance of the operations by a single surgeon and the use of Turkish-adapted and validated scoring systems to assess the difference.

One limitation of our study is that some patients had sexual disorders before the surgery, so postoperative improvement may be expected. We can design another study to examine the change in sexual functions of patients who did not have sexual problems, who were operated on solely for aesthetic concern. Another limitation of the study is the short follow-up time of the cases. Also, all women included in the study were heterosexuals, we have not assessed lesbian couples. Among all, 77.8% of the patients participating in the study are high school graduates and above, hence, these women have a higher self-awareness. If we had evaluated these patients together with those with low education levels, we would have obtained different results. More comparative studies are needed in patients without sexual dysfunction and who are operated due to aesthetic concerns only.

Conclusion

Labiaplasty is a comfortable, safe method with a short recovery period, satisfactory aesthetic results, and low complication rates. With radiofrequency at trimming technique, patients' sexual functions and overall quality of lives improved, along with their body image and self-confidence.

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Investigating the relationship of serum levels of afamin and interleukin-10 with insulin resistance in infertile women with polycystic ovary syndrome

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Ethics Committee Approval
The study was conducted with the permission of the Research Ethics Committee Istanbul Medeniyet University Goztepe Training and Research Hospital (Permission granted/CAAE number: 02.12.2020, Decision no: 2020/0703). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The prevalence of Polycystic Ovary Syndrome (PCOS) is between 6-10% globally, and more than 50% of patients with PCOS are obese. The development of insulin resistance (IR) and hyperinsulinemia due to overweight can contribute to this syndrome's clinical complications. This study aimed to investigate the relationship between serum levels of afamin and Interleukin-10 (IL-10) with IR in infertile women with PCOS.

Methods: Eighty-eight participants between the ages of 18 and 36 years, with at least one year of unsuccessful attempts to have children were included in this prospective case-control study. The PCOS and healthy controls were divided into two groups based on IR. Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), Prolactin, Thyroid Stimulating Hormone (TSH), Free T4, Anti-Mullerian Hormone (AMH), Hemogram, total cholesterol, LDL, HDL, Triglyceride, fasting blood glucose, fasting insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), afamin, IL-10 values were measured.

Results: The body mass indexes (BMIs) of the groups were significantly different (P<0.001); and the highest BMI was observed in the PCOS group with IR (HOMA-IR ≥2.5). Fasting insulin was significantly higher in the two groups with IR: 15.3 (6.09) in PCOS patients and 12.7 (2.8) in patients without PCOS (P=0.02). There was a weak positive correlation between BMI and Afamin (P=0.005), a strong negative correlation between BMI and IL-10 (P<0.001), a moderate negative correlation between Waist Hip Ratio (WHR) and IL-10 (P<0.001), a weak negative correlation between fasting insulin and IL-10 (P=0.001), and a weak positive correlation between monocyte and IL-10 (P=0.03).

Conclusion: Our results showed an increase in Afamin and a decrease of interleukin-10 in infertile women with polycystic ovary syndrome and insulin resistance.

Keywords: Polycystic ovary syndrome, Insulin resistance, Afamin, IL-10

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Introduction

Polycystic ovary syndrome (PCOS) manifests in women of reproductive age and is the most important cause of infertility due to lack of ovulation [1]. It begins after puberty, and the maximum age of onset is 20 to 40 years [2]. The prevalence of this syndrome is about 6-10% [4]. More than 50% of patients with PCOS are obese [3, 4]. Body fat usually accumulates centrally and an increase in the waist-to-hip circumference ratio (WHR) increases the risk of cardiovascular diseases and diabetes mellitus (DM) [1-3].

Although obesity is not an essential feature or an inherent defect of PCOS [5], the development of hyperinsulinemia and Insulin Resistance (IR) due to overweight can contribute to the clinical complications of this syndrome [5-7]. About 50-70% of women with PCOS have IR to some degree [7, 8], which may result from obesity or associated with hyperandrogenism [9]. It has been suggested that IR can also play a significant role in the pathogenesis of PCOS [7-9].

Studies show that Afamin increase is correlated with metabolic syndrome in PCOS patients [10-12]. Afamin was first identified in 1994 as the fourth member of the human albumin gene family, including vitamin D binding protein, alpha-fetoprotein, and human serum albumin [11]. As an 87 kDa human plasma glycoprotein, afamin has 55% amino acid sequence similarity to albumin and includes 15% carbohydrate [12]. Studies have shown that elevated levels of the human afamin gene increase the body weight, glucose, and fat concentration in the bloodstream [13-15]. Some other studies have also shown an association between afamin, IR and metabolic syndrome [16-18].

Chronic inflammation in the body can be considered a stimulus for IR and type 2 DM [19]. Studies have shown that various adipose tissue hormones, such as interleukin-10 (IL-10), can significantly inhibit the expression and synthesis of proinflammatory cytokines [19-21]. IL-10 is an essential anti-inflammatory cytokine that can limit the inflammatory response caused by tissue damage [20]. IL-10 also prevents the exacerbation of inflammation by reducing inflammatory responses and suppresses the production of cytokines such as interleukin-6 and interleukin-1 [20, 21]. Studies have shown that exogenous use of IL-10 prevent IR due to fat accumulation [21, 22], and decreased serum levels of IL-10 have been associated with increased prevalence of metabolic syndrome and type 2 DM [23].

Although the role of afamin and IL-10 in IR and inflammation reduction has been studied separately, there is still limited and conflicting information about the role of PCOS on anti-inflammatory adipokines such as IL-10 and their mechanism of action. This study aimed to investigate the relationship between serum levels of afamin and IL-10 with IR in infertile women with PCOS.

Materials and methods

This prospective observational study was conducted on 88 patients admitted to Istanbul Medeniyet University Goztepe Training and Research Hospital Gynecology and Obstetrics Clinic and Private Medistate Kavacık Hospital Gynecology and Reproductive Medicine Clinic between December 2020 and February 2021. Patients underwent routine IVF clinic examinations, and no special procedures were performed in the examination, treatment, and follow-up processes.

The study was performed according to the regulations established by the Clinical Research and Ethics Committee and the Helsinki Declaration of the World Medical Association. The study was conducted with the permission of the Research Ethics Committee of Istanbul Medeniyet University Goztepe Training and Research Hospital (Permission granted/CAAE number: 02.12.2020, Decision no: 2020/0703). All patients signed informed consents.

The criteria for inclusion in the study were consenting to participate in the study, being aged between 18 and 36 years, and having unsuccessfully attempted conceiving for at least one year. Those who disagreed to participate, those with DM, endocrinopathy, or hypertension, patients who smoked, or used drugs that altered the metabolism of insulin, lipids, and hormones up to three months before the study, patients with a deficiency of vitamins B6 and B12 and those taking vitamin supplements up to 6 months before the study were excluded.

Participants were divided into study and control groups based on PCOS diagnosis. The PCOS group consisted of women aged 18-36 years, who were referred to an infertility clinic during the study period and diagnosed with PCOS according to the 2003 Rotterdam Consensus criteria [24]. Women referred to our clinic for infertility during the study period and not diagnosed with PCOS were included in the control group. The PCOS and control group participants were divided into two groups based on IR, which was identified with The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index ≥2.5. Sample size calculation with G*Power 3.1 and assessment of the mean of two groups with ANOVA test revealed that with an effect size of 35%, df of 4, power of 70% and 0.05 type 1 error, at least 16 patients were required in each group. Therefore, twenty-two patients were included in each group. The control groups were divided into two groups as those with and without IR so that the exact effect of IR could be measured in patients with PCOS and to minimize the potential bias. The final groups were as follows: 1) PCOS non-IR (HOMA-IR <2.5), 2) PCOS+IR (HOMA-IR ≥2.5), 3) Control+non-IR (HOMA-IR <2.5), 4) Control+IR (HOMA-IR ≥2.5).

Body Mass Index (kg/m^2) was calculated by measuring the height (m) and body weight (kg) obtained in the routine examination at the first visit. Waist circumference, hip circumference, and WHR were noted.

We examined the patients on the third day of their instrumentation after the examination. Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), Prolactin, Thyroid Stimulating Hormone (TSH), Free T4, Anti-Mullerian Hormone (AMH), Hemogram, total cholesterol, LDL, HDL, Triglyceride, fasting blood glucose, fasting insulin, and HOMA-IR values were measured.

Serum samples were obtained by centrifuging venous blood samples for 10 minutes at 4000 rpm after a 30-minute coagulation period. Serum samples collected for biochemical and hormonal evaluation were analyzed in Medistate Kavacık Hospital's biochemistry and hormone laboratory. Afamin and IL-10 measurement were performed with Human AFM Antibody

Enzyme-Linked Immunosorbent (ELISA) and IL-10 ELISA Kits (Reader Biotek ELx800). The plates provided by the manufacturer were pre-coated with Human AFM/IL-10 antibody. AFM/IL-10 in the samples were bound to antibodies coated on the wells. The biotinylated Human AFM/IL-10 antibody was then added and bound to AFM/IL-10 in the sample. Streptavidin-HRP was added and bound to the Biotinylated AFM/IL-10 antibody. In between all steps and after the final incubation, the plates were washed. After final incubation, the substrate solution was added, which caused a color change proportional to the amount of Human AFM/IL-10 in the initial sample. The reaction was terminated by the addition of acid-stopping solution, and absorbance evaluation was made at 450 nm. Quantification was performed by calculation of concentrations from absorbance values according to the slope of the calibration curve obtained with the respective standards included in each ELISA kit.

Statistical analysis

Data were analyzed using SPSS for Windows, Version 23.0 (Armonk, NY: IBM Corp). A two-way ANOVA test was used to evaluate the significant difference between the studied variables in the PCOS/Control groups with different IR. The non-normal study variables were converted to normal by standardization, after which the appropriate test was used. The correlation of variables with Afamin and IL-10 was examined with the Pearson correlation test. For all tests, a *P*-value <0.05 was considered statistically significant.

Results

The mean age and BMI of all participants were 26.8 (5.1) years (range: 18-36 years) and 25.3 (4.3) kg/m^2 (range: 18.6 to 41.1 kg/m^2), respectively. The BMI, WHR, AMH and LG values significantly differed between the groups, which were all highest in PCOS patients with IR (HOMA-IR ≥2.5) (*P*<0.001 for all).

As expected, fasting insulin was significantly higher in the two groups with IR (*P*=0.02). The Hematocrit and mean corpuscular volume (MCV) values significantly differed between the groups (*p*=0.02 and *p*=0.03, respectively), both being highest in the PCOS-IR group. The complete two-way ANOVA results for all groups are given in Table 1.

The results of Pearson correlation for Afamin and IL-10 variables are shown in Table 2. Afamin weakly positively correlated with BMI (*P*=0.005), and Hematocrit (*P*=0.001), moderately positively correlated with AMH (*P*<0.001), LH (*P*<0.001), and fasting insulin (*P*=0.001), weakly positively correlated with fasting blood glucose (*P*=0.02), and LDL (*P*=0.002), and weakly negatively correlated with leukocyte (*P*=0.003), and neutrophil count (*P*=0.002).

IL-10 was strongly negatively correlated with BMI (*P*<0.001), moderately negatively correlated with waist circumference (*P*<0.001), hip circumference (*P*<0.001), WHR (*P*<0.001), AMH (*P*<0.001), and LH (*P*<0.001), weakly negatively correlated with fasting insulin (*P*=0.001), MPV (*P*=0.04), and MCV (*P*=0.05), weakly positively correlated with monocyte count (*P*=0.03), and very weakly negatively correlated with hematocrit (*P*=0.05).

Table 1: Results of two-way ANOVA comparisons between the groups

	PCOS HOMA-IR <2.5	PCOS HOMA-IR ≥2.5	Controls HOMA-IR <2.5	Controls HOMA-IR ≥25	*P*-value
Afamin	178.7(46.6)	231.7(30.9)	75.9(17.6)	113.7(34.9)	0.2
IL-10	679.8(119.9)	181.4(52.09)	291.9(85.3)	487.5(116.9)	0.000
BMI	21.9(2.06)	30.2(4.3)	25.1(1.9)	23.7(2.4)	0.000
Waist circumference	75.5(9.2)	97(13.2)	87.9(12.8)	75.09(5.3)	0.000
Hip Circumference	95.7(6.1)	111.7(11.16)	105.5(11.01)	97.9(5.4)	0.000
WAIST HIP RATIO (WHR)	0.77(0.06)	0.8(0.1)	0.8(0.07)	0.7(0.05)	0.000
Age	26.5(5.3)	24.5(5.2)	27.2(5.04)	26(5.1)	0.3
AMH	1.5(0.3)	2.5(0.6)	1.6(0.5)	1.3(0.3)	0.000
FSH	6.04(1.8)	5.8(1.2)	5.5(1.6)	6.3(1.6)	0.1
LH	4.7(1.9)	9.8(4.04)	4.6(1.7)	5.3(1.8)	0.000
Estradiol	42.9(9.05)	43.5(19.7)	44.7(18.8)	44.1(20.3)	0.8
Free T4	1.09(0.2)	1.07(0.1)	1.6(2.1)	1.8(3.2)	0.8
TSH	2.02(0.7)	2(1.1)	1.8(1.02)	2.09(1.2)	0.6
Prolactin	15.8(5.5)	15.3(5.9)	16.8(5)	15.05(7.4)	0.6
Fasting blood glucose	91.7(8.1)	96.3(8.9)	85.8(5.4)	96.1(8.9)	0.09
Fasting insulin	6.4(1.9)	15.3(6.09)	7.4(1.5)	12.7(2.8)	0.02
Total Cholesterol	200.7(28.8)	188.2(40.3)	218.9(67.6)	192.8(50.5)	0.2
LDL	121.2(30.8)	124.5(31.3)	105.7(39.6)	93.3(35.7)	0.5
HDL	69.3(11.4)	60.8(15.2)	61.9(14.5)	64.5(24.8)	0.1
Triglyceride	107.7(31.2)	104.1(41.3)	114.1(67.8)	96.5(26.1)	0.4
Leukocyte	7.9(1.6)	7.8(1.8)	9.1(2.3)	9.4(2.3)	0.7
Neutrophil	4.6(1.5)	4.4(1.3)	5.6(1.6)	5.9(1.9)	0.4
Basophil	0.04(0.02)	0.1(0.3)	0.04(0.01)	0.06(0.02)	0.2
Lymphocyte	2.2(0.5)	2.3(0.7)	2.4(0.8)	2.4(0.7)	0.8
Monocyte	0.66(0.20	0.5(0.2)	0.5(0.2)	0.590.1)	0.5
Hemoglobin	13.2(2.6)	13.7(0.7)	12.8(1.2)	12.9(1.1)	0.5
Hematocrit	38.4(2.9)	41.1(2.5)	37.8(3.3)	37.7(2.7)	0.02
Platelet	242636.3 (58359.70	272240.9 (38293.6)	247409.1 (51100.8)	271181.8 (40079.2)	0.7
PCT	0.22(0.06)	0.24(0.03)	0.23(0.06)	0.23(0.1)	0.7
RDW	13.5(1.1)	12.5(1.3)	13.3(1.3)	12.8(0.8)	0.3
MPV	10.2(0.6)	9.5(0.7)	10.2(0.9)	9.9(0.7)	0.3
MCV	83.8(4.02)	86.4(3.2)	84.2(5.06)	82.8(5.3)	0.03

IL-10: Interleukin 10, BMI: Body mass index, AMH: Anti–Mullerian Hormone, FSH: Follicle stimulating hormone, LH: Luteinizing Hormone, TSH: Thyroid stimulating hormone, LDL: Low-density lipoprotein, HDL: High density lipoprotein, PCT: Procalcitonin, RDW: Red cell distribution width, MPV: Mean platelet volume, MCV: Mean corpuscular volume

Table 2: The Pearson correlation for Afamin and IL-10

	Afamin		IL10	
	Person Correlation	*P*-value	Person Correlation	*P*-value
Afamin			-0.08	0.4
IL-10	-0.08	0.4		
BMI	0.29	0.005	-0.67	0.000
Waist circumference	0.13	0.2	-0.57	0.000
Hip Circumference	0.1	0.3	-0.51	0.000
Waist Hip Ratio (WHR)	0.10	0.3	-0.47	0.000
Age	-0.02	0.8	-0.09	0.3
AMH	0.4	0.000	-0.47	0.000
FSH	0.03	0.7	0.16	0.1
LH	0.42	0.000	-0.4	0.000
Estradiol	-0.008	0.9	-0.14	0.18
Free T4	-0.06	0.5	-0.058	0.5
TSH	-0.04	0.7	0.05	0.5
Prolactin	-0.04	0.7	0.05	0.6
Fasting blood glucose	0.24	0.02	-0.05	0.6
Fasting insulin	0.35	0.001	-0.34	0.001
Total Cholesterol	-0.17	0.1	0.02	0.8
LDL	0.32	0.002	-0.002	0.9
HDL	0.09	0.4	0.13	0.2
Triglyceride	-0.07	0.4	-0.08	0.4
Leukocyte	-0.31	0.003	0.001	0.9
Neutrophil	-0.33	0.002	0.02	0.8
Basophil	0.12	0.2	-0.13	0.2
Lymphocyte	-0.11	0.2	-0.045	0.6
Monocyte	0.007	0.9	0.22	0.03
Hemoglobin	0.18	0.09	0.000	0.9
Hematocrit	0.33	0.001	-0.02	0.05
Platelet	0.02	0.8	-0.12	0.2
PCT	-0.03	0.7	-0.10	0.3
RDW	-0.066	0.5	0.16	0.1
MPV	-0.16	0.10	0.21	0.04
MCV	0.16	0.1	-0.2	0.05

IL-10: Interleukin 10, BMI: Body mass index, AMH: Anti –Mullerian Hormone, FSH: Follicle stimulating hormone, LH: Luteinizing Hormone, TSH: Thyroid stimulating hormone, LDL: Low-density lipoprotein, HDL: High density lipoprotein, PCT: Procalcitonin, RDW: Red cell distribution width, MPV: Mean platelet volume, MCV: Mean corpuscular volume

The different Afamin and IL-10 values in the four groups are presented in Figures 1 and 2, respectively.

Figure 1: Afamin values in the groups

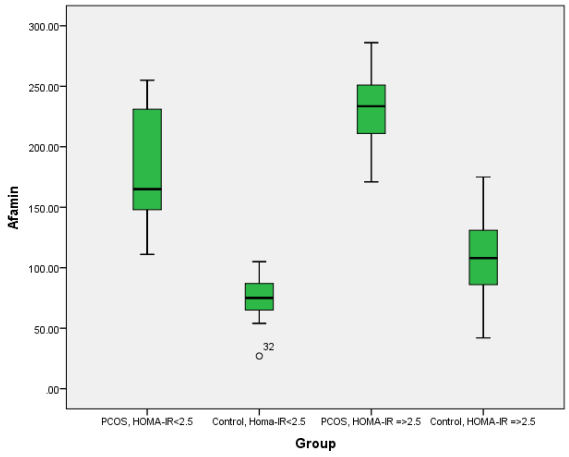
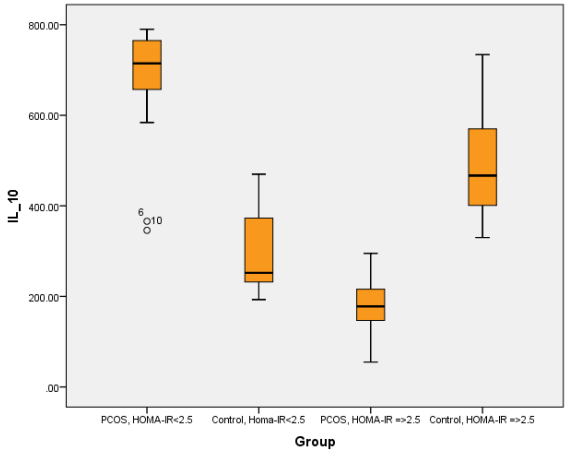


Figure 2: IL-10 values in the groups



Discussion

IR is an incomplete response of glucose to a certain amount of insulin [4]. In many of these patients, circulating insulin levels increase to neutralize this deficiency and maintain stable glucose levels. It is correlated with a wide range of manifestations, including cardiovascular disease, hypertension, type 2 DM, and lipid disorders. IR is prevalent in patients with PCOS, particularly in obese patients [2, 3]. However, the relationship between IR and variables such as afamin and IL-10 is unclear. Our results showed that afamin levels significantly increase in patients with PCOS compared to healthy groups and with increasing BMI. These results are consistent with Seeber et al. (25). In our study, afamin levels were significantly higher PCOS patients with IR compared to those without. Studies have shown that increased levels of afamin have been observed in patients with oxidative stress and inflammation [12-15]. A positive correlation between these two variables could be explained with the fact that inflammation and oxidative stress are common in PCOS patients with IR. In their study, Li et al. showed that afamin levels were significantly correlated with HOMA-IR in patients with PCOS. Because the authors found no correlation between increased afamin levels and BMI, they concluded that IR plays a major role in increasing PCOS patients' afamin levels [26].

Afamin level can be useful in IR-related tests. For example, afamin may be able to determine the need for an oral glucose tolerance test (OGTT), which is expensive and time-consuming. However, since the replacement of OGTT-related biomarkers is beyond the scope of this study, these results can only be interpreted as preliminary findings.

Studies have shown that PCOS is associated with hyperinsulinemia and oxidative stress [27-29]. Since afamin is known as an E-binding protein [15], and vitamin E relates to the non-enzymatic antioxidants group, afamin may be a marker of vitamin E-related oxidative stress. Therefore, future studies are recommended to evaluate the oxidative stress status in PCOS patients and its relationship with afamin.

In this study, the results showed that the amount of IL-10 in the groups with IR was significantly lower than in those without IR. These results are consistent with previous findings [30-33]. IL-10 is an anti-inflammatory cytokine that is found less in overweight individuals [19, 20]. Our results also found a significant negative correlation between WHR and IL-10, indicating a decrease in IL-10 in overweight individuals. IR is one of the most common features of metabolic disorders such as diabetes and obesity [1, 2]. Although the relationship between IR and obesity is widely accepted, its mechanisms remain complex and controversial.

IR is common in patients with PCOS, especially obese patients [1-4]. Our study results showed that in patients with IR and obesity, the greatest decrease is observed in IL-10. These findings are consistent with the results of previous studies [20-23].

Obesity has a prevalence of more than 50% in PCOS patients [6]. Although obesity is not an integral or inherent complication of PCOS [7, 8], the development of IR and hyperinsulinemia due to overweight can contribute to the clinical complications of this syndrome [5]. About 50-70% of women with PCOS have some degree of IR [10], which may result from obesity or independently, and is associated with hyperandrogenism [13]. It has been suggested that IR can also play a leading role in the pathogenesis of this disease [9].

The present study observed that the mean HOMA-IR was significantly higher among PCOS patients compared to the healthy group, consistent with various other studies [34-37]. Contrarily, some studies showed this difference only in obese women with PCOS [38, 39]. This may be because of the effect of obesity on IR, independent of PCOS.

In this study, serum IL-10 levels were significantly lower in PCOS patients than in healthy women. Panidis et al. also observed a significant difference between serum IL-10 levels in PCOS patients and normal-weight healthy women (BMI <25) [40]. Ardawi et al. reported that IL-10 was lower in women with PCOS than in healthy women of similar weight [41]. While there was a significant difference in fasting insulin between the groups, no significant difference was observed in terms of fasting glucose. These findings were consistent with the findings of Tarkun et al., which found higher fasting insulin and similar fasting glucose levels among women with PCOS [42].

Limitations

One of the limitations of this study is the small number of samples. It is recommended that further studies be performed with a larger number of patients to investigate the different variables and the independent effect of each on IR in PCOS patients. Lack of information about the distribution of fat in the women studied is another limitation of the present study.

Therefore, a more detailed study with more variables is required to investigate changes in IL-10 and afamin levels and evaluate the effect of central fat mass on it. Whether IR results from obesity or PCOS should also be considered more carefully.

Conclusion

In this study, the effect of afamin and IL-10 on IR in patients with PCOS was investigated. Our results showed that afamin levels in PCOS patients with IR increased significantly, which could be a sign of oxidative stress, while that of IL-10 levels decreased, which can be attributed to obesity. Further studies are needed to determine the relationship between IR, obesity, and PCOS.

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Efficacy of tocilizumab treatment in COVID-19 patients with cytokine release syndrome

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Ethics Committee Approval
The study was conducted with the permission of The Medical Research Ethics Committee of the Bakirkoy Dr. Sadi Konuk Training and Research Hospital, 30/04/2020, 2020/162.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Cytokine release syndrome, a potentially life-threatening condition in SARS-CoV-2 (COVID-19) patients, plays a critical role that may lead to the prioritization of tocilizumab (TCZ) in the treatment of this disease. We aimed to present our TCZ-treated SARS-CoV-2 patients' data that might help and guide clinicians in dealing with this infectious disease in their daily practice and research.
Methods: This is a retrospective multicenter cohort study from two Turkish pandemic centers. A total of 5165 patients' data who were hospitalized due to SARS-CoV-2 pneumonia from March 16 to May 20, 2020 were screened and 72 patients treated with TCZ were included in the study. We evaluated patients' demographic data, laboratory and imaging studies, and clinical outcomes and the effect of TCZ treatment on patients' laboratory and clinical results.
Results: O_2 saturation levels significantly increased, and fever significantly decreased on the 5th day after TCZ therapy compared to before its initiation (P=0.001, P=0.010, respectively). The decrease in troponin-I, creatinine, LDH, fibrinogen, CRP, procalcitonin, CK, and ferritin levels after TCZ therapy were significant (P<0.05 for all). There was no significant difference in mortality rates with regards to CT results, duration of hospitalization, and the location of initiation of TCZ therapy (clinic vs. ICU) (P>0.05 for all). Importantly, we found a significant increase in mortality rates in patients who received azithromycin, oseltamivir, and ascorbic acid treatments compared to those who did not receive those treatments (P<0.05 for all).
Conclusion: Our results showed that TCZ treatment may improve the SpO_2 levels, fever and laboratory findings and repress further deterioration of severe SARS-CoV-2 patients. TCZ treatment can be given to the patients in non-ICU clinical beds. It is obvious that randomized controlled studies are needed to observe the efficacy of tocilizumab treatment in COVID-19 patients more clearly.

Keywords: COVID-19, tocilizumab, SARS-CoV-2, cytokine release syndrome

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak was announced by the World Health Organization (WHO) on 30 January 2020 as a public health emergency of international concern (PHEIC) and a pandemic on 11 March 2020. There have been 37,109,851 laboratory-confirmed cases and 1,070,355 deaths globally as of October 11, 2020 [1].

In its most severe form, SARS-CoV-2 (COVID-19) causes life-threatening pneumonia and acute respiratory distress syndrome, which has a mortality rate of up to 40-50 percent [2,3]. Although the mechanisms of SARS-CoV-2 induced lung injury are still being elucidated, studies showed that the cytokine release syndrome (CRS) -a.k.a. cytokine storm- contributes to the mortality of SARS-CoV-2. CRS, a potentially life-threatening condition mediated by overproduction of proinflammatory cytokines is observed in most critical patients infected with SARS-CoV-2 [4,5]. The pathophysiology of the hyperinflammation caused by SARS-CoV-2 has not been well studied, but first studies regarding the pathological alterations in the peripheral blood of these patients, which showed increased differentiation of CD4 T cells to proinflammatory CCR6 + Th17 cells, excessive activation of T cells, and high cytotoxicity of CD8 T cells, partly explain the severe immune injury in these patients [6]. This excessive and dysregulated host immune response may contribute to the development of ARDS in patients infected with SARS-CoV-2 [7, 8].

The cytokine profile in SARS-CoV-2 patients resembles Macrophage Activation Syndrome / secondary hemophagocytic lymphohistiocytosis (MAS/sHLH) and is characterized by increased serum levels of interleukin (IL)-1β, IL-2, IL-6, IL-7, IL-10, IL-18, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α [5, 9, 10].

A recent retrospective, multicenter study of 150 confirmed SARS-CoV-2 cases showed an association between mortality and elevated serum IL-6 levels of the patients. All these findings suggest that mortality might be due to SARS-CoV-2 driven severe immune injury [11]. The increased levels of proinflammatory cytokines in patients infected with SARS-CoV-2 and the relationship between mortality and hyperinflammation in these patients brought up immunosuppressive therapy. The similarity of cytokine profile of SARS-CoV-2 patients and MAS/sHLH patients and the opinion that IL-6 levels may play a critical role in these patients led to the prioritization of tocilizumab (TCZ) in the treatment of immunosuppression [12-14].

TCZ, a recombinant monoclonal antibody against the human IL-6 receptor (IL-6R), specifically binds both soluble IL-6R and membrane IL-6R, and blocks signaling pathways involving IL-6 [15]. Currently, TCZ is not approved for use by the Food and Drug Association (FDA) in patients with COVID-19-induced CRS but it is already approved for adult and pediatric patients for the treatment of CRS caused by chimeric antigen receptor (CAR) T -cells [16, 17]. It is used for rheumatoid arthritis and the studies conducted on animals regarding long- term toxicity showed it was well tolerated. Also, in other clinicopathological studies of this drug, no substantial abnormalities were detected [18, 19].

Early identification and management of the CRS are of crucial importance for patients infected with SARS-CoV-2. However, there are limited real-life data about the effect of TCZ on the inflammatory activity in newly observed SARS-CoV-2 patients [20]. In this retrospective observational study, we aimed to provide treatment-related outcomes associated with TCZ use in COVID-19 patients as well as guidance to clinicians.

Materials and methods

Study design and patients

This is a retrospective, multicenter cohort study from two pandemic state hospitals of Turkey. The study data were gathered from the records of those patients who were treated with at least a single dose of 400 mg TCZ infusion. The only available TCZ drug and form in our country is Actemra® (400 mg/20 cc flacon) (Roche Pharma [Schweiz] Ltd, B2084B21). The study flow chart was shown in Figure 1.

The Turkish Ministry of Health's Coronavirus Scientific Advisory Board recommendations were followed by the clinicians dealing with the management of SARS-CoV-2 infection at Turkish hospitals. The advised contraindications to this drug in SARS-CoV-2 infected patients were as follows: Presence of pregnancy, other active other viral infections (such as viral hepatitis, HIV), active or suspicious bacterial infection(s), having an absolute neutrophil count <500 /mm^3, platelet count <50000 /mm^3, and a history of diverticulitis. Before treatment, patients were screened and questioned for contraindications. Patients whose outcome, laboratory and/or clinical finding data could not be obtained and those younger than 18 years of age were excluded from the study. Receiving TCZ treatment between March 16 to May 20, 2020 for CRS was considered the inclusion criteria. To prevent selection bias, different researcher groups gathered and evaluated the patient data.

The Medical Research Ethics Committee of the University of Health Sciences Bakirkoy Dr. Sadi Konuk Training and Research Hospital approved the study (Approval number: 2020/162–30/04/2020). We are committed to protecting patient privacy and comply with the Helsinki Declaration.

This cross-sectional study is reported according to the STROBE statement (http://www.strobe-statement.org).

Diagnosis of CRS

CRS diagnosis was made by a consensus between the pulmonologists, rheumatologists, internal medicine, and infectious disease physicians in relevant hospitals according to The Turkish Ministry of Health's Coronavirus Scientific Advisory Board recommendations and the guideline prepared by scientific committee of both hospitals.

Treatment

All patients participating in our study received standard care according to the National Guideline for the Diagnosis and Treatment Protocol for SARS-CoV-2 Infection [21], including hydroxychloroquine (HCQ), favipiravir, azithromycin (AZT), low-molecular-weight heparin (LMWH), methylprednisolone, other symptom relievers, and oxygen therapy. Patients who were

diagnosed with CRS received 400 mg TCZ intravenously once a day for a single or two consecutive days.

Laboratory studies

Complete blood count (CBC), procalcitonin, ferritin, C reactive protein (CRP), D-dimer, activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR) and routine biochemical tests were obtained before the initiation of and 5 days after TCZ treatment. Patients whose laboratory data were not available before or after TCZ administration were considered study dropouts.

All laboratory tests were performed at the central laboratories of the hospitals. Both are accredited laboratories with standardized internal quality control and external quality assurance measures to monitor the accuracy and precision of the performed tests. All biochemical tests including alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), lipase, total bilirubin, direct bilirubin, ferritin, triglycerides (TG), D-dimer, Troponin-I, procalcitonin, CRP, creatine kinase (CK), magnesium (Mg), phosphorus (P), sodium (Na), and potassium (K) levels were determined using Beckman Coulter AU5800 clinical chemistry analyzer (Beckman Coulter, Brea, CA, USA). CBC was analyzed with ADVIA 2120i hematology autoanalyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). For coagulation assay (Fibrinogen), blood samples were collected into (0.105 mol/L) trisodium citrate- containing test tubes. The samples were centrifuged at 2000g for 15 minutes. All analytical procedures were performed on a random- access coagulation analyzer (Beijing Succeeder Technology Inc. China) and the reagents were used according to manufacturer's protocol.

Radiological evaluation

Patients were scanned with spiral computerized tomography (CT) on admission using a low-dosage, 64-slice, helical CT scanner (Somatom Somatom 64, Siemens Healthcare, Forchheim, Germany). Whole-lung CT images were evaluated and reported by at least one experienced radiologist. Radiological findings of SARS-CoV-2 pneumonia were classified into four types (mild involvement, moderate involvement, severe involvement, and no radiological finding) according to chest computed tomography severity score (CT-SS) published by Yang et al. [22].

Patients' demographic data and clinical outcome

The demographic, comorbidity, and clinical outcome data of the patients were gathered from the medical records of hospitals. Clinical outcomes were evaluated by overall survival. The lowest value of O_2 saturation and the highest value of fever before TCZ administration were selected as baseline values before TCZ therapy and those obtained 5 days after TCZ administration were considered after TCZ therapy values.

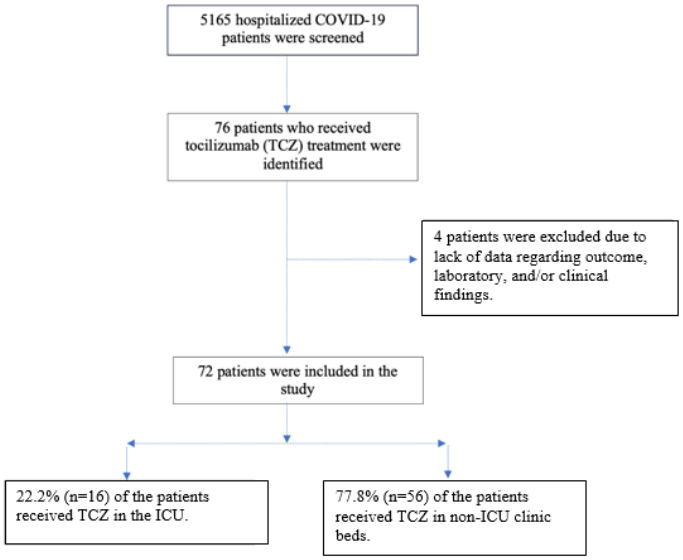
Statistical analysis

To determine the number of patients that should be included in the study, the data of the study conducted by Aomar-Millan et al. [23] were used. It was concluded that forty-five patients should be included in the sample for maximum power. However, considering that patient data may be missing, all seventy-two patients who could be reached were included in the study. NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistics were used when evaluating the study data. The suitability of quantitative data to normal distribution was assessed by Shapiro-Wilk test and graphical evaluations. Student's t-test or Mann Whitney U was used for comparing two groups. In the comparison of qualitative data, Pearson Chi-Square test, Fisher-Freeman-Halton Exact test and Fisher's Exact test were used. Paired Sample t-test was used for pre- and post-drug comparisons of normally distributed parameters, and Wilcoxon Signed Ranks test was utilized for non-normally distributed parameters. No imputation was made for missing data. Significance was evaluated at the level of $P<0.05$.

Results

A total of 5165 patients were retrospectively screened, out of which seventy-six patients had received TCZ. Four patients were excluded based on the exclusion criteria and seventy-two patients' data were included in this study. The study flow chart is presented in Figure 1.

Figure 1: Study Flow Chart



Demographics and clinical characteristics of the patients

Among 72 patients who received TCZ, 22.2% (n=16) were females and 77.8% (n=56) were males. The mean age of the study population was 54.58 (11.45) (min-max: 22-73) years. While 41.7% (n=30) of the patients did not have any comorbidities, 58.3% (n=42) of them had at least one comorbid disease (CD). The fever on the admission of the patients ranged between 36 to 40 °C, with an average of 37.11 (0.86) °C, and the SpO_2 measurements on admission were between 67% and 99% with an average of 90.27% (6.66). Regarding the CT results of the patients, 11.1% (n=8) of the cases had mild involvement, 33.3% (n=24) had moderate involvement and 55.6% (n=40) had severe involvement. While 22.2% (n=16) of all cases received TCZ therapy in ICU, 77.8% (n=56) received TCZ therapy in non-ICU clinic beds. Demographics and clinical characteristics of the patients are presented in Table 1.

Follow-up and clinical outcomes of the patients

The duration of hospitalization ranged from 4 to 50 days with an average of 18.82 (9.36) days (median: 17 days). While 44.4% (n=32) died, 55.6% (n=40) were discharged from the hospital. Intensive care unit (ICU) admission was observed in

66.7% (n=48) of the cases before, after, or at the time of TCZ treatment (Table 1).

Table 1: Demographics, baseline characteristics, and clinical outcomes of the patients

		n	%
Age (year)	Min – Max (Median)	22 - 73 (56)	
	Mean (SD)	54.58 (11.45)	
Sex	Female	16	22.2
	Male	56	77.8
Participating hospitals	Bakirkoy Dr. Sadi Konuk Training and Research Hospital	43	59.7
	Bagcilar Training and Research Hospital	29	40.3
Comorbidity	No	30	41.7
	Yes	42	58.3
# of comorbid diseases	No	30	41.7
	1	20	27.8
	2	10	13.9
	3	10	13.9
	4	2	2.8
Fever on admission (°C)	Min – Max (Median)	36 - 40 (37)	
	Mean (SD)	37.11 (0.86)	
SpO2 on admission (%)	Min – Max (Median)	67 - 99 (91)	
	Mean (SD)	90.27 (6.66)	
CT results	Mild involvement	8	11.1
	Moderate involvement	24	33.3
	Severe involvement	40	55.6
ICU admission	No	24	33.3
	Yes	48	66.7
The location of initiation of TCZ therapy	ICU	16	22.2
	Clinic	56	77.8
Outcome	Dead	32	44.4
	Discharged	40	55.6
Duration of hospitalization (day)	Min – Max (Median)	4 - 50 (17)	
	Mean (SD)	18.82 (9.36)	

CT: Computerized Tomography, ICU: Intensive Care Unit, TCZ: Tocilizumab

Treatments other than TCZ of the patients

While all patients (n=72) received HCQ, 97.2% (n=70) received LMWH, 97.2% (n=70) received favipiravir, 87.5% (n=63) received AZT, 75.0% (n=54) received acetylsalicylic acid (ASA), 68.1% (n=49) received oseltamivir, and 51.4% (n=37) received ascorbic acid. The treatments of the patients are shown in Table 2.

Comparison of demographic and clinical findings of the patients according to clinical outcome

There was no statistically significant difference in mortality rates by age and gender. While there was a significant correlation between the presence of CD and mortality (P=0.037), no significant correlation was found between the number of CDs and mortality (see Table 3 for p values). There was no significant difference in mortality rates according to the location of the initiation of TCZ therapy (clinic vs. ICU), CT results, and the duration of hospitalization (P>0.05 for all). The fever on admission was significantly higher in patients who died than those discharged (P=0.032), however, there was no such significance with regards to SpO_2 levels on admission (P=0.331). The mortality rate was significantly higher in patients admitted to the ICU than those who were not (P=0.001). Comparison of demographic and clinical findings of the patients according to clinical outcomes are shown in Table 3.

Evaluation of the effect of the treatments other than TCZ on clinical outcome

Since all our cases received HCQ, LMWH, Favipiravir, and TCZ treatments, there was no significant difference between mortality rates and these drugs, as expected. No significant difference was found in mortality rates between patients who did and did not receive ASA (P=0.584). Importantly, we found a significant increase in mortality rates in patients who received AZT, oseltamivir, or ascorbic acid treatments compared to those who did not (P<0.05 for all) (Table 4).

Table 2: Treatments those patients received other than TCZ

			n	%
HCQ	Receiving Status	Not received	0	0
		Received	72	100
	Days taken	Min – Max (Median)	4 - 14 (9)	
		Mean (SD)	8.65 (2.71)	
	Initiation day of the therapy after admission	Min – Max (Median)	1 - 14 (1)	
		Mean (SD)	1.33 (1.70)	
AZT	Receiving Status	Not received	9	12.5
		Received	63	87.5
	Days taken	Min – Max (Median)	2 - 10 (5)	
		Mean (SD)	5.30 (1.23)	
	Initiation day of the therapy after admission	Min – Max (Median)	1 - 8 (1)	
		Mean (SD)	1.29 (1.20)	
Oseltamivir	Receiving Status	Not received	23	31.9
		Received	49	68.1
	Days taken	Min – Max (Median)	0 - 10 (5)	
		Mean (SD)	4.67 (1.92)	
	Initiation day of the therapy after admission	Min – Max (Median)	0 - 6 (1)	
		Mean (SD)	1.08 (0.73)	
LMWH	Receiving Status	Not received	2	2.8
		Received	70	97.2
	Days taken	Min – Max (Median)	2 - 40 (15)	
		Mean (SD)	16.33 (7.77)	
	Initiation day of the therapy after admission	Min – Max (Median)	1 - 10 (1)	
		Mean (SD)	2.14 (2.05)	
Favipiravir	Receiving Status	Not received	2	2.8
		Received	70	97.2
	Days taken	Min – Max (Median)	4 - 9 (5)	
		Mean (SD)	5.31 (0.93)	
	Initiation day of the therapy after admission	Min – Max (Median)	1 - 15 (3.5)	
		Mean (SD)	3.74 (2.72)	
TCZ	Receiving Status	Not received	0	0
		Received	72	100
	Days taken	Min – Max (Median)	1 - 3 (2)	
		Mean (SD)	1.92 (0.44)	
	Initiation day of the therapy after admission	Min – Max (Median)	1 - 25 (7)	
		Mean (SD)	8.43 (4.91)	
ASA	Receiving Status	Not received	18	25.0
		Received	54	75.0
	Days taken	Min – Max (Median)	1 - 32 (10)	
		Mean (SD)	11.11 (6.23)	
	Initiation day of the therapy after admission	Min – Max (Median)	1 - 35 (6)	
		Mean (SD)	6.07 (5.77)	
Ascorbic acid	Receiving Status	Not received	35	48.6
		Received	37	51.4
	Days taken	Min – Max (Median)	1 - 25 (6)	
		Mean (SD)	7.95 (5.91)	
	Initiation day of the therapy after admission	Min – Max (Median)	1 - 16 (5)	
		Mean (SD)	5.41 (3.22)	

HCQ: Hydroxychloroquine, AZT: Azithromycin, LMWH: Low-Molecular-Weight-Heparin, TCZ: Tocilizumab, ASA: Acetylsalicylic acid

Comparison of clinical and laboratory findings before and 5 days after the tocilizumab therapy

The O_2 saturation levels significantly increased, and fever significantly decreased on the 5th day after TCZ treatment (mean estimate of difference: 4.97 [95% CI 2.49 to 7.46, P=0.001]) and 0.34 [95% CI 0.08 to 0.61, P=0.010], respectively). While the change in AST, GGT, urea, D-dimer, WBC, NEU, HB, and APTT levels after TCZ treatment was not significant, ALT, lipase, lymphocyte, and PLT levels significantly increased after TCZ administration (see Table 5 for p values). The decreases in troponin-I, creatinine, LDH, CRP, procalcitonin, CK, ferritin, PTZ, and INR levels after TCZ therapy were significant (see Table 5 for P-values and the comparison results of rest of the laboratory findings).

Table 3: Evaluation of the relationship between mortality and demographic and clinical features

		Outcome		Test value	*P*-value
		Discharged (n=40) n (%)	Death (n=32) n (%)		
Age (year)	Min – Max (Median)	22 - 73 (54.5)	24 - 72 (57.5)	t: 0.254	[c]0.800
	Mean (SD)	54.28 (10.93)	54.97 (12.24)		
Sex	Female	7 (17.5)	9 (28.1)	χ^2: 1.161	[d]0.281
	Male	33 (82.5)	23 (71.9)		
Comorbidity	No	21 (52.5)	9 (28.1)	χ^2: 4.346	[d]0.037*
	Yes	19 (47.5)	23 (71.9)		
# of comorbid diseases	No	21 (52.5)	9 (28.1)	χ^2: 7.200	[d]0.066
	1	11 (27.5)	9 (28.1)		
	2	5 (12.5)	5 (15.6)		
	≥3	3 (7.5)	9 (28.2)		
Fever on admission (°C)	Min – Max (Median)	36 – 38.5 (36.8)	36 - 40 (37.2)	t: 2.182	[c]0.032*
	Mean (SD)	36.91 (0.79)	37.35 (0.90)		
SpO2 on admission (%)	Min – Max (Median)	71 - 99 (91.5)	67 - 98 (91)	t: -0.978	[c]0.331
	Mean (SD)	90.95 (6.39)	89.39 (7.01)		
CT results	Mild involvement	3 (7.5)	5 (15.6)	χ^2: 5.780	[e]0.054
	Moderate involvement	18 (45.0)	6 (18.8)		
	Severe involvement	19 (47.5)	21 (65.6)		
ICU admission	No	24 (60.0)	0 (0)	χ^2: 28.800	[d]0.001**
	Yes	16 (40.0)	32 (100)		
The location of initiation of TCZ therapy	ICU	7 (17.5)	9 (28.1)	χ^2: 1.161	[d]0.281
	Clinic	33 (82.5)	23 (71.9)		
Duration of hospitalization (day)	Min – Max (Median)	5 - 50 (17)	4 - 37 (16)	Z: -1.056	[f]0.291
	Mean (SD)	20.20 (10.39)	17.09 (7.71)		

[c] Student t Test, [d] Pearson's chi-squared test, [e] Fisher Freeman Halton Exact Test, [f] Mann Whitney U Test, * *P*<0.05, ** *P*<0.01, CT: Computerized Tomography, ICU: Intensive Care Unit, TCZ: Tocilizumab

Table 4: Evaluation of the relationship between mortality and treatments that patients received other than TCZ

		Outcome		Test value	*P*-value
		Discharged (n=40) n (%)	Death (n=32) n (%)		
HCQ	Not received	0	0	-	-
	Received	40 (100)	32 (100)		
AZT	Not received	8 (20.0)	1 (3.1)	χ^2: 4.629	[g]0.037*
	Received	32 (80.0)	31 (96.9)		
Oseltamivir	Not received	17 (42.5)	6 (18.8)	χ^2: 4.613	[d]0.032*
	Received	23 (57.5)	26 (81.3)		
LMWH	Not received	0	2 (6.3)	χ^2: 2.571	[g]0.194
	Received	40 (100)	30 (93.8)		
Favipiravir	Not received	0	2 (6.3)	χ^2: 2.571	[g]0.194
	Received	40 (100)	30 (93.8)		
TCZ	Not received	0	0	-	-
	Received	40 (100)	32 (100)		
ASA	Not received	11 (27.5)	7 (21.9)	χ^2: 0.300	[d]0.584
	Received	29 (72.5)	25 (78.1)		
Ascorbic acid	Not received	26 (65.0)	9 (28.1)	χ^2: 9.677	[d]0.002**
	Received	14 (35.0)	23 (71.9)		

[d] Pearson's chi-squared test, [g] Fisher's Exact Test, * *P*<0.05, ** *P*<0.01, HCQ: Hydroxychloroquine, AZT: Azithromycin, LMWH: Low-Molecular-Weight-Heparin, TCZ: Tocilizumab, ASA: Acetylsalicylic acid

Table 5: Comparison of laboratory findings and clinical characteristics before and 5 days after the TCZ therapy

		n	Min – Max (Median)	Mean (SD)	Test value	*P*-value
SpO2	Before	54	64 - 99 (89)	88.07 (7.88)	t:-4.022	[a]0.001**
	After	54	65 - 100 (94.5)	93.06 (6.19)		
Fever (°C)	Before	60	34 - 39 (36.5)	36.65 (0.97)	t:-2.656	[a]0.010*
	After	60	36 – 37.3 (36.1)	36.30 (0.36)		
AST (U/L) (range: 0-40)	Before	60	22 - 296 (58.5)	77.05 (52.73)	Z:-0.286	[b]0.775
	After	60	16 - 561 (55.5)	88.83 (101.93)		
ALT (IU/L) (range: 0-41)	Before	60	13 - 341 (46.5)	67.32 (67.25)	Z:-2.970	[b]0.003**
	After	60	12 - 736 (72.5)	105.73 (117.93)		
GGT (U/L) (range: <55)	Before	58	14 - 478 (47)	83.16 (92.49)	Z:-1·878	[b]0.060
	After	58	19 - 609 (61)	118.34 (133.78)		
Direct Bilirubin (mg/dL) (range: 0-0.2)	Before	60	0 – 1.7 (0.2)	0.25 (0.24)	Z:-2.664	[b]0.008**
	After	60	0 – 1.5 (0.1)	0.19 (0.21)		
Indirect Bilirubin (mg/dL) (range: 0-1.2)	Before	61	0.1 – 1.3 (0.5)	0.48 (0.23)	Z:-1.288	[b]0.198
	After	61	0 – 1.4 (0.4)	0.44 (0.28)		
Lipase (U/L) (range: 0-67)	Before	45	1.8 - 186 (32.5)	50.21 (42.40)	Z:-2.799	[b]0.005**
	After	45	12.5 - 493 (60)	92.85 (91.41)		
Troponin-I (pg/mL) (range: 0-17.5)	Before	58	0 – 2984.9 (12)	129.97 (433.07)	Z:-3.350	[b]0.001**
	After	58	0 - 1268 (6.7)	66.55 (192.61)		
Creatinine (mg/dL) (range: 0.7-1.2)	Before	60	0.3 – 7.4 (0.8)	1.08 (1.17)	Z:-3.353	[b]0.001**
	After	60	0.2 – 6.3 (0.7)	0.90 (0.85)		
Urea (mg/dL) (range: 17-43)	Before	60	9 – 295.6 (38.4)	49.27 (40.54)	Z:-1.823	[b]0.068
	After	60	18 – 225.2 (39.2)	55.62 (42.60)		
LDH (U/L) (range: 135-248)	Before	60	225 - 1512 (544.5)	582.42 (251.85)	Z:-2.102	[b]0.036*
	After	60	6.1 - 1717 (495)	519.37 (261.46)		
D-dimer (µg FEU/mL) (range: 0-0.5)	Before	60	0 – 8.6 (0.8)	2.05 (2.64)	Z:-1.351	[b]0.177
	After	60	0 – 7.8 (1.8)	2.24 (1.84)		
Fibrinogen (mg/dL) (range: 200-400)	Before	43	108 - 905 (607)	588.70 (189.40)	Z:-5.020	[b]0.001**
	After	43	150 - 905 (340)	345.70 (137.03)		
Triglyceride (mg/dL) (range: 0-200)	Before	35	52 - 355 (113)	147.47 (83.72)	Z:-3.292	[b]0.001**
	After	35	82 - 614 (184)	222.31 (127.6)		
# WBC (10e3/uL) (range: 3.7-10.1)	Before	60	1.9 – 31.9 (8.1)	9.81 (5.60)	Z:-0.015	[b]0.988
	After	60	1.6 – 39.8 (7.9)	9.73 (6.42)		
# LYM (10e3/uL) (range: 1.09-2.99)	Before	60	0 – 3.6 (0.8)	0.89 (0.56)	Z:-3.087	[b]0.002**
	After	60	0.1 – 4.9 (1)	1.28 (0.95)		
# NEU (10e3/uL) (range: 1.63-6.96)	Before	60	0.5 – 28.8 (6.9)	8.16 (5.38)	Z:-0.226	[b]0.821
	After	60	1 – 34.7 (6.5)	7.78 (6.07)		
# PLT (10e3/uL) (range: 155-366)	Before	60	24 - 657 (227)	254.67 (131.19)	Z:-3.386	[b]0.001**
	After	60	27 - 634 (323)	314.40 (139.78)		
Hb (g/dL) (range: 12.9-15.9)	Before	60	6.3 – 15.4 (12.3)	11.89 (2.00)	t:1.144	[b]0.257
	After	60	6.9 – 16.6 (11.6)	11.68 (2.26)		
CRP (mg/L) (range: <5)	Before	60	1.3 – 422.6 (183.6)	185.24 (109.54)	Z:-6.670	[b]0.001**
	After	60	0.7 – 250.6 (11)	27.26 (47.37)		
Procalcitonin (ng/mL) (range: <0.5)	Before	60	0 - 66 (0.3)	2.50 (8.94)	Z:-5.416	[b]0.001**
	After	60	0 – 15.9 (0.1)	0.63 (2.31)		
Ferritin (µg/L) (range: 23.9-336.2)	Before	60	101.1 - 6903(1025.5)	1165.71 (966.93)	Z:-4.627	[b]0.001**
	After	60	54.6 - 3554 (581.6)	744.62 (638.76)		
Magnesium (mg/dL) (range: 1.8-2.6)	Before	54	1.6 – 4.5 (2.2)	2.27 (0.44)	t:0.444	[a]0.659
	After	54	1.6 – 4.2 (2.2)	2.23 (0.38)		
Sodium (mmol/L) (range: 136-145)	Before	60	123 - 156 (136)	137.03 (6.47)	t:-2.842	[a]0.006**
	After	60	126 - 157 (139)	139.30 (6.56)		
Potassium (mmol/L) (range: 3.5-5.1)	Before	60	0.5 – 5.7 (4.1)	4.08 (0.76)	t:-1.763	[a]0.083
	After	60	3 – 5.7 (4.3)	4.30 (0.62)		
Phosphorus (mg/dL) (range: 2·5-4·5)	Before	60	0.5 – 9.6 (3)	3.11 (1.32)	t:-1.118	[a]0.268
	After	60	1.5 – 7.3 (3.1)	3.38 (1.16)		
APTT (sec.) (range: 27-45)	Before	60	24.1 – 60.8 (38)	38.78 (6.99)	t:0.915	[a]0.364
	After	60	19.6 – 74.8 (36.4)	37.85 (9.13)		
PT (sec.) (range: 11-15)	Before	41	12.3 - 22 (15.7)	16.12 (2.33)	t:3.680	[a]0.001**
	After	41	11.4 – 21.8 (14.6)	14.73 (1.90)		
INR (range: 0.8-1.2)	Before	42	1 – 1.8 (1.2)	1.24 (0.18)	Z:-3.978	[b]0.001**
	After	42	0.9 – 1.7 (1.1)	1.13 (0.13)		
CK (U/L) (range: 0-171)	Before	59	16 - 5316 (134)	409.03 (847.23)	Z:-3.569	[b]0.001**
	After	59	0.2 - 2406 (69)	199.02 (402.59)		

[a] Paired Samples, t Test, [b] Wilcoxon Signed Ranks Test,* *P*<0.05, ** *P*<0.01, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma Glutamyl Transferase, LDH: Lactate dehydrogenase, WBC: White Blood Cells Count, LYM: Lymphocyte count, NEU: Neutrophil count, PLT: platelet count, Hb: Hemoglobin, CRP: C-reactive protein, APTT: Activated Partial Thromboplastin Time, PT: Prothrombin Time, INR: International Normalized Ratio, CK: Creatine Kinase

Discussion

In this study, we retrospectively evaluated the efficacy of TCZ treatment in critically ill SARS-CoV-2 patients. The overall mortality rate of SARS-CoV-2 pneumonia was 4.9% in the hospitals who participated in the study (unpublished data) whereas the overall mortality rate of our study population who received TCZ therapy was 55% over a median follow-up of 17 days. The initiation rate of TCZ was 1.3%. While the true mortality rate of SARS-CoV-2 infection is not known, studies published so far indicate that the crude death rate (the number of reported deaths divided by the reported cases) of SARS-CoV-2 infection is around 4% [13]. Although the definition of 'critically-ill patient' has not been clearly determined in SARS-CoV-2 patients, mortality rates among patients with worsened clinical and laboratory findings, despite the recommended standard treatments, can reach up to around 66% [2,24]. Because effective treatment is yet to be determined in critically ill patients, high mortality rates among these patients indicate that we need treatments that can prevent the development of critical illness and findings that can predict this course. In previous studies, mortality rates have been reported up to 78% in severe cases who need invasive ventilation, admission to ICU, or both [25-31]. The wide variation in these mortality rates may be due to lack of standardized national and/or international criteria guidelines for intensive care admission of SARS-CoV-2 infected patients. These criteria vary from country to country, even from hospital to hospital. For example, early invasive ventilation is recommended in some places, while in others, delaying invasive ventilation and early intensive care follow-up are recommended. Therefore, although the patients in these studies appear in a similar category, indeed they are not so. They include patients at different critical levels.

In our study, we observed a significant decrease in troponin-I, LDH, CRP, and ferritin levels along with an increase in O_2 saturation percent and a decrease in fever values on the 5^{th} day after TCZ treatment. These findings show that TCZ treatment provides clinical and laboratory improvement in these patients. Since we did not have a control group in our study, we could not determine whether TCZ treatment has a definite effect on mortality and median follow-up time. Among all patients, 77.8% received TCZ treatment in non-ICU clinical beds. The discharge rates among patients who received TCZ in non-ICU and ICU beds were 59% and 43%, respectively. It should be taken into consideration that one of the reasons for the higher mortality rate in ICU may be due to the delayed initiation of TCZ treatment to those patients. These findings suggest that TCZ treatment can be given safely to the patients in non-ICU clinical beds. If these findings could be supported with new randomized controlled studies, it might be of paramount importance to clinicians dealing with such patients (especially in centers lacking sufficient ICU beds).

In our study, we did not find a relationship between mortality, age and gender in patients receiving TCZ treatment. While there was a correlation between the presence of CD and mortality, there was no such correlation between the number of CDs and mortality. Although we observed that the fever level on admission was higher in patients who died (in comparison to patients who survived), the same relationship was not detected with SpO_2. Similarly, we did not find a relationship between mortality and CT results on admission.

Since all our patients received HCQ, LMWH, Favipiravir, and TCZ treatments, their relationship with mortality was out of evaluation, but ASA treatment did not affect mortality. Interestingly, mortality was significantly higher in patients receiving AZT, oseltamivir, and ascorbic acid therapies. In our study, it would not be rational to decide the effects of these treatments on mortality alone due to the insufficient number of patients receiving these treatments alone. Therefore, studies involving more patients are needed at this point.

Among the important limitations of our study are the limited number of patients and the absence of comparison between our study population and a control group. Our study is an observational study, and a significance bias might exist. Also, not including the safety outcomes, such as adverse events or infections constitutes another limitation. Still, the findings of this study might guide the more detailed and randomized studies in this field.

Future directions

There are currently ongoing global phase III trials including the COVACTA, EMPACTA, and REMDACTA trials that aim to show the efficacy of TCZ in COVID-19 patients.

COVACTA trial, which aimed to improve the clinical situation in COVID-19 patients with pneumonia and reduce patient mortality, could not reach its neither primary nor secondary endpoints. However, the study is ongoing, and researchers are determined to further investigate TCZ in other treatment settings, including in combination with an antiviral agent [32].

Phase III EMPACTA study showed 44% less mechanical ventilation or death in COVID-19-associated pneumonia patients receiving TCZ treatment in addition to standard care when compared to patients receiving placebo plus standard care [33]. EMPACTA also showed that non-ICU patients can receive TCZ during COVID-19.

Another ongoing, phase III, randomized, double-blind, multicenter study, REMDACTA, aims to investigate the efficacy and safety of the combination of remdesivir plus tocilizumab in hospitalized patients with severe COVID-19 pneumonia [34].

Conclusion

Our study results show that TCZ treatment may improve SpO_2, fever levels and laboratory findings, and may repress the deterioration of severe SARS-CoV-2 patients. Since there was no control group in our study, we could not determine whether TCZ treatment had a definite effect on mortality and median follow-up time. If these findings could be supported with new randomized controlled studies, it might be of paramount importance to clinicians dealing with such patients (especially in centers lacking sufficient ICU beds). It is obvious that to see the efficacy of tocilizumab treatment in COVID-19 patients with cytokine release syndrome more clearly, the results of the ongoing studies and further randomized large studies are needed.

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The impact of oral nutritional supplementation in children treated for cancer

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Ethics Committee Approval
All procedures involving study participants were approved by Kocaeli University Non-interventional Clinical Research ethics committee, Istanbul on 19.06.2019 with session number 1037. Authors state that they have obtained the required informed patient consents prior to the study. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Malnutrition is a dangerous comorbidity in children with cancer that can affect tolerance to treatment modalities such as chemotherapy and radiotherapy. It also adversely affects the treatment outcome and overall survival. It has been known that low Z score of body mass index (BMI) indicates malnutrition. This study aims to underline the effects of oral nutritional supplementation (ONS) on pediatric oncology patients.

Methods: All records were collected from Kocaeli University Hospital, Department of Pediatric Oncology, Kocaeli, Turkey, and analyzed. Weight, height, and BMI status of sixty patients who received ONS with cancer treatment were recorded during visits up to 8 months after the start of ONS. Statistical analyses were maintained on the whole cohort as well as on following tumor sub-groups: CNS tumors (13.3%), lymphoma (18.3%), other tumors (68.3%).

Results: Sixty malnourished pediatric oncology patients (64.6% male, 35.4% female) were included in the study cohort. BMI values of the majority (60%, $P<0.05$) of patients increased after ONS treatment while those of 40% decreased. BMI values also increased in the case of other tumors and lymphoma sub-groups ($P<0.001$ and $P=0.012$, respectively).

Conclusion: This study underlined the benefits of ONS treatment in terms of BMI status among pediatric oncology patients. The recovery rate of nutritional status depends on malignancy, cancer type and location.

Keywords: Pediatrics, Malnutrition, Cancer, Body mass index

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Introduction

Poor nutrition is detrimental for all stages of life including childhood [1] and under-nutrition is linked to lower survival rates among children in low- and middle-income countries [2]. The presence of malnutrition as a comorbidity with severe disease states such as malignancy can critically influence the outcome. The underlying oncologic pathology as well as the adverse effects of treatment regimens such as chemotherapy and radiotherapy lead to weight loss and malnourishment in pediatric oncology patients [3]. Weight loss and malnutrition in cancer is hypothesized to be induced by insufficient energy intake and inflammation [4]. Inadequate energy intake leads to loss of fat mass whereas inflammation mostly leads to loss of muscle mass. An additional risk factor is cachexia in these patients, possibly resulting from depletion of body protein mass [5]. Collectively, these factors affect tolerance to treatment modalities such as chemotherapy and radiotherapy, lead to discontinuation of the treatment more frequently [6-8] and ultimately adversely influence the treatment outcome and overall survival [9, 10].

Body mass index (BMI), a formula based on weight and height, is a widely accepted measurement of nutritional state along with conventional measurements, such as ideal body weight (IBW) and weight-for-height (WFH). It is known that negative and positive Z scores of BMI indicate malnutrition and overnutrition, respectively [11, 12]. BMI is also accepted by World Health Organization (WHO) as a significant and cost-effective measurement for monitoring the nutritional state [13, 14].

Not only under-nutrition but also over-nutrition may result in poor clinical outcomes such as increased rate of relapse and mortality in patients treated for cancer [15]. While survivors of most childhood cancers are at risk for weight loss, survivors of some malignancies such as ALL and brain tumors have been shown to be at risk for weight gain due to the treatment they received for cancer [16].

Enteral feeding is safe and effective in pediatric oncology patients, leads to weight gain and corrects nutritional status. However, the correlation between oral feeding and the magnitude of the benefit in different cancer types has not been fully investigated [17]. This is a retrospective study aiming to demonstrate the probable impact of oral nutritional supplementation (ONS) in BMI scores in children with heterogenous malignancies.

Materials and methods

A retrospective cohort was formed from pediatric oncology patients aged between 0-18 years who were treated for cancer in Pediatric Oncology department of Kocaeli University, Medical Faculty. Appropriate oncology patients were identified by a retrospective scan of the medical records. Study inclusion criteria consisted of oncology patients who received a conventional anti-cancer treatment.

Weight, height and BMI statuses of the patients who received nutritional support along with cancer treatment were followed up for a period of 8 months post-ONS [18]. Tumor sub-groups were organized as follows: CNS tumors, lymphoma, and other tumors with the majority being Wilms tumor, Ewing sarcoma, neuroblastoma, and rhabdomyosarcoma with the addition of less frequent tumor types.

Initially, sixty-five patients were identified from the medical records. Five patients who discontinued treatment were excluded. Patients less than 2 years of age were excluded from the BMI-z score analysis but were included in BMI analysis. Diagnosis of malnutrition was based on weight-for-height (WFH) -2 SD threshold, coherent with WHO. Gender age and adjusted z-scores were calculated using raw BMI values according to growth charts for patients between 2–18 years of age. In the case of measurements belonging to patients <24 months of age, BMI scores were replaced with length-for-weight (LFW) [19].

Ethical Approval

All procedures involving study participants were approved by Kocaeli University Non-interventional Clinical Research ethics committee, Istanbul on 19.06.2019 with session number 1037. Informed patient consents were obtained from the legal guardians of all patients prior to the study.

Statistical analysis

All statistical analyses were maintained by MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) program. Normality of the data was checked with the Shapiro-Wilk test. Wilcoxon test was used to evaluate the statistical relationship between two dependent non-parametric data sets. Parametric data were assessed with repeated measures ANOVA, followed by Wilks' lambda multivariate test. Bonferroni correction ($P<0.05$) was used in pairwise analysis in repeated measures ANOVA. Statistical significance was evaluated at $P<0.05$.

Results

Study cohort consisted of sixty malnourished pediatric oncology patients (64.6% male, 35.4% female). Statistical analyses were performed on the whole cohort as well as on following tumor sub-groups: CNS tumors (13.3%), lymphoma (18.3%), other tumors (n=41, 68.3%), which included Wilms tumor, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, and less frequent tumor types.

Mean overall ONS treatment period was 3 months. The BMIs of 36 (60%, $P<0.05$) patients increased while that of 24 patients (40%) decreased after ONS treatment (Figure 1 and Table 1). BMIs mostly increased in patients with other tumors (BMI increase in 24 patients versus BMI decrease in 17 patients, $P<0.001$) and lymphoma (BMI increase in 8 patients versus BMI decrease in 3 patients, $P=0.012$) sub-groups. Despite the insignificant result obtained in the CNS sub-group ($P=0.068$), it showed a p value close to the threshold of significance ($P<0.05$) in terms of BMI improvement (BMI increase in 4 patients versus BMI decrease in 4 patients, $P=0.068$) (Table 2).

Figure 1: Impact of oral nutritional supplementation on body mass index in pediatric cancer patients

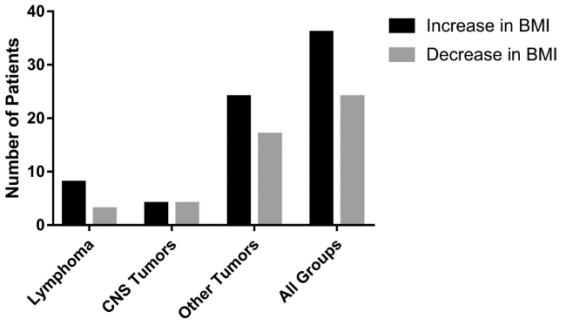

Table 1: First visit versus last visit BMI values of pediatric cancer patients in different tumor sub-groups according to BMI increase or decrease after nutritional intervention

Group	Disease type	Pre-ONS BMI n=60	Post ONS BMI (8th Month) n=60
BMI Increase	Lymphoma, mean (SD)	15.8 (3.1)	16.6 (3.0)
	Med. (Min.-Max.)	15.3 (11.1-20.1)	16.5 (11.7-20.2)
	CNS Tumors, mean (SD)	15.6 (1.9)	16.4 (1.8)
	Med. (Min.-Max.)	15.6 (13.2-18.1)	16.1 (14.5-18.8)
	Other Tumors, mean (SD)	15.5 (2.7)	17.1 (3.6)
	Med. (Min.-Max.)	14.8 (11.7-24)	15.9 (11.9-29.7)
	All Patients, mean (SD)	15.6 (2.6)	16.9 (3.2)
	Med. (Min.-Max.)	15.2 (11.1-24)	16.0 (11.7-29.7)
BMI Decrease	Lymphoma, mean (SD)	18.7 (4.6)	17.7 (4.9)
	Med. (Min.-Max.)	17.9 (14.6-23.7)	17.3 (13-22.8)
	CNS Tumors, mean (SD)	15.7 (2.1)	14.6 (1.9)
	Med. (Min.-Max.)	15.4 (13.7-18.3)	14.9 (12.2-16.5)
	Other Tumors, mean (SD)	17.2 (2.8)	16 (2.9)
	Med. (Min.-Max.)	16.7 (13.8-24.0)	15.8 (11.3-23.3)
	All Patients, mean (SD)	17.1 (2.9)	16.0 (3.0)
	Med. (Min.-Max.)	16.7 (13.7-24)	15.8 (11.3-23.3)
P-value	All Patients	0.037	
	BMI increase, n (%) versus BMI decrease, n (%)	36 (60%) versus 24 (40%)	

SD: Standard deviation, Med: median, CNS: central nervous system

Table 2: First visit versus last visit BMI z-score values and their p values of pediatric cancer patients in different tumor sub-groups according to BMI increase or decrease after nutritional intervention

Group	Disease Type	Pre-ONS BMI n=60	Post ONS BMI (8th Month) n=60	*P*-value
BMI Z-score Increase	Lymphoma, mean (SD)	-0.7 (1.9)	0.37 (1.5)	0.028
	Med. (Min.-Max.)	-0.8 (-3.4-2.3)	0.22 (-1.05-2.6)	
	CNS Tumors, mean (SD)	-1.9 (1.4)	0.46 (1.4)	0.109
	Med. (Min.-Max.)	-2.3 (-2.9--0.4)	-0.27 (-0.49-2.1)	
	Other, mean (SD)	-1.8 (2.2)	-0.9 (2.0)	<0.001
	Med. (Min.-Max.)	-1.3 (-9.1-0.8)	-0.53 (-7.8-1.5)	
	P-value [2]	0.531	0.321	
BMI Z-score Decrease	Lymphoma, mean (SD)	-0.06 (0.9)	-0.72 (1.0)	0.068
	Med. (Min.-Max.)	-0.1 (-1-0.98)	-0.68 (-1.79-0.24)	
	CNS Tumors, mean (SD)	0.48 (0.9)	-1.12 (2.0)	0.068
	Med. (Min.-Max.)	0.95 (-1-1.04)	-0.6 (-3.9-0.55)	
	Other, mean (SD)	-0.17 (1.5)	-1.21 (2.1)	0.001
	Med. (Min.-Max.)	-0.23 (-2.8-1.9)	-1.21 (-5.6-1.67)	
	P-value [2]	0.705	0.953	

SD: Standard deviation, Med: median, CNS: central nervous system, BMI z-score: BMI-for-age percentile

Discussion

Prevalence of malnutrition at diagnosis in children with cancer ranges between 10-50% in industrialized countries and reach levels as high as 50% in developing countries [3]. Furthermore, frequent complications of chemotherapy and radiotherapy such as oral and GI mucositis complicate the attempts to correct the nutritional status via oral feeding and lower the quality of life for the children [20]. The risk of developing these complications depend partly on specific combination of chemotherapeutic agents utilized in the treatment for specific cancers [21] and partly on the specific cancer type being treated [22]. Timely and accurate identification of changes in BMI during treatment will facilitate the implementation of preventive measures and improve the outcome. This is also important as nutritional status at diagnosis is a predictor of weight outcome at final height in patients who received radiotherapy or chemotherapy [23].

Brinksma et al. [24] showed that the greatest changes occur in the BMIs of children under treatment for hematological, solid and brain malignancies within 3 months of diagnosis. Decreased level of activity and tube feeding were both identified as significant contributing factors to increased fat mass percentage (FM) and BMI, respectively. In our study, we observed that significantly more patients have shown an increase in BMI than those who have shown a decrease when treated with oral nutritional supplementation. This finding is in line with previous observations for benefits of enteral feeding in pediatric oncology patients [17]. However, it should be kept in mind that low initial BMI at the time of diagnosis in cancer patients can contribute to relative increases in BMI. This may also be due to exceedingly increased energy intake relative to energy requirements. For example, low level of activity is associated with increased body weight in patients treated with cancer, mainly due to increased FM [27, 28]. Furthermore, in this study, patients with brain malignancies showed an increase in BMI that started immediately after diagnosis; whereas patients with hematological and solid malignancies showed an initial decrease followed by an increase later in the course. Stagnation of growth in height was also a contributing factor to BMI increase. In contrast, other studies reported an increase in BMI from the start of treatment in patients with ALL [18-22, 24, 25] and craniopharyngioma [26].

Protein needs must be met to treat or prevent under-nutrition in these patients while energy intake must be well balanced with the level of physical activity. Corticosteroid use as part of anti-cancer regimens is another contributing factor that should be considered in persons with increased BMI, as corticosteroids change body composition [29-31]. In children with lymphoma whose treatment regimen included corticosteroids, FM increased in the first 6 months of the treatment whereas in patients with solid tumors, FM remained the same [31]. Moreover, in lymphoma, the incidence of oral mucositis and associated gastrointestinal adverse events such as anorexia, diarrhea and dysphagia are high, which negatively effects both the nutritional status and the quality of life of the patient [20].

The reason that we could not detect a change in BMI among patients with CNS tumors may be because change in body composition is more valid for CNS tumors and thus, only measuring body weight and height is not enough; body composition by fat free mass (FFM) and FM should be measured in this group [24, 32]. Low FFM may result in loss of muscle strength, intolerance to chemotherapy, increased susceptibility to infections and poor treatment outcome.

Limitations

The number of patients included in the study is low, which negatively effects the statistical significance of the results. We acknowledge that FFM is an important factor when assessing nutritional status in patients with cancer and absence of FFM is a limitation to our study. As the design of our study is retrospective, some of the missing measurements in patient records such as triceps skin fold thickness (TSFT) that estimates fat mass (FM) and mid-upper arm circumference (MUAC) that estimates lean

body mass (LBM) [2, 5] have limited our results. Tools such as Bio-electrical impedance assessment (BIA) and dual energy x-ray absorptiometry (DXA), which would be more precise in showing these variables, are not currently in use in routine clinical practice in the country.

Conclusion

This study underlined the benefits of ONS treatment in terms of BMI status among pediatric oncology patients. However, it should be noted that the recovery rate of nutritional status depends on the malignancy type and location. Further studies with larger cohorts are required to demonstrate the rate of improvement for each tumor sub-group to estimate the type of the nutritional intervention more fittingly.

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Comparison of computerized tomography angiography and digital subtraction angiography in aneurysmal subarachnoid hemorrhage

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Abstract

Background/Aim: A subarachnoid hemorrhage (SAH) usually occurs between the ages of 45-60 years and its prevalence is 2-32 per hundred thousand. Approximately 70-80% of SAHs develop as a result of aneurismal hemorrhage. Studies examining the two methods in the literature are insufficient. The goal of this study was to compare CT angiography (CTA) and digital subtraction angiography (DSA) in the management of patients with aneurysmal subarachnoid hemorrhage (ASH).

Method: In this retrospective cohort study, the CTA and DSA records of patients who were followed up due to aneurysmal SAH were retrospectively examined. The location and size of the aneurysm were measured. The patients were transported to the DSA unit within 1-12 hours once they stabilized and the records of the patients who underwent DSA for Anterior Communicating Artery (Ant.Com.A), Basilar Artery (BA), MCA and Posterior Communicating Artery (Post.Com.A.) for diagnostic purposes were assessed.

Results: Our study included a total of 69 aneurysm cases complying with our criteria. Twenty-four (34.8%) were at the Ant.Com.A, 6 (8.7%) were at the BA, 32 (46.4%) were at the MCA and 7 (10.1%) were at the Post.Com.A. When the alignment between DSA and CTA results was examined according to the location, eighteen cases with Ant.Com.A aneurysm, and eighteen cases with MCA aneurysm were coherent, while six and fourteen cases of Ant.Com.A and MCA aneurysm, respectively, were not (p>0,05). An analysis in terms of size revealed that DSA was more sensitive in patients with aneurysms <1 cm, while both DSA and CTA showed equal rates of sensitivity in aneurysms>1 cm. Overall, no significant difference was found (Ƙ=-0.075, -0.120; π= -0.107, -0.200; P=0.600) between DSA and CTA in terms of accuracy of showing aneurysmal location (Ƙ=-0.050, π= -0.076; P=0.650).

Conclusion: In SAH due to aneurysms, CTA can be preferred, and treatment can be planned based on its results because it is more accessible and cheaper, does not require specially trained physicians and technicians, enables easier control of post-operative brain CT, and reduces patient referrals between health institutions for diagnostic purposes.

Keywords: Subarachnoid hemorrhage, Aneurysm, CT angiography, DSA

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Introduction

Approximately 70-80% of subarachnoid hemorrhages (SAH) develop due to aneurysmal hemorrhage [1, 2]. SAH usually occurs between the ages of 45-60 years and its prevalence is 2-32 per hundred thousand [3]. Ninety percent of patients with SAH due to aneurismal hemorrhage visit the emergency room with complaints of severe headache, and these patients may exhibit signs of increased intracranial pressure. Overall mortality rate in patients with SAH is over 70%. In bleeding aneurysms, rebleeding risk is 50% within the first 6 months, while the bleeding risk of non-bleeding aneurysms is 1% within the first year [4].

The etiology of spontaneous intracerebral hemorrhage in some patients is brain aneurysms. When patients with spontaneous intracerebral hemorrhage visit the emergency room or the polyclinic, these patients must first undergo cranial computed tomography angiography (CTA) and then digital subtraction angiography (DSA) scan to rule out aneurysm [5]. Usually, cranial CT or CTA scan is performed first since it is easier and more practical [6]. When CT scan is performed within the first 12 hours, it shows the hemorrhage at a rate of 98-100%. Both CTA and DSA are recommended methods for investigating the presence of an aneurysm. Obviously, both imaging methods have their specific advantages and disadvantages. We know that FLAIR MRI has also been used recently. However, it is currently believed that the best diagnostic modality is DSA [7], which yields better images of aneurysms in deep and complex anatomical locations. Based on DSA imaging, 10-20% of aneurysms are multiple [8].

The sensitivities of CTA and MRI are 95% and 94%, respectively, in aneurysms over 3 mm. Sensitivity reduces as size decreases [9]. An error rate of 15% is observed in CT angiography. It is argued that DSA is more sensitive when performed ideally; however, it also involves an error rate of 16%. No intervention is required for CT angiography and it is cheap, while DSA requires a special unit at the hospital, specifically trained personnel, and physicians. DSA is a costly diagnostic modality which is not available in most centers [10].

The aim of the present study is to compare CTA and DSA for the diagnosis and follow-up of patients with SAH.

Materials and methods

In this retrospective cohort study, the CTA and DSA records of patients followed up due to aneurysmal SAH in Adiyaman Training and Research Hospital Neurosurgery Clinic between 30.06.2017-01.04.2020 were evaluated retrospectively. Data collection were performed through the Picture Archiving and Communications System (PACS) of the hospital. Approval was obtained from Adiyaman University Ethics committee on 18.05.2020 with the decision number 2020/5-19 prior to starting the study. Criteria for inclusion were as follows: Spontaneous SAH, diagnosis of aneurysm, hospitalization in the intensive care unit or the ward, and having underwent CTA and DSA scan. Patients with traumatic subarachnoid hemorrhage, hypertensive thalamic hemorrhage, tumoral hemorrhage, post-infarct hemorrhage, arterio-venous hemorrhages, and negative results in both DSA and CTA were not included in the study. Patients who visited the emergency room of our hospital with a SAH diagnosis were administered 0,625-2,5 ml of contrast agent and CTA scan was performed within 5-10 seconds. In cases with aneurysm, the location and size of the aneurysm were measured. After stabilization, the patient was transported into the DSA unit within 1-12 hours, and 4-vessel DSA was performed with ioheksol, an opaque agent, and recorded for diagnostic purposes.

Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) software was used to analyze the variables. The compliance between the CTA and DSA methods were evaluated by Kappa and Phi statistics. Categorical variables were presented in percentage. Variables were examined with 95% reliability level, and $P<0.05$ was considered statistically significant.

Results

A total of sixty-nine aneurysm cases (Alpha (α) error: 0.05, Beta (ß) error: 90%, Strength of Study: 0.90) were included in our study. Power analysis and sample size calculation were performed with Gx POWER 3.1.9.7 program. Twenty-four (34.8%) of these aneurysms were at the Ant.Com.A, 6 (8.7%) were at the BA, 32 (46.4%) were at the MCA and 7 (10.1%) were at the Post.Com.A. Among patients who underwent DSA and CTA, 17 (24.6%) and 13 (18.8%) patients, respectively, were not diagnosed with aneurysm, while 52 (75.4%) and 56 (81.2%), respectively, were (Tables 1, 2).

Table 1: Distribution of the aneurysm locations and sizes

	n	%
Location		
AntComA	24	34.8%
BA	6	8.7%
MCA	32	46.4%
PComA	7	10.1%
DSA		
Absent	17	24.6%
Present	52	75.4%
CT angiography		
Absent	13	18.8%
Present	56	81.2%
Size		
< 1 cm	33	47.8%
> 1 cm	36	52.2%

Table 2: DSA and BT angiography diagnosis rates

	DSA	CT angiography: Absent n (Row %) (Column %)	CT angiography: Present n (Row %) (Column %)	Total	Ƙ (SE)	π	*P*-value
Location	AntComA						
	Absent	0	5 (100) (21.7)	5 (20.8)	-0.075 (0.065)	-0.107	0.600
	Present	1 (5.3) (100)	18 (94.7) (78.3)	19 (79.2)			
	Total	1 (4.2)	23 (95.8)	24 (100)			
	BA+PComA						
	Absent	0	0	0 (0)	-	-	-
	Present	10 (76.9) (100)	3 (23.1) (100)	13 (100)			
	Total	10 (76.9)	3 (23.1)	13 (100)			
	MCA						
	Absent	0	12 (100) (40)	12 (37.5)	-0.120 (0.078)	-0.200	0.258
	Present	2 (10) (100)	18 (90) (60)	20 (62.5)			
	Total	2 (6.3)	30 (93.8)	32 (100)			
Size	< 1 cm						
	Absent	0	16 (100) (61.5)	16 (48.5)	-0.419 (0.125)	-0.503	0.004
	Present	7 (41.2) (100)	10 (58.8) (38.5)	17 (51.5)			
	Total	7 (21.2)	26 (78.8)	33 (100)			
	> 1 cm						
	Absent	0	1 (100) (3.3)	1 (2.8)	-0.050 (0.044)	-0.076	0.650
	Present	6 (17.1) (100)	29 (82.9) (96.7)	35 (97.2)			
	Total	6 (16.7)	30 (83.3)	36 (100)			
Total							
	Absent	0	17 (100) (30.4)	17 (24.6)	-0.271 (0.050)	-0.275	0.022
	Present	13 (25) (100)	39 (75) (69.6)	52 (75.4)			
	Total	13 (18.8)	56 (81.2)	69 (100)			

Kappa Statistics test, Ƙ: Kappa Coefficient, π: Phi Coefficient, SE: Standard Error

The sensitivities of DSA and CTA were examined with regards to location. The results of 18 aneurysms at the Ant.Com.A, and 18 aneurysms at the MCA were accurate, while those of 6 and 14 cases, respectively, were not. No significant difference was found between the sensitivities of the two modalities with regards

to location (Ƙ=-0.075, -0.120; π= -0.107, -0.200; *P*=0.600, 0.258, respectively). Aneurysms at the BA+P Com. region were mildly more accurately shown by DSA compared to CTA.

In aneurysms <1 cm in size, the aneurysm was accurately shown in 10 patients, while the contrary was true in 23 cases. A significantly negative correlation was found between aneurysm size and the accuracy of the imaging modality (Ƙ=-0.419, π= -0.503; *P*=0.004). This means that although DSA was more sensitive in aneurysms under 1 cm, both methods were more sensitive in identifying aneurysms over 1 cm (Ƙ=-0.050, π= -0.076; *P*=0.650).

When all cases were examined, the aneurysms of thirty-nine cases were shown accurately while those of 30 cases were not. DSA and CTA showed aneurysms at the Ant.Com.A. and MCA equally accurately, while DSA provided mildly superior results in showing aneurysms at the Basilar Artery and P.Com.A. regions (Ƙ=-0.271, π= -0.275; *P*=0.022).

Discussion

Morgani and Buimid discovered that aneurysmal bubbles in brain vessels caused hemorrhage in the 18th century. Egas and Monis introduced cerebral angiography in 1927. The first internal carotid artery aneurysm surgery was performed in 1931, which was followed by the first surgery to clip an aneurysm in 1939. In later stages, microvascular surgeries were performed with microscopes, and additional endovascular treatments have been used for the last 10 years [4]. SAHs mainly occur due to trauma; however, the most common reason for spontaneous SAHs is aneurysm. Aneurysms occur because of dilatation of the vessel due to pulsation at the weakest segment of the vessel wall. Various factors, such as hypertension, smoking, alcohol use and hereditary variables contribute to the formation of an aneurysm. Aneurysms are classified based on their sizes and shapes as follows: Small (10 mm and smaller), large (10-25 mm), giant (over 25 mm), saccular, fusiform, and dissecting [11]. Most are found in the anterior communicating artery, middle cerebral artery, posterior communicating and basilar artery, in decreasing order [4]. The anatomical distributions of our patients' aneurysms were in line with the literature, such that Ant. Com. A. was the most common aneurysmal location in our study group. CTA, MRI-FLAIR and DSA are diagnostic modalities of aneurysm. CTA can be used to image intracranial and extracranial structures [11]. The timing of contrast must be adjusted carefully especially during angiography to yield useful images. Although it is a noninvasive method, contrast is administered to these patients. Compared to MRI angiography, CT angiography produces less artifact, is faster, and easier to perform in intubated patients. It is less time-consuming, cheaper and facilitates scanning patients with pacemakers or other metals. Another feature of CTA is that it provides the best images which show the relationship between aneurysms, vessels, and bone structures [13,14]. CTA was performed first in our patients due to its easiness, cost-effectiveness, and ability to show the relationship with bony structures. MRI angiography was used in unclear or exceptional cases. Embolus, bleeding, encephalopathy, and headache are encountered less frequently in CTA compared to DSA [15]. It also shows the calcifications in the aneurysm neck or vascular structures. In CTA, 100cc 60% Meglumine diatrizoate is administered in bolus form, and scanning is performed in 1- or 1.5-mm sections which can then be converted to 3D form [6]. Patients with SAH who visited the emergency room of our hospital were administered 50cc of the contrast agent ioheksol, after which CTA and 3D imaging were performed by the radiologist within 5-10 seconds. The location and size of the aneurysm were measured. In our cases, vascular calcifications, or calcifications around the aneurysm were also occasionally found.

DSA is used in carotid end-arterectomy, bypasses involving the superficial temporal artery and middle cerebral artery, for the detection of intracerebral aneurysms and during endovascular coiling [16]. We only scanned four vessel angiographies in our patients for diagnostic purposes and checked the location and size of cerebral aneurysm. DSA may yield 25% negative results in subarachnoid hemorrhage [17]. In the study conducted by Paez Granda [10], it has been reported that DSA may be mistaken at a rate of 15%. In the study conducted by Zwanzger et al. [8] it has been emphasized that CTA and DSA have separate advantages based on location. Pozzi-Mucelli [18] reported no significant differences between CTA and DSA. In our study, we observed that CTA was more accurate in some locations, while DSA was better in anatomically complex and deep aneurysms. DSA scans may present better results; however, it is difficult to perform and requires a specialist, a trained team and separate radiological equipment. It is also more expensive. DSA has more side effects compared to CT angiography and MRI angiography, and it may cause cortical blindness, bilateral amblyopia or amaurosis, impairment in eye movements, headache, memory loss, aphasia, hemiparesis, mental function disorder, coordination disorder, confusion, seizure or even coma. Although most of these complications recover within 12 hours, they may last for a few weeks [19-21]. In the study conducted by Miao Li et al. [22], cortical blindness is observed more commonly in patients with chronic hypertension. As Tan et al. [23] emphasized in their study, hemodynamics and some severe chronic diseases must not be present in patients to safely perform a DSA scan. These comorbidities present less risk in CT angiography. Our patients had particularly high Glasgow coma scores and those we could evaluate in terms of consciousness had headache, nausea, and vomiting, and temporary short-term confusion. One patient experienced a seizure in the follow-up period and no patient became comatose.

The symptoms of these patients start with severe headache, and may continue with nausea, vomiting, confusion, double vision, and seizures. Patients with an aneurysm may experience complications such as rebleeding, hydrocephalus, vasospasm, and hyponatremia [24]. There are two approaches for treating these patients. The first one is clipping the aneurysm by microdissection using microscope under open surgery, and the other one is endovascular coiling which has improved within the last 10 years [25]. For classification of these patients, brain CT and Fisher scale, Hunt and Hess scale, modified Rankin score and World Federation of Neurological Surgeons (WFNS) scales are used [26].

The limitations of the study are the small number of cases, its single center design, and the lack of follow-up after two years.

Conclusion

CTA, MRI angiography or DSA can be performed to rule out aneurysm in a patient presenting with SAH. CTA is the fastest and cheapest diagnostic method with no less reliability than other methods and it provides better images in some locations. We wanted to emphasize that CTA scan must be the first imaging choice and treatment can be planned based on its results. This way, patient referrals between health institutions for DSA may be reduced, and DSA can be performed in brain-CT-negative and deep aneurysms. CTA is more common among health institutions, cheaper, does not require specially trained physicians and technicians, and enables easier obtainment of postoperative control brain CT.

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Evaluation of the effect of patient position in the management of chronic heart failure patients presenting with dyspnea

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Ethics Committee Approval
This study was initiated in the emergency department of a university hospital following the ethics committee approval. (Düzce University Non-Invasive Health Research Ethics Committee's approval with decision number 2020/55, March 16, 2020)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: One of the pathomechanisms of congestive heart failure is inadequate cardiac load, and one of the physiological ways to reduce cardiac load is to decrease venous return. Based on this mechanism, we aimed to reduce venous return and alleviate cardiac load in patients by drooping their legs. In this study, we aimed to evaluate the impact of leg position on patients' comfort and treatment, emphasize that patient position is valuable enough to be included in the treatment algorithm, and determine the effects of the patient sitting with legs hanging down position in an armchair (sitting position), or upright with the straight knees position on a stretcher with the stretcher's head at 90°C (high Fowler's position) on the patient's perception of dyspnea in chronic heart failure (CHF).

Methods: Patients over 18 years of age, followed-up with CHF diagnosis who presented to the emergency department (ED) with dyspnea were included in this case control study. The participants were divided into high Fowler's and sitting groups. According to the Visual Analog Scale (VAS) scoring, patients were asked to point to the severity of dyspnea. Patients' vital signs, 30-day mortality, and VAS scores were recorded at the 0^{th}, 15^{th}, 30^{th}, and 60^{th} minutes.

Results: A total of seventy-four patients were included in the study. Thirty-eight patients in the high Fowler's group, and thirty-six patients in the sitting group were treated. VAS started to decrease significantly at 15 minutes in sitting position. Although baseline VAS scores were higher at sitting than at the high Fowler's position, the end of the 60^{th} minute VAS scores and respiratory rate were significantly lower in the sitting group (P=0.016, and P=0.008, respectively). The mortality rate was significantly higher in the high Fowler's group (P=0.028).

Conclusions: We concluded that patient position plays a vital role in patients' perception of dyspnea and mortality in the acute treatment of CHF patients presenting with dyspnea. Perception of dyspnea disappears earlier, and mortality is lower in the sitting position.

Keywords: Dyspnea, Heart failure, Patient position, Upright sitting, Fowler's position

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Introduction

The most common reason for patients with chronic heart failure (CHF) presenting to the emergency department (ED) is dyspnea [1]. Relieving dyspnea is the primary target of acute heart failure treatment. Dyspnea is a regulatory criterion for the approval of novel therapeutic agents and the common endpoint in clinical studies on acute heart failure [2, 3].

There is still no accurate, safe, reproducible, and methodology-validated tool for the assessment of dyspnea. The most used scale to evaluate the level of dyspnea is Visual Analog Scale (VAS), which provides better results in the assessment of dyspnea severity [4-6].

A decrease in a patient's perception of dyspnea is essential for patients, physicians, and clinical studies. Studies about the importance of patient position in assessing the severity and management of dyspnea are limited [7]. Therefore, we planned this study to emphasize the importance of patient position in acute treatment protocols for heart failure and show that it should be considered in the treatment algorithm.

There are differences in dyspnea perception, including the differences in patient profile, cultural interpretation of dyspnea, and other factors. To determine the effects on dyspnea interpretation, we included the vital parameters of the patient, such as heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and arterial blood gas (ABG) values in the assessment together with VAS.

In the supine position, venous blood in the abdomen and lower extremities are mobilized, and venous return to the thoracic compartment increases (250-500 mL), further elevating pulmonary venous and capillary pressures. This may result in pulmonary edema, decreased pulmonary compliance, increased airway resistance, and dyspnea [8]. We tried to reduce the contribution of venous circulation in the lower extremities by giving the patient a sitting position with legs hanging down and revealing the effect of this position on dyspnea.

Patients are usually positioned on a stretcher with the stretcher's head at 90ºC, and the patients in upright position with legs stretching straight forward.

The objective of this study was to determine the effects of upright sitting with legs hanging down in an armchair (sitting position) or sitting upright with straight knees on a stretcher with the head of the stretcher at 90°C (high Fowler's position) on the severity of dyspnea and heart failure treatment and emphasize that patient position is valuable enough to be included in the treatment algorithm.

Materials and methods

Study setting and design

This is a case control study conducted on patients with CHF who presented to the ED with dyspnea complaints between April 1, 2020- September 1, 2020. The study was initiated after the approval of the Ethics Committee of our institution (ID: 2020/55; 16 March 2020).

This study was conducted in the ED of a tertiary care university hospital, which admits about 75,000 patients per year. Treatment was administered in accordance with the "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure" [9]. To avoid bias, the patients who met the inclusion criteria were included in the groups consecutively and sequentially according to the order of admission to the hospital.

Participants and measurements

Patients in the chair (sitting group) were seated upright with legs hanging down (sitting position). Patients in the stretcher (high Fowler's group) were given an upright sitting position with legs stretching straight forward on a stretcher, with the stretcher's head at 90°C (high Fowler's position). Patients' gender, age, comorbidities were recorded, HR, RR, SBP, DBP, oxygen saturation (SpO_2), and ABG were measured after being seated on a chair or a stretcher. Chest ultrasonographic (US) examination was performed with the bedside LOGIQ P9 ultrasonography device (GE Healthcare, Tampa, USA), B lines were examined, and ejection fraction (EF) was measured with an echocardiography (echo) device. The researcher who conducted the study had a certificate showing that he was capable of ultrasonographic and echocardiographic evaluation.

The patient was asked to indicate the severity of shortness of breath according to the VAS score, assigning a number between 0-10. Zero indicated no dyspnea, while ten indicated the most severe dyspnea the patient has ever experienced. HR, RR, SBP, DBP, SpO_2, and VAS scores were measured at minutes 0, 15, 30 and 60. Blood gas was routinely monitored with Radiometer ABL800 flex device (Radiometer, Istanbul, Turkey) at minutes 0, 30, and 60 after beginning the treatment. Effect of the treatment position on the dyspnea perception and treatment were compared between the sitting and high Fowler's groups.

Inclusion criteria: Patients with a diagnosis of heart failure, COPD, and those who fulfill the following criteria were included in the study: Being over 18 years of age and presenting to the ED with moderate-to-severe dyspnea, RR >20 breaths/minutes, use of accessory respiratory muscles, bilateral rales on chest auscultation, pH <7.35, partial pressure of arterial oxygen (PaO_2) <60mm Hg, SpO_2<94 at room air, typical findings on chest X-ray, and B lines on chest ultrasonography.

Exclusion criteria: Illiterate patients, those who did not sign an informed consent form to participate in the study, who required non-invasive mechanical ventilation, were intubated, or required intubation, those who had cardiac arrest during treatment, those with pH <7.1, SBP <90 mm Hg, acute myocardial infarction, or a history of trauma were excluded.

Sample size

The minimal sample size required for the study was fifty-four with 0.5 effect size, 95% confidence interval and 5% significance level, as determined by the G*Power (Version 3.1.9.4) program. The study was performed with all seventy-four patients who met the inclusion criteria and who were admitted to the emergency department within 6 months.

Statistical analysis

The normality of continuous variables was checked with the Shapiro-Wilk test. Student's t-test was used to analyze two normally distributed ($p>0.05$) data sets, while Mann-Whitney U test was utilized to compare two sets of non-normally distributed ($p<0.05$) data. ANOVA was applied on repeated measures to compare normally distributed data between several time points in the same group. If the result was statistically significant, multiple

comparisons were made using the paired t-test with Bonferroni correction. Friedman's test (Dunn-Bonferroni test for multiple comparisons) was used as a nonparametric alternative to ANOVA for Repeated Measures. The correlation between two categorical variables was analyzed with Pearson's Chi-square test. Normally distributed variables were expressed as mean (standard deviation (SD)); non-normally distributed variables were presented with median (interquartile range (IQR)). Categorical variables were reported as a percentage. All analyses were performed using the statistical software SPSS version 19.0 (SPSS Inc., Armonk, NY). $P<0.05$ values were considered statistically significant.

Results

A total of seventy-four patients were included in the study. The median ages in the high Fowler's group (n=38, 55.3% males) and the sitting group (n=34, 58.3% males) were 73 (64.8-78) years and 71.5 (64-78.8) years, respectively. The patients' distribution in terms of age, gender, and chronic disease are shown in Table 1, which were similar between the two groups ($P>0.05$).

Table 1: Demographic characteristics of the groups

	High Fowler's (n=38)	Sitting (n=36)	*P*-value
Age - Median (IQR)	73 (64.8-78)	71.5 (64-78.8)	0.774
Gender - n (%)			
Female	17 (44.7)	15 (41.7)	0.790
Male	21 (55.3)	21 (58.3)	
Comorbidities - n (%)			
Diabetes			
No	25 (65.8)	26 (72.2)	0.550
Yes	13 (34.2)	10 (27.8)	
Hypertension			
No	16 (42.1)	12 (33.3)	0.437
Yes	22 (57.9)	24 (66.7)	
Chronic Obstructive Pulmonary Disease			
No	21 (55.3)	22 (61.1)	0.610
Yes	17 (44.7)	14 (38.9)	
Coronary artery disease			
No	12 (31.6)	16 (44.4)	0.254
Yes	26 (68.4)	20 (55.6)	

IQR: Interquartile range

Table 2 shows vital signs measured at admission and the 15th, 30th and 60th minutes in both sitting and high Fowler's groups. Post-hoc analysis revealed that HR, RR, and SBP significantly decreased at 30 minutes, SpO_2 increased dramatically at 60 minutes compared to the baseline values, while VAS significantly reduced at 15 minutes compared to the baseline in the high Fowler's group. In the sitting group, HR did not decrease substantially during the 1-hour treatment, while a significant drop in RR started at the 15th minute. SpO_2 significantly increased at 60 minutes, SBP began to drop significantly at 15 minutes, and DBP significantly decreased at 60 minutes compared to the baseline values. VAS started to significantly drop at 15 minutes in the sitting group.

No statistically significant difference was observed between the groups in terms of HR and SpO_2 at the specified time points. Simultaneously, RR was significantly lower in the sitting group at the 60th minute ($P=0.045$). Although the sitting group's VAS scores were significantly higher than the high Fowler's group at the time of admission, these scores were significantly lower in the sitting group at the end of 60 minutes ($P=0.016$).

The comparison of vital values according to the changes at the specified time intervals between the sitting and high Fowler's groups is given in Table 3. While HR significantly decreased in the sitting group at 30 minutes compared to the baseline values ($P=0.020$), RR's decrease was significantly higher in this group ($P=0.008$). No statistically significant difference was found between the groups in terms of SPO_2 at different times ($P>0.05$). The change in SBP at 30 minutes was significantly higher in the sitting group ($P=0.047$), which further increased at the 60th minute ($P=0.040$). There was no significant difference in terms of DBP ($P>0.05$). VAS was significantly in favor of the sitting group with a difference that started to increase at 15 minutes and further increased gradually at 30 and 60 minutes ($P<0.001$).

Table 2: Comparison of body positions in terms of vital signs and VAS scores

		Time points				Within groups	Post Hoc analysis
		Baseline	15	30	60	*P*[b]	
HR	High Fowler's (n=38)	109.1 (28.4)	102.8 (23.3)	98.3 (21)	98.7 (21.8)	0.007	BL>30** BL>60*
	Sitting (n=36)	102.5 (27)	105 (32.8)	97.5 (25.8)	97 (33)	0.182	-
		100.4 (22.8)	98.8 (23.9)	99.5 (23.1)	97 (23)		
		95 (23.3)	94 (26.5)	97 (28)	96.5 (30.5)		
Between groups	*P*[a]	0.119	0.358	0.961	0.752[c]		
RR	High Fowler's	29.7 (7.1)	28 (6.1)	27.4 (6.8)	25.9 (6.1)	<0.001	BL>30** BL>60***
	Sitting	28 (9)	26.5 (8.3)	25 (9.3)	25 (9.3)		15>60**
		30.9 (5.1)	27.6 (5.1)	24.9 (5.2)	23.2 (5.5)	<0.001	BL>15**15>60***
		30 (6.8)	28 (8.3)	25 (6)	23 (8.3)		BL>30***30>60* BL>60***15>30**
Between groups	*P*[a]	0.290	0.987	0.172	0.045[c]		
SpO_2	High Fowler's	89.3 (9.7)	93.2 (5.9)	94.5 (3.7)	94.8 (5.1)	0.001	BL<30* BL<60**
	Sitting	93 (11)	93 (5.3)	95 (7)	96.5 (5)		
		90 (9.3)	92.3 (8.9)	94.3 (4.9)	95 (4.5)	<0.001	BL<30* BL<60***
		91.5 (9)	94 (7)	96 (5.5)	96 (5.8)		15<60*
Between groups	*P*[a]	0.850	0.765	0.815	0.887		
SBP	High Fowler's	137.8 (28.4)	130.3 (25.9)	127.1 (21.3)	125.4 (21.2)	0.010	BL>30** BL>60***
	Sitting	131 (30.3)	126.5 (36)	128.5 (25)	125 (25.5)		
		156.6 (28.9)	145 (27.4)	136.2 (26.3)	133.8 (23.5)	<0.001	BL>15**15>60** BL>30***
		152.5 (43)	138 (43.5)	131 (39.8)	130 (35.8)		BL>60***
Between groups	*P*[a]	0.006[c]	0.033	0.222	0.215		
DBP	High Fowler's	81.8 (17.1)	75.6 (17.2)	73 (16.4)	71.9 (14)	<0.001[d]	BL>15** BL>30**
	Sitting	81 (22.3)	74.5 (20.3)	72.5 (26.3)	68 (24.3)		BL>60**
		90.8 (20.3)	85.2 (15.5)	81.9 (15.8)	79.9 (13.7)	0.001[d]	BL>30* BL>60**
		93 (32.8)	87 (26.8)	80.5 (19.8)	79 (23.8)		
Between groups	*P*[a]	0.044[c]	0.013[c]	0.020[c]	0.016[c]		
VAS	High Fowler's	7.4 (1.7)	5.7 (1.6)	4.4 (1.8)	3.1 (2)	<0.001	BL>15**15>60*** BL>30***15>30**
	Sitting	7.5 (2)	6 (2)	4 (2.3)	3 (3.3)		BL>60*** 30>60**
		8.3 (1.2)	4.6 (1.9)	2.9 (1.6)	1.6 (1.5)	<0.001	BL>15**15>60*** BL>30***15>30**
		9 (1)	4 (3)	2 (2)	1 (1)		BL>60***30>60**
Between groups	*P*[a]	0.010	0.007	0.001	<0.001		

Variables are presented as mean (SD) (first row) and median (IQR) (Second row); [a]: Comparison between Upright and Sitting groups (Mann Whitney-U test); [b]: Comparison between Baseline (BL); 15-, 30- and 60-min groups (Friedman test); [c]: Student t test; [d]: Repeated measure ANOVA; Post-hoc analysis with Bonferroni correction; *: $P<0.10$; **: $P<0.05$; ***: $P<0.001$. HR: Heart rate; RR: Respiratory Rate; SpO_2: oxygen saturation; SBP: Systolic Blood Pressure DBP: Diastolic Blood Pressure VAS: Visual Analog Scale

Table 3: Comparing patient positions in terms of changes in vital signs and VAS scores according to time intervals

	Time interval	High Fowler's	Sitting	*P*-value
HR	Baseline- 15 min	1 (14.3)	2 (11.5)	0.914
	Baseline- 30 min	7 (16.5)	1.5 (12.5)	0.020
	Baseline- 60 min	5.5 (21)	3.5 (24.8)	0.289
	15 - 30 min	2 (13.5)	-1 (12.3)	0.117
	15 - 60 min	1 (15.3)	1.5 (21.5)	0.657
	30 - 60 min	1 (12)	2.5 (13.3)	0.369
RR	Baseline- 15 min	2 (4)	2 (2)	0.117
	Baseline- 30 min	3 (5.8)	4 (4.5)	0.008
	Baseline- 60 min	4 (4)	7 (6)	0.001
	15 - 30 min	1 (4.5)	2 (2)	0.020
	15 - 60 min	2 (4)	4 (2.8)	0.006
	30 - 60 min	1 (4)	2 (1.8)	0.359
SpO_2	Baseline- 15 min	-2 (6.5)	-1.5 (5.8)	0.704
	Baseline- 30 min	-3 (11)	-2.5 (5.8)	0.996
	Baseline- 60 min	-4 (11)	-2.5 (7)	0.584
	15 - 30 min	-1 (4)	0 (3)	0.723
	15 - 60 min	-1.5 (5)	-1 (4)	0.794
	30 - 60 min	-1 (3)	-0.5 (2)	0.750
SBP	Baseline- 15 min	5 (18.8)	10 (23.8)	0.147
	Baseline- 30 min	10.8 (16.3)	20.4 (24.1)	0.047
	Baseline- 60 min	12.4 (19.7)	22.9 (23.4)	0.040
	15 - 30 min	3.2 (11)	8.8 (15.5)	0.081
	15 - 60 min	2 (20.3)	9 (20.8)	0.101
	30 - 60 min	1.7 (8.6)	2.5 (15.6)	0.783
DBP	Baseline - 15 min	6.3 (11.9)	5.6 (16.4)	0.826
	Baseline- 30 min	8 (16.8)	11.5 (26.5)	0.729
	Baseline- 60 min	9.9 (14.3)	10.9 (18.4)	0.801
	15 - 30 min	1 (12.8)	2 (20.3)	0.808
	15 - 60 min	3.6 (12.7)	5.3 (16)	0.613
	30 - 60 min	3.5 (12.3)	0.5 (12)	0.615
VAS	Baseline- 15 min	2 (1.3)	4 (2.8)	<0.001
	Baseline- 30 min	3 (2.3)	6 (3)	<0.001
	Baseline- 60 min	4 (3)	7 (2)	<0.001
	15 - 30 min	1 (1)	2 (1)	0.121
	15 - 60 min	3 (2.3)	3 (2)	0.416
	30 - 60 min	1 (1)	1 (1)	0.846

SD: Standard deviation; IQR: Interquartile range; HR: Heart rate; RR: Respiratory Rate; SpO_2: oxygen saturation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure VAS: Visual Analog Scale; Numerical variables are presented as mean (SD), or median (IQR).

Changes in ABG values were compared between the high Fowler's and sitting groups for all specified time intervals (Table 4). No significant difference was found between the high Fowler's and sitting groups in terms of the difference in lactate levels. pH differences between baseline values, and 30 and 60 minutes were significantly higher at the sitting position (BL-30: P=0.002, BL-60: P=0.003). O_2 differences were higher in the sitting group at 30-60 minutes (P=0.003). CO_2 values dropped more profoundly from baseline at the 30th and 60th minutes in the sitting group (BL-30: P=0.024, BL-60: P=0.012). SpO2 values were markedly higher at the 60th minute compared to baseline in the sitting group (P=0.012)

Table 4: Comparing patient positions in terms of differences in blood gas parameters according to time intervals

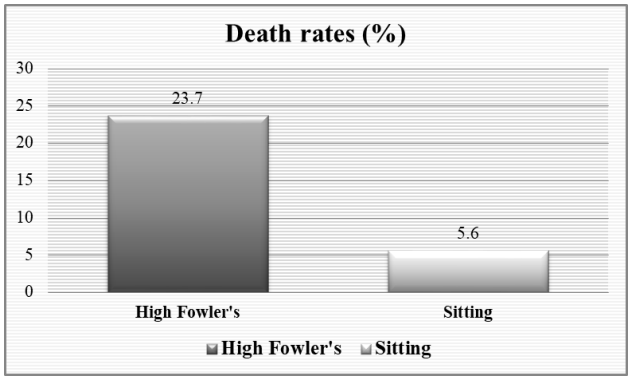
	Time interval	High Fowler's	Sitting	*P*-value
pH	Baseline- 30 min	-0.015 (0.1)	-0.045 (0.1)	0.002
	Baseline- 60 min	-0.02 (0.1)	-0.065 (0.1)	0.003
	30 - 60 min	-0.01 (0)	-0.01 (0.1)	0.597
O_2	Baseline- 30 min	-9.8 (14.4)	-8.6 (17.5)	0.991
	Baseline- 60 min	-13.1 (14.6)	-18.1 (15.7)	0.163
	30 - 60 min	-2 (6)	-5.4 (9.2)	0.003
CO_2	Baseline- 30 min	1.8 (11.7)	4.8 (4.6)	0.024
	Baseline- 60 min	2.2 (13.4)	5.2 (5.6)	0.012
	30 - 60 min	1 (5)	1.1 (5.4)	0.824
Lactate	Baseline- 30 min	0.5 (0.8)	0.7 (0.6)	0.398
	Baseline- 60 min	0.9 (1.3)	1 (0.6)	0.523
	30 - 60 min	0.5 (0.8)	0.5 (0.5)	0.700
$ASpO_2$	Baseline- 30 min	-2.6 (5.1)	-4.5 (6.2)	0.143
	Baseline- 60 min	-2 (5.8)	-4.8 (8.4)	0.012
	30 - 60 min	-0.5 (2.8)	-1.1 (5)	0.112

$ASpO_2$: SpO_2 value in arterial blood gas. The values are presented as median (IQR).

Echocardiography was performed in all patients within the first hour. No significant difference was found between the groups regarding EF values measured with echo (P=0.243).

The rate of mortality was significantly higher in the high Fowler's (23.7%) group than in the sitting (5.6%) group (P=0.028) (Figure 1).

Figure 1: Mortality rates of the high Fowler's position and sitting position



Discussion

Literature review showed that the effect of patient position on the perception of dyspnea, which is the most common cause of presentation to the ED in heart failure, has not been studied. This study will contribute to finding the best approach for providing comfort to CHF patients diagnosed with dyspnea and reducing the density in emergency services. We found that dyspnea was affected by patient position. According to the VAS score, when the patients self-assessed dyspnea, a significantly more effective decrease was observed in the sitting position compared to the high Fowler's position.

Classification of patients' dyspnea complaints may play an essential role in evaluating the patient, planning interventions, and predicting the prognosis. Previous studies have shown that VAS better captures the changes in dyspnea over time compared to other scales and that positioning the patient during measurement (sitting upright vs. supine) affects the reactions [5, 10]. Therefore, we preferred VAS in our study because it is used more widely, and its validity and reliability have been proven in many studies [3, 11].

Timing of dyspnea measurement is essential. It would be ideal to measure dyspnea at its peak to calculate the greatest difference from the worst dyspneic status. Although most patients present with dyspnea, they recover with standard treatment. Thus, measurement delay can affect the patient selection and limit the opportunity to demonstrate new treatments' effectiveness [5]. Patients included in the studies are usually evaluated and reported within the first hour.

Being in an upright or semi-sitting position reduces venous return and is beneficial in patients with heart failure [12]. Studies evaluating the effect of body position on pulmonary function have found that pulmonary function improved both in healthy subjects and patients with pulmonary disease, cardiac disease, neuromuscular diseases, and obesity with a more upright posture [13]. Recumbent positions induce an increase in airway resistance and possibly large airways, limiting expiratory volumes and flow [14, 15].

We investigated the effect of patient position on dyspnea perception and vital signs. SBP, RR and VAS significantly decreased in the sitting group in the first 15 minutes, while HR, RR, and SBP significantly reduced in the upright group at 30 minutes. This result indicates that the sitting group responds to treatment faster in terms of vital signs. However, VAS significantly decreased in both groups at 15 minutes, suggesting no significant difference between both groups in terms of dyspnea perception at 15 minutes, although the VAS score was

significantly lower in the sitting group at the end of the 60th minute.

Studies showing the relationships between patient relief following dyspnea treatment, mortality rate, or hospitalization due to heart failure have reported mortality rates between 5-15% [16, 17]. Our study's mortality rate was 23.7% in the high Fowler's position and 5.6% in the sitting group. The mortality rate was significantly higher in the high Fowler's group, and accordingly, it can be said that patient position affected mortality.

Dyspnea develops not because of a single pathophysiological mechanism but after disruption in numerous systems. Both cardiac and pulmonary reasons are prominent in the etiology in about one-third of patients presenting to the ED with the complaint of dyspnea. In our study, 22 patients had hypertension, 17 patients had chronic obstructive pulmonary disease, and 26 had coronary artery disease, in line with the literature.

Studies have shown that vital hemodynamic parameters and cardiac output may change depending on the body position in CHF patients [18]. In a study by Vitacca et al. [19], it was observed that HR did not increase, while cardiac index and left atrium pressure decreased in the supine position. In our study, HR significantly decreased in the high Fowler's position at 30 minutes. This may be due to different patient positions.

Studies about vasodilators have shown that a rapid drop can be provided in cardiac filling pressure between the right-left sides in CHF, resulting in dyspnea relief [20, 21]. When the patient is in the sitting position, the blood will be pooled in the periphery, resulting in a decrease in cardiac filling pressure and dyspnea relief.

Limitations

The first limitation of the study was its single centered design. Second, the patient's body positions were not evaluated when the stretcher head was at different angles.

Conclusion

We concluded that in the acute treatment of CHF patients who presented with dyspnea, the patient's body position plays an essential role in hemodynamics, mortality, and the patient's perception of shortness of breath. The perception of shortness of breath in the sitting position disappears significantly earlier, and the mortality rate in these patients is lower. In CHF patients' acute management, choosing the patient position, especially the sitting position, will contribute positively to patient comfort.

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Examination of craniofacial parameters in Turkish males with golden ratio in piriform aperture size

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Ethical permission was obtained from Bolu Abant Izzet Baysal University, Clinical Research Ethics Board for this study on 29.09.2020 with the decision number of 2020/235.
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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Piriform aperture, an anatomical structure usually in the form of a pear, is created by the maxilla and nasal bone. The shape and width of PA have significant effects on nasal breathing and are also aesthetically important. In the present study, it was aimed to reveal normal morphometric values by evaluating the craniofacial parameters of young Turkish male cases at the piriform aperture with the help of computerized tomography.

Methods: A total of six craniofacial parameters were examined from the 3-dimensional computerized tomography reconstruction images of 103 young adult male cases with golden ratios between the ages of 21 and 30 years. Three indices were calculated from these craniofacial parameters and nine parameters were evaluated. The cases were divided into four groups according to the ratio of the piriform aperture. The descriptive values for the data obtained from craniofacial parameters and indices were calculated as mean and standard deviation. In terms of measurements, the differences between the groups were examined with ANOVA analysis.

Results: In our study, there were five cases in the 1st group, 39 cases in the 2nd group, 38 cases in the 3rd group, and 19 cases in the 4th group. Two cases were not included in any of the groups. Significant differences were detected between the groups in terms of maximum cranial width, bizygomatic width, nasal width and upper face index parameters (P<0.05).

Conclusion: Differences were detected between the groups in which craniofacial parameters of all male cases were examined. In the inter-group examination, the craniofacial parameters of only a few cases fit the golden ratio fully. For this reason, we recommend examining the identifying values of the craniofacial parameters of more faces on which the piriform aperture is fully compatible with the golden ratio.

Keywords: Golden ratio, Piriform aperture, Facial aesthetics, Craniofacial parameters, Young adult Turkish males

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Introduction

Piriform aperture (PA) is an anatomical structure usually in the form of a pear, created by the maxilla and nasal bone from facial bones [1]. The shape and width of PA have significant effects on the effectiveness of nasal breathing and are also aesthetically important because the PA is at the center of the face [2, 3].

When the limited number of studies conducted on PA were examined in the literature, it was seen that the effects of gender and ethnic differences, particularly morphometric properties, were evaluated [3-5]. Morphometric studies concentrated on PA height and width parameters, and the golden ratio related to these parameters were detected by us in male cases for the first time [6]. Other researchers examining the golden ratio in PA studied the effect of gender and age on this rate [7].

The golden ratio is approximately 1:1.618, which is widely found in nature and is believed to represent an excellent agreement by ancient Greeks. Because of this feature of the golden ratio, there are studies conducted on facial aesthetics [8-10].

In the literature, the morphometric measurements of the parameters of the bony structure of the face were not evaluated among people with the golden ratio. It is also known that facial bones are affected by aging [11]. For this reason, there are no studies limiting the age range of cases and investigating the normal morphometric values of craniofacial parameters of cases with a golden ratio in the face area.

The purpose of this study was to limit the age range in Turkish male cases with the golden ratio in PA, evaluate the craniofacial parameters of young adults with the help of computerized tomography (CT), and determine the normal morphometric measurement values of these parameters.

Materials and methods

This study was conducted in Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Radiology. Ethical permission was obtained from Bolu Abant Izzet Baysal University, Clinical Research Ethics Board on 29.09.2020 with the decision number of 2020/235. The principles of the Helsinki Declaration were obeyed when the study was conducted.

In the literature, studies only include young adult male with a golden ratio of nasal height to PA height (n-ns:rh-ns) [6]. In this study, a total of 103 male cases aged between 21-30 years were evaluated with head CT images. The age range was limited because of the age-related change of the body midface skeleton and the bony tissue on the PA margins [11]. In our previous study [6], the average ratio of nasal height to PA height was calculated as 1.6658 (0.16671), which was presented as the golden ratio. In this study, the cases were divided into 4 groups, considering the deviations from the golden ratio.

• Cases that were fully compatible with the golden ratio (1.618) were included in the first group,

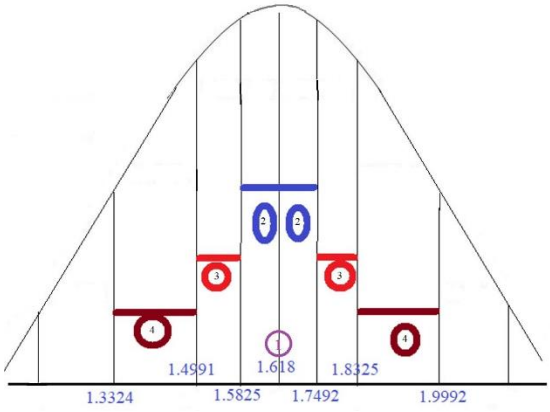
• Cases with values ranging between 1.5825-1.7492 were included in the second group (0.5 standard deviation (SD) from the golden ratio),

• Cases in the third group had a ratio of 0.5 SD to 1 SD from the golden ratio (at least 0.5 SD lower to 1 SD higher) (1.4991-1.8325),

• Cases with ratios of at least 1 SD, at most 2 SD from the golden ratio (1.3324-1.9992) were included in the fourth group.

Groups are graphically summarized in Figure 1.

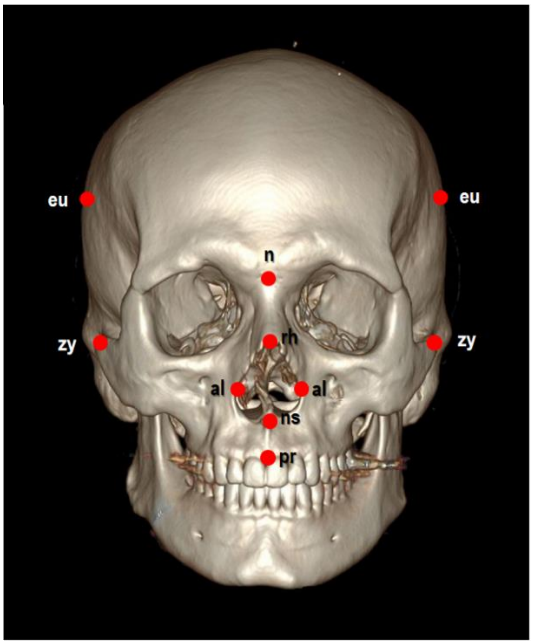
Figure 1: Groups formed by the ratio of nasal height to PA height



The six craniofacial parameters of the cases were measured by a radiologist with 3-Dimensional Computerized Tomography (3D-CT) reconstruction images of the head; and three facial indices were calculated from these measurements.

The seven different anatomical points and abbreviations regarding our parameters are euryon (eu), nasion (n), rhinion (rh), zygion (zy), alare (al), nasospinale (ns) and prosthion (pr), as presented in Figure 2.

Figure 2: Image of 7 different anatomic points in craniofacial skeleton



CT protocol

All patients underwent CT with 64-slice Multi-Detector CT (MDCT) device (Revolution EVO, GE healthcare, Waukesha, WI, the USA) with the same examination protocol using 64x0.5 mm collimation scanner with a gantry rotation speed of 400 ms/rotation, range of box of 450-500, image thickness of 5 mm, standard pitch factor of 0.641, reconstruction interval of 0.625 mm and a total exposure time of 11 seconds. Each scan was obtained with a tube voltage of 120KV and 320mAs. Images were transferred to a separate workstation (GE, Advantage Workstation 4.4) for measurements.

Measurements of parameters

A total of 6 different craniofacial parameters were measured in the head 3D-CT reconstruction images [12,13]. The

parameters were measured in millimeters (mm) and had a one-decimal measurement sensitivity. In addition, the age and six craniofacial parameter measurements were recorded for each patient in Excel Program.

1) Piriform aperture height (rh-ns): It is the distance between rhinion and nasospinale points.

2) Nasal height (n-ns): It is the distance between nasion and nasospinale points.

3) Upper face height (n-pr): It is the distance between nasion and prosthion points (Figure 3).

4) Maximum cranial width (eu-eu): This measurement, which is also called as maximum transverse width, is the distance between the euryon points on both parietal bones.

5) Bizygomatic width (zy-zy): This measurement, which is called face width, is the distance between the zygion points, i.e. the most lateral points on the zygomatic arcs.

6) Nasal width (al-al): It is the distance between the most lateral points of nasal alaria (Figure 4).

Figure 3: The representation of the 3 craniofacial parameters on 3D-CT reconstruction: 1) rh-ns; 2) n-ns; 3) n-pr

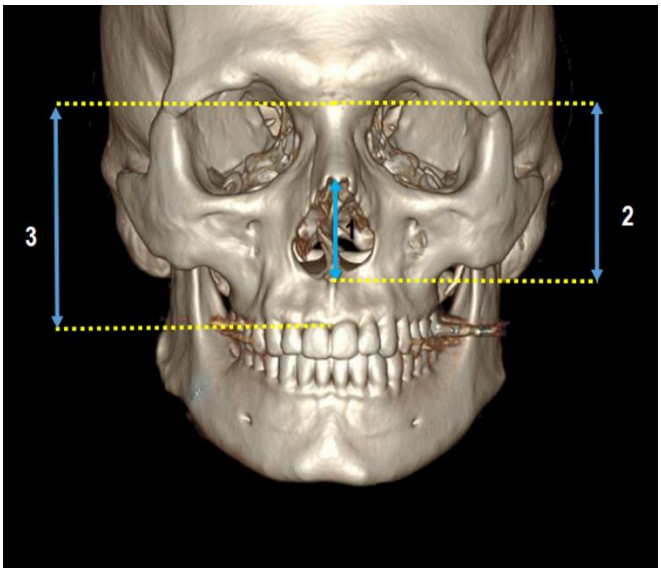
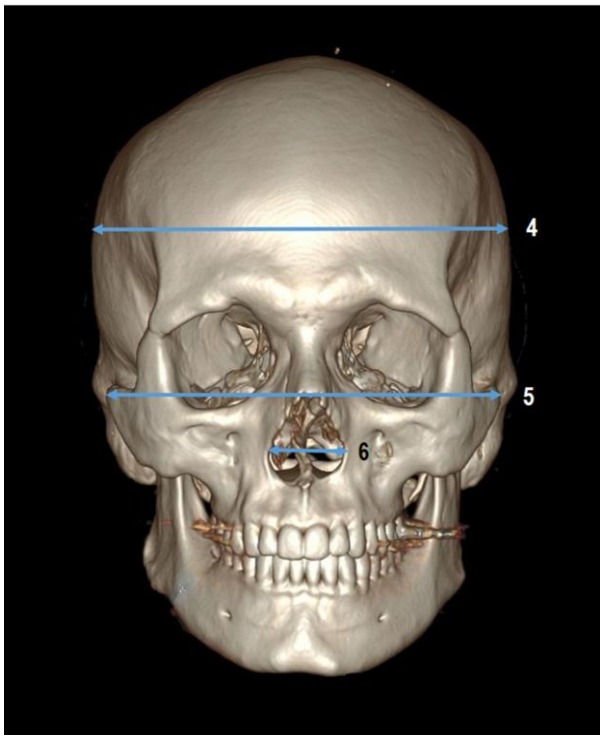


Figure 4: The representation of the 3 craniofacial parameters on 3D-CT reconstruction: 4) eu-eu; 5) zy-zy; 6) al-al



From the six craniofacial parameters measured, three indices were calculated using zy-zy, eu-eu, n-pr, al-al and n-ns parameters.

The explanations and abbreviations of the three indices calculated:

1) Transverse Craniofacial Index (TCFI): Calculated as (zy-zy) / (eu-eu) x 100.

2) Upper Face Index (UFI): Calculated as (n-pr) / (zy-zy) x 100.

3) Nasal Index (NI): Calculated as (al-al) / (n-ns) x 100.

Statistical analysis

The descriptive values of the data obtained were calculated as mean (Standard deviation). The fitness of the measurements to normal distribution was evaluated with the Kolmogorov-Smirnov Test, and the differences between the groups were examined with the ANOVA Model. Significant differences were determined with the Post-Hoc Tukey Test. $P<0.05$ was considered significant, and the SPSS (ver. 23) Program was used for calculations.

Results

A total of 103 cases aged between 21-30 years were examined in four groups. There were five cases in the 1st group, 39 cases in the 2nd group, 38 cases in the 3rd group, and 19 cases in the 4th group. Two cases were not included in any of the groups. The descriptive values of all cases are presented in Table 1.

The cases were grouped considering the mean and standard deviation values of the golden ratio index of PA. In the 1st group, the mean age of five patients who fully complied with the golden ratio of 1.618 was 27.80 (3.35) years. The craniofacial parameters of these cases are presented in Table 2.

Table 1: The descriptive values of 103 male cases with the golden ratio

n=103	Mean	SD	Minimum	Maximum
Age (years)	25.45	3.58	21	30
Golden ratio (n-ns:rh-ns)	1.667	0.14	1.368	2.019
rh-ns (mm)	32.34	2.23	25.60	38.90
n-ns (mm)	53.65	2.41	49.10	64.60
n-pr (mm)	73.78	3.66	66.90	85.40
eu-eu (mm)	152.87	6.80	137.10	167.80
zy-zy (mm)	139.94	5.17	124.70	150.60
al-al (mm)	24.11	1.80	20.30	27.90
TCFE (zy-zy:eu-eu)	91.60	2.43	86.05	97.00
UFI (n-pr:zy-zy)	52.76	2.65	47.61	61.46
NI (al-al:n-ns)	45.01	3.53	35.30	51.06

SD: Standard Deviation

Table 2: The descriptive values of the craniofacial parameters and indices of the male cases in group 1

n=5	Mean	SD	Minimum	Maximum
Golden ratio (n-ns:rh-ns)	1.6143	0.0023	1.6110	1.6161
rh-ns (mm)	32.82	0.63	32.30	33.60
n-ns (mm)	52.95	1.00	52.10	54.30
n-pr (mm)	72.44	3.60	67.90	77.50
eu-eu (mm)	154.36	7.15	147.20	165.30
zy-zy (mm)	139.24	4.59	135.90	147.20
al-al (mm)	23.88	1.45	21.70	25.60
TCFE (zy-zy:eu-eu)	90.26	1.99	88.58	92.55
UFI (n-pr:zy-zy)	52.02	1.60	49.27	53.46
NI (al-al:n-ns)	45.09	2.98	41.33	49.04

The mean age of 39 individuals in Group 2, who had the closest value to the golden ratio, was 24.97 (3.55) years. The craniofacial parameters of these cases are given in Table 3.

In the 3rd group, there were 38 cases with a mean age of 25.79 (3.50) years. The craniofacial parameters of these cases are given in Table 4.

Group 4 comprised 19 cases with a mean age of 24.89 (3.90) years. The craniofacial parameters of these cases are presented in Table 5.

Table 3: The descriptive values of the craniofacial parameters and indices of the male cases in group 2

n=39	Mean	SD	Minimum	Maximum
Golden ratio (n-ns:rh-ns)	1.6587	0.0568	1.583	1.744
rh-ns (mm)	32.04	1.36	28.20	35.00
n-ns (mm)	53.08	1.59	49.10	58.90
n-pr (mm)	74.04	2.95	68.60	79.10
eu-eu (mm)	155.67	7.50	137.10	167.80
zy-zy (mm)	141.75	4.43	130.40	148.50
al-al (mm)	23.53	1.59	20.80	26.30
TCFE (zy-zy:eu-eu)	91.15	2.11	88.34	95.36
UFI (n-pr:zy-zy)	52.24	1.71	49.68	58.47
NI (al-al:n-ns)	44.36	3.30	37.01	50.00

SD: Standard Deviation

Table 4: The descriptive values of the craniofacial parameters and indices of the male cases in group 3

n=38	Mean	SD	Minimum	Maximum
Golden ratio (n-ns:rh-ns)	1.6256	0.1197	1.504	1.820
rh-ns (mm)	33.08	1.78	29.20	37.40
n-ns (mm)	53.59	2.09	50.50	58.40
n-pr (mm)	72.89	3.14	66.90	79.10
eu-eu (mm)	151.82	5.35	142.10	161.00
zy-zy (mm)	139.28	5.33	124.70	150.60
al-al (mm)	24.69	1.55	21.10	27.00
TCFE (zy-zy:eu-eu)	91.77	2.64	86.09	97.00
UFI (n-pr:zy-zy)	52.39	2.88	47.61	61.46
NI (al-al:n-ns)	46.13	3.25	36.30	51.06

Table 5: The descriptive values of the craniofacial parameters and indices of the male cases in group 4

n=19	Mean	SD	Minimum	Maximum
Golden ratio (n-ns:rh-ns)	1.7444	0.2296	1.368	1.996
rh-ns (mm)	31.59	3.84	25.60	38.90
n-ns (mm)	54.35	3.14	50.10	60.90
n-pr (mm)	74.40	4.61	68.50	84.50
eu-eu (mm)	148.93	6.05	138.30	160.60
zy-zy (mm)	137.46	5.62	125.90	147.50
al-al (mm)	23.97	2.33	20.30	27.90
TCFE (zy-zy:eu-eu)	92.33	2.59	86.05	96.49
UFI (n-pr:zy-zy)	54.15	3.02	49.68	59.29
NI (al-al:n-ns)	44.19	4.35	35.30	50.80

Two cases with a mean age of 27.50 (2.12) years were incompatible with the golden ratio and not included in the study groups. The craniofacial parameters of these cases were as follows: n-ns:rh-ns: 2.0111±0.0108, rh-ns: 30.25±2.47 mm, n-ns: 60.85±5.30 mm, n-pr: 83.25±3.04 mm, eu-eu: 152.15±0.07 mm, zy-zy: 142.20±0.85 mm, al-al: 26.60±0.28 mm, TCFE: 93.46±0.51, UFI: 58.54±1.79 and NI: 43.86±3.36.

The mean ages of the groups were similar (P=0.374). In terms of all the parameters that were examined, the mean values of only group 4 were significantly lower in terms of eu-eu measurements compared to the mean values of the 1st and 2nd groups (P=0.005). In terms of the other parameters (i.e. zy-zy measurements), the mean value of only group 4 was significantly lower than the mean value of the 2nd group (P=0.033). In terms of al-al measurements, which is the PA width, the mean value of group 3 was significantly higher than the other groups (P=0.014). The mean UFI value of group 4 was significantly higher compared to the 1st, 2nd, and 3rd groups (P=0.001). No significant differences were detected between the groups in terms of other features not defined above (P>0.05).

Discussion

Anthropometry is the biological science of human body measurements [14]. Radiological imaging methods in anthropometric studies are modern methods which decrease the time and costs needed for analyses [15]. In our study, the purpose was to examine the craniofacial parameters of male cases with a golden ratio in the PA skeleton with the help of CT, and to interpret the relations of these parameters with different golden ratio groups.

According to the results of our study, differences were found in eu-eu, zy-zy, al-al, and UFI values among the four groups.

The n-ns:rh-ns indices in AP were fully compatible with the golden ratio in five individuals who were included in Group 1 (4.85%). The distribution frequency of the cases with a similar golden ratio index was not equal among the other three groups. However, the craniofacial parameters of all young adult males in four groups varied among the groups except for 2 cases that were not compatible with the golden ratio.

Studies that investigate PA in morphometric terms are limited in the literature. The golden ratio in PA was first detected in our study [6]. The study of Kabakci et al. [7] on the golden ratio was conducted considering the effects of age and gender on the index between PA height and PA width. It was found that although there was no difference between the genders in this index, there was a difference between age groups. This shows that the PA skeleton is affected by age. In our study, the normative data of the craniofacial parameters were obtained by limiting the age range of the cases by ensuring that the measurement values of the craniofacial skeleton may be affected by age.

In another study conducted with the help of CT on PA, PA height, PA width and the indices between PA height and PA width were evaluated in 120 cases [16]. In this study, a difference was detected between gender groups in terms of PA height, PA width and PA height and PA width. Only the nasal bone sizes were examined as craniofacial parameters in male cases in which the PA length was 3.34±0.29 cm. In a different study conducted with the help of CT, the PA length was 38.24±7.82 mm [17]. In the study investigating the upper and lower width of PA according to age groups, the mean PA subwidth was 23.6±0.5 mm among males [2]. Other studies assessing the PA width did not evaluate the craniofacial parameters [18, 19].

In the present study, the age range was limited, and individuals between 21 and 30 of age were included. In other studies, the age ranges were very wide [16-19]. Hommerich et al. [2] conducted a study and found that the mean of the data varied with age after they categorized their cases in terms of age into groups of ten. The PA subwidth was 23.6 mm on average among male cases. In our study, PA width was 23.29±1.86 mm and PA height was 32.74±2.94 mm. Although the age ranges in these studies were different, the results were similar to ours except for the value of PA width parameter reported in the study of Abdelaleem et al. [17].

Dry bone studies of craniofacial parameters on the cranium investigated the distance between the anthropometric points of 149 male craniums, revealing a range of 43.41±12.88 mm, and the following mean values: eu-eu: 140.86±10.76 mm, n-ns: 51.25±3.88 mm, n-pr: 68.85±5.41 mm, zy-zy: 127.02±5.97 mm and al-al: 25.83±2.72 mm [20].

In another study, the parameters of 44 male craniums with unknown age were evaluated, and the following values were reported: zy-zy: 128.9±4.41 mm, rh-ns: 53.7±3.54 mm, al-al: 24.8±2.21 mm and n-pr: 71.3±3.91 mm. The craniofacial parameters of 90 males with a high average age (68.94 (13.41) years) were examined to yield the following values: zy-zy: 130.54±5.13 mm, n-pr: 69.38±6.56 mm, al-al: 23.98±2.54 mm and rh-ns: 51.60±3.04 mm [13]. The fact that the measurements

were not performed with the help of CT, the variety of anatomical points to measure, and the different age range make the study results difficult to compare. In our study, these parameters were as follows: rh-ns: 32.34±2.23 mm, n-ns: 53.65±2.41 mm, n-pr: 73.78±3.66 mm, zy-zy: 139.94±5.17 mm, al-al: 24.11±1.80 mm and eu-eu: 152.87±6.80 mm.

Some researchers analyzed craniofacial skeletal parameters; however, until now, no studies evaluated the craniofacial parameters and relevant indices of the cases with a golden ratio in the face.

The present study provided new data for the analysis and interpretation of the anatomical characteristics of craniofacial parameters of male young adults with the golden ratio at the center of the facial skeleton. Detailed data are provided in our results for professionals interested in plastic surgery, maxillofacial surgery, and anthropometry with a better understanding of this complex clinical anatomic area, which as aesthetic significance.

Conclusion

The descriptive values of the craniofacial parameters of young adult Turkish males with a golden ratio in PA were determined with the results of our study. Differences were found in some craniofacial parameters between the groups. In this inter-group study, the craniofacial parameters of only five males fully met the golden ratio at PA. We recommend that further studies are conducted with an increased number of individuals with golden ratios at PA and the descriptive values of the craniofacial parameters of these cases are examined.

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Changes in adipose tissue and biochemical parameters after aerobic exercise in overweight and obese women

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Ethics Committee Approval
This study was approved on 01.02.2021 with the decision number 1591 by the Clinical Research Ethics Committee of Fatih Sultan Mehmet Training and Research Hospital.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Obesity is a global epidemic, and it is more common in women due to physiological differences. Exercise programs are the cornerstones of obesity treatment. This retrospective study aimed to examine the effect of moderate-intensity continuous aerobic exercise (MICT) program on body composition, biochemical parameters, and cardiovascular risk in overweight and obese female.
Methods: This retrospective cohort study analyzed the data of overweight and obese women who exercised for 12 weeks. The exercise program was maintained under the supervision of a physiotherapist three non-consecutive days a week. Each session was performed for 60 minutes at an intensity of 50% to 65% of maximum heart rate (HRmax). Body composition was evaluated by TANITA bioelectrical impedance analysis system, and aerobic capacity was assessed with 6-minute Walking Test (6-MWT). Biochemical parameters were analyzed in the laboratory. All results of the participants were obtained from the patient files.
Results: Body Mass Index (BMI), Fat Mass (FM-kg), Fat-free Mass (FFM-kg), Total Body Water (TBW-kg), and aerobic capacity improved after the implementation of the exercise program ($P<0.05$ for all). There was no significant change in blood parameters except HDL ($P=0.002$). An 11% reduction was observed in cardiometabolic risk factors due to the increased HDL.
Conclusion: The MICT program appears suitable for improving body composition and aerobic capacity with 50-65% intensity for 12 weeks. However, we think that exercise intensity should be increased for more biochemical benefits.

Keywords: Overweight, Moderate-intensity continuous aerobic training, Body composition, Aerobic capacity, Cardiovascular risk

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Introduction

Obesity is the most common health problem in many countries, and its worldwide prevalence is rising every day [1]. A society comprising over 30% overweight individuals is referred to as "obese." Turkey has become one of the obese countries with 32.1% gender-neutral obesity, and this rate is higher than 40% among females [2]. Accordingly, weight-related systemic illnesses have also increased among women [3-5]. Physical activity is frequently used as a method of treatment or prevention of these secondary health problems. The American College of Sports Medicine (ACSM) guideline recommends a minimum of 150 minutes of moderate-intensity continuous aerobic exercise (MICT) in a week to improve weight-related health outcomes [6].

Prolonged inactivity leads to a decrease in the enzymatic activity of lipoprotein lipase (LPL), which burns fat cells, and impaired carbohydrate metabolism because of reduced muscle contractions [7]. The increase of muscle mass and strength caused by aerobic exercises accelerate fat utilization by increasing energy consumption and basal metabolic rate. Furthermore, LPL is activated, cardiorespiratory capacity is increased, carbohydrate metabolism is regulated, and the risk of cardiovascular events is reduced by controlling the blood lipid profile through exercise [8–10].

Different studies exploring the relationship between obesity and exercise can be found in the literature [10-18]. Most of these studies do not have consistent findings because they include both genders. Our paper aimed to analyze the effects of routine exercise programs in the sports center for females. Because females and males have different metabolic and physical features, their responses to the exercises also differ. We think that the results may be affected due to the gender disproportion and gender-based characteristics. For this reason, we only investigated women in this study to eliminate gender-related variations. We obtained the results of female patients who exercised more than 12 weeks to determine the effectiveness of long-term exercise on body composition, aerobic capacity, biochemical parameters, and cardiovascular risk factors.

Materials and methods

Subjects

Sixty-eight overweight and inactive obese women were recruited in this study. The inclusion criteria were (1) having a sedentary lifestyle (not performing strenuous physical activity once a week or walking more than 20 min/day less than three times in a week), (2) being aged 18-65 years, (3) BMI > 25 kg/m^2. Exclusion criteria were (1) participating in moderate or high-intensity physical activities within the last three months (2) over 2 kg weight loss or unstable gain weight in the previous three months, (3) using medications which induce weight loss or decrease appetite, (4) taking lipid-lowering medications, (5) a history of angina pectoris or myocardial infarction within the last 12 months, (6) having uncontrolled hypertension. This study was approved by the Clinical Research Ethics Committee of Fatih Sultan Mehmet Education and Research Hospital on 01.02.2021 with the decision number 1591, and conformed to the principles of the Declaration of Helsinki.

Study design

The aerobic exercise program was designed as moderate-intensity continuous training. Routine nutrition habits of all subjects were encouraged to continue throughout the study. The exercise program consisted of 10 minutes of warm-up, 30-45 minutes of aerobic exercise, and 10 minutes of cool-down. The subjects were recruited non-consecutively and attended three supervised exercise sessions per week for 12 weeks in the sports center. All assessments were obtained before and after the 12-week exercise program.

Moderate Intensity Continuous Aerobic Training

The Karvonen formula was used to calculate the patient's HRmax. This formula is frequently used to calculate relative heart rate reserve using resting pulse and age during training sessions [19]. Blood pressure and heart rate were measured after the 10 minutes resting period at sitting position before the sessions. Exercise intensities were checked regularly with pulse oximetry during exercise.

The MICT program consisted of three parts: (1) 10-minute warm-up, (2) walking continuously for 30-45 min at 50–65% of HRmax on the treadmill, and (3) 10 min cool-down period. The exercise protocol progressed from 30 minutes and 50% HRmax to 45 minutes and 65% HRmax by the fifth week of this program. The program maintained 65% HRmax and sessions lasted 45 minutes between the fifth-twelfth weeks.

Body composition

Total body fat distributions were measured by bioimpedance analysis system (TANITA). The system has three main parts for assessment: (1) Stainless foot-pad electrodes, (2) hand electrodes, and (3) computer analysis. Demographic values were entered into the software interface. Every subject took off jewelry, shoes, and socks before the test, and they stood in erect position on the platform barefoot and held the hand probes [20].

Biochemistry parameters

Values of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein cholesterol (LDL), and triglyceride were obtained from the clinical records.

Aerobic Capacity

The 6-minute walk test (6-MWT) shows the effectiveness of interventions and aerobic capacities. This test was performed according to the American Thoracic Society guidelines in an enclosed corridor [21]. Two cones were placed at the terminals of the 20-meter-long corridor. Assessor notified to patients walk as much as possible for six minutes, not run or jog. At the end of every minute, the assessor informed the patient about how much time was left. The distance was noted in meters. Heart rate, blood pressure, and perceived exertion were recorded before and after the test [22].

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows. Data are expressed as mean and standard deviation. The one-sample Kolmogorov-Smirnov test was performed to assess the distribution of data. Comparison of variables before and after the exercise program were compared by the paired sample t-test. *P*-value of less than 0.05 was considered significant.

Results

Subject characteristics

The data of sixty-eight women who had 100% participation in the exercise program between 2019-2020 were included in the study. During this time, no adverse events were reported. The age mean was 48.19 (9.30) years. BMI scores of obese and overweight subjects were 34.97 (3.26) kg/m^2 and 27.25 (1.37) kg/m^2, respectively.

Body Composition and Aerobic Capacity

There was a significant improvement in body composition parameters between baseline and the post-intervention period. Weight, BMI, fat mass FM (kg), fat-free mass FFM (kg), and total body water TBW (kg) significantly differed baseline and post-intervention. In addition to improving these parameters, aerobic capacity also increased considerably from 442 (33) m to 478 (34) m (P=0.001). Results are shown in Table 1.

Table 1: Body composition and aerobic capacity values

Parameter	Baseline	Post Intervention	*P*-value
Weight	80.08 (13.20)	77.90 (12.12)	0.001
BMI	31.45 (5.16)	30.56 (4.50)	0.001
FM (%)	37.26 (7.18)	37.18 (5.92)	0.116
FM (kg)	30.70 (8.91)	29.40 (8.20)	0.001
FFM (%)	16.71 (1.72)	16.83 (1.59)	0.056
FFM (kg)	13.22 (1.73)	12.99 (1.58)	0.003
TBW (%)	45.03 (7.15)	44.29 (7.32)	0.001
TBW (kg)	36.16 (4.60)	35.51 (4.31)	0.001
6-MWT	442 (33)	478 (34)	0.001

Data are presented as mean (standard deviation), BMI: body mass index, FM: fat mass, FFM: fat-free mass, TBW: total body water, 6-MWT: 6-minute walking test

Blood profile

The LDL, total cholesterol and triglycerides values insignificantly decreased at the end of the exercise program (P=0.470, P=0.484, and P=0.695, respectively). Only the HDL value and total Cholesterol/HDL ratio (cardio-metabolic risk factor) showed a statistically significant improvement at the end of the program (P=0.002, P= 0.001). All biochemical results are shown in Table 2.

Table 2: Biochemical parameters and cardiometabolic risk factors

Parameter	Baseline	Post Intervention	*P*-value
Fasting Blood Glucose (mg/dL)	95.16 (9.96)	95.93 (9.72)	0.517
Postprandial Blood Glucose (mg/dL)	95.78 (19.23)	92.02 (20.22)	0.294
HbA1c (mg/dL)	5.71 (0.77)	5.77 (0.36)	0.580
LDL (mg/dL)	140.07 (31.00)	138.49 (30.80)	0.470
Triglyceride (mg/dL)	136.50 (72.29)	131.98 (78.12)	0.484
HDL (mg/dL)	50.82 (10.97)	54.06 (11.39)	0.002
Total Cholesterol (mg/dL)	218.84 (37.32)	219.85 (3.41)	0.695
Total Cholesterol / HDL	4.43 (1.05)	4.17 (0.93)	0.001

Data are presented as mean (standard deviation).

Discussion

Regular physical activity programs play a crucial role in the improvement of health-related gains. Obese people should perform 150 minutes of moderate-intensity or 75 minutes of a vigorous-intensity exercise program per week to gain benefit [23]. This paper's main findings are that the 12-week MICT program has successfully improved body composition, aerobic capacity, and cardiovascular risk factors in overweight and obese women.

Exercise, the main component of obesity treatment, is part of a lifestyle change. Some studies show that the aerobic exercise program reduces visceral adipose tissue independently [24], and we found similar results in the literature. According to our results, weight, BMI, fat mass, free fat mass, and total body water parameters statistically improved after the exercise. Two exercise protocols with different intensities were compared for body composition gains in the literature. Kong et al. performed the study with two different aerobic exercise types, such as high-intensity interval training (HIIT) and the MICT protocol. The MICT groups completed all sessions with 65% VO2max for 40 minutes and had statistically significant improvement in total lean mass compared to the HIIT [25]. When the MICT program with 55-65% VO2max was compared with the high-intensity interval program, the fat percentile improved in the MICT group [26]. In another study, Martins et al. evaluated MICT and the HIIT programs for 12 weeks, and neither was superior to each other in terms of body composition change [27]. A meta-analysis reported that body fat decreased in 11 studies, and BMI decreased in 9 studies with the MICT protocol [28]. Our results of body composition were similar to those mentioned above. People use large muscle groups during gait-based physical activity. Therefore, energy needs and consumption increase [29,30]. We know that the energy obtained from the glucose is spent in the first minutes of the exercise. For this reason, the fat-burning mechanism is activated to supply the increasing energy need. As a result of this mechanism, the body increases its basal metabolism to adapt to this condition and weight loss process accelerates [31].

The reduction of VO2max is more related to mortality than excessive fat mass [32]. Besides, mortality risk increases further with a decrease in VO2max and excessive fat in obese people. The MICT program can be used to avoid most adversities by using the known general benefits of exercise. One of these benefits is an improvement in aerobic capacity, and the reduction of aerobic capacity correlates with the risk of death. In our results, aerobic capacity showed improvement after the exercise program. Our findings are consistent with other studies mentioned below. The short-term MICT program has been found useful in increasing aerobic capacity [33]. Further research was performed by Cocks et al., who investigated the effect of the MICT program on the aerobic capacity in obese men. This program maintained 20 sessions with 65% for 40-60 minutes, and the MICT protocol lead to an improvement in aerobic capacity [16]. The studies had different intensities between 60-85% HRmax, and the minimum duration was 30 minutes [34-37]. We used a protocol compatible with the literature at our sports center. Our patients completed the aerobic exercise program with 65% HRmax for 45 minutes except for warm-up and cooling-down periods.

Exercise is described as a non-drug treatment method for different diseases, and it is known that regular exercise causes an increase in mitophagy capacity and mitochondria life, as well as regulating mitochondrial functions [38]. A study reported a positive correlation between mitochondrial function and aerobic capacity [39]. Exercise capacity is regulated by increased mitochondrial electron flow, decreased oxidative damage, improved mitochondrial respiratory chain, regulated enzymatic activity in mitochondria, and increased mitochondria in skeletal muscle mechanisms with aerobic exercise programs [40]. This is one of the possible mechanisms of the effect of exercise on increased aerobic capacity in our study. Also, regular aerobic exercises cause increases in oxygen consumption. The stroke volume, heart rate, and cardiac output increase the blood need of tissues. As a result of this accommodation, cardiac hypertrophy and bradycardia occur, and heart contractility increases. After increased contractility, heart rate volume and aerobic capacity

increase. However, exercise must be continued for at least six weeks for the cardiorespiratory adaption [41].

Aerobic exercise regulates the hormonal system, the parasympathetic system, and vagus nerve activities. It also provides autonomic control for body systems, improvement in the blood parameters, and a reduction in cardiovascular diseases risk such as hypertension, myocardial infarcts, and atherosclerosis [12, 26]. In our study, the 12-week moderate-intensity exercise program resulted in no significant changes in LDL, triglyceride, HbA1c, and total cholesterol values. Improvement was seen in HDL and Total Cholesterol/HDL ratio as a cardiovascular risk factor and risk was reduced by 11% due to increased HDL. According to the Canadian working group, the "Total Cholesterol/HDL" ratio formula is more sensitive and specific for cardiovascular risk assessment than individual blood parameters [42]. Mathunjwa et al. [43] showed that while HDL cholesterol increases with the MICT program, the LDL, triglyceride, and total cholesterol decrease, and 2% improvement occurs in cardiovascular risk. In another study, obese individuals exhibited a significant reduction in total cholesterol, HDL, and Framingham risk score after the MICT program that was performed 150 min/week for eight weeks [13]. A study consisted of aerobic exercise (30 minutes, 3 days in a week for 8 weeks) and showed decreased triglyceride and increased HDL levels [44]. According to our results, the improvement in biochemical parameters except HDL was not statistically significant, and these results were not compatible with the literature. We progressed the exercise intensity when patients' heart rate did not increase during exercise. Patients who reached 45 minutes of exercise at 65% HRmax were included in the study. We think that this exercise intensity might be insufficient to improve these biochemical parameters, which may be positively affected by increasing exercise intensity or duration. This exercise program was initiated as a public service for three months to help gain exercise habits in addition to traditional treatment. At the end of three months, assuming that the patients gained exercise habits, the exercise programs were terminated, and other patients were recruited in the sports center's exercise program. Based our results, aerobic exercise programs with higher intensity can be applied to the participants in our center.

Limitations

Our study was conducted retrospectively and did not include a control group. Conducting the study prospectively and including a control group may affect the quality of the study. In addition, the study did not include follow-up, which could be useful to examine the long-term effects of exercise.

Due to the retrospective nature of the study, the medical files of the participants were examined. The files of the patients who did not meet the study criteria and had a missing data were excluded. This may have changed the characteristics of the study universe. Also, the evaluator was not blind because he followed the pre-determined protocol used in the clinic. However, all evaluation and treatment processes were conducted by the same physiotherapist. In this way, inter-rater bias was prevented.

Conclusions

Moderate intensity exercise programs help reduce adipose tissue, increase cardiorespiratory capacity, improve lipid profile, and reduce cardiovascular disease risk by increasing metabolic and hormonal activities. These effects are reversible, and physical activity needs to be transformed into a lifestyle for ongoing gains. The addition of regular and supervised nutrition programs to the exercise will increase the profits.

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Comparison of the efficacy of aflibercept and ranibizumab after a 3-month loading dose in patients with diabetic macular edema

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Ethics Committee Approval
For the present study, the approval of the Ethics Committee of Karabuk University was obtained (decision no:2020/248, dated:09/06/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Diabetic macular edema (DME) is the main cause of visual loss in diabetic patients. Aflibercept and ranibizumab are among the most commonly used intravitreal agents in the DME. This study aims to compare the short-term anatomic and functional results of aflibercept and ranibizumab in the treatment of DME.

Methods: This retrospective cohort study included newly diagnosed and treatment-naive DME patients. The patients were administered intravitreal aflibercept (IVA) or intravitreal ranibizumab (IVR) as a loading dose throughout 3 months. Pre-treatment and 1- and 3-month examinations were made of best corrected visual acuity (BCVA)and central macular thickness (CMT). After the treatment, the patients were classified in the 3rd month as those with good or poor response according to the early anatomic response. A good response to the treatment was considered the formation of foveal contour and full recovery of macular edema. Patients where macular edema was not fully resolved and/or foveal contour had not formed were classified as having poor response. Later, IVA and IVR were compared with each other in terms of response to treatment.

Results: Evaluation was made of 67 eyes of 54 patients, comprising 31 (57.4%) females and 23 (42.6%) males with a mean age of 62.7 (7.3) years (range, 46-78 years). IVA was applied to 33 (49.3%) eyes and IVR to 34 (50.7%) eyes. In the IVA group, BCVA was determined as 0.75 (0.39) LogMAR pre-treatment, 0.53 (0.37) LogMAR at 1 month and 0.38 (0.30) LogMAR at 3 months (P<0.001 for each). CMT was measured as 400 (82) µm pre-treatment, 349 (95) µm at 1 month and 313 (79) µm at 3 months (P<0.001 for each). In the IVR group, BCVA was determined as 0.71 (0.34) LogMAR pre-treatment, 0.52 (0.34) LogMAR at 1 month and 0.39 (0.30) LogMAR at 3 months (P<0.001 for each). CMT was measured as 426 (92) µm pre-treatment, 365 (74) µm at 1 month and 323 (60) µm at 3 months (P<0.001 for each). A good response to treatment was determined in 24 eyes (72.7%) in the IVA group, and in 18 eyes (52.9%) in the IVR group. Although a good response to treatment was achieved at a higher rate in the IVA group, the difference was not statistically significant (P=0.09).

Conclusion: Both visual and anatomic success was achieved with a 3-month loading dose in both the IVA and IVR groups. No statistically significant superiority was determined of one drug over the other in the 3-month period.

Keywords: Aflibercept, Ranibizumab, Diabetic macular edema

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that develops when sufficient insulin is not produced in the pancreas or the produced insulin is not used effectively [1]. In 2013, the number of diabetic patients was 382 million worldwide and this is predicted to increase by 55% to reach 592 million by 2035 [2].

Chronic hyperglycemia that emerges in diabetes causes microvascular and macrovascular complications. Diabetic retinopathy (DR) is the most frequently seen microvascular complication [3]. Diabetic macular edema (DME) is a reason for sight loss in DM and can be seen at any stage of DR [4]. In a prevalence study based on optic coherence tomography (OCT), Acan et al. reported the prevalence of DME as 15.3% in 443 diabetic patients [5]. Various methods have been described for DME treatment, the most frequently used of which are laser photocoagulation, intravitreal steroids, and anti-vascular endothelial growth factor injections (VEGF) [6-8]. Aflibercept and ranibizumab are anti-VEGF drugs approved for use in DME treatment [3, 7-10]. Anti-VEGF agents are currently preferred as the first treatment option in DME treatment [11]. In the Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol T study, aflibercept was shown to provide better visual results than both the bevacizumab and ranibizumab group in a 1- year follow-up period, especially in patients with low visual acuity (<0.4) [12].

The aim of this study was to compare the short-term anatomic and functional results of aflibercept and ranibizumab in the treatment of DME.

Materials and methods

For the present study, the approval of the Ethics Committee of Karabuk University was obtained (decision no:2020/248, dated:09/06/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

This retrospective study included patients diagnosed with DME and treated with intravitreal aflibercept (IVA) and intravitreal ranibizumab (IVR) in the Ophthalmology Clinic of Karabuk University Training and Research Hospital between 01.09.2017 and 31.05.2018. Informed consent was obtained from all patients before starting treatment.

The patients included were those who were newly diagnosed with DME, had not previously received any treatment, received loading doses of aflibercept or ranibizumab for the first 3 months, and completed a minimum follow-up period of 4 months. Patients were excluded if they had any retinal disease other than DME, or if they had previously undergone any intravitreal injection or laser photocoagulation treatment.

The data related to patient age, gender, lens status, drugs used, best corrected visual acuity (BCVA) and central macular thickness (CMT) at pre-treatment, 1 month and 3 months were examined from the patient records. At each follow-up examination, BCVA was measured with a projection chart at 4 meters, intraocular pressure (IOP) was measured with an air tonometer (Canon, TX-20P, Canon, Japan), CMT was measured with optical coherence tomography (OCT) (Cirrus HD-OCT 4000, Carl Zeiss Meditec, Germany) and detailed biomicroscopic and fundus examinations were performed after dilation. Fundus fluorescein angiography (Canon Cx-1, Canon, Japan) was only used pre-treatment, but was repeated in cases where patient sight deteriorated for no known reason during the follow-up period. OCT was used to determine DME and measure CMT. In diagnosis, CMT >300µm indicated DME. The CMT values were calculated from the mean thickness of the neurosensorial retina in a central area of 1mm diameter, using the OCT mapping software.

Following treatment, the patients were classified at the end of 3 months as good or poor according to the early anatomic response. A good response to the treatment was accepted as the formation of foveal contour and full recovery of macular edema. Patients where macular edema was not fully resolved and/or foveal contour had not formed were classified as poor response. The groups were compared in terms of the response to IVA and IVR treatments.

All injections were administered in the operating theatre under sterile conditions. The eyelids and surrounding areas were wiped with a sterile gauze pad soaked in 10% povidone-iodine. Anesthesia of topical proparacaine hydrochloride was applied then the eye was washed with 5% povidone-iodine. The injections were administered from the supero-temporal quadrant, with a 27-gauge needle, at 4mm behind the limbus in phakic eyes, and at 3.5mm in pseudophakic eyes in 3 doses at 1-month intervals as 2mg/0.05ml Aflibercept (Eylea, Regeneron, New York, USA and Bayer Health Care, Berlin, Germany) or 0.5 mg/0.05 ml Ranibizumab (Lucentis, Genentech Inc., San Francisco, USA). To prevent leakage after the injection, a sterile cotton swab stick was pressed onto the entry site then Vigamox (moxifloxacin) drops were instilled in the eye and the drops were continued for 7 days at a dose of 4 drops per day. Patients were instructed to return to the hospital immediately without waiting for the follow-up appointment if they experienced any reduced vision, eye pain, or any new symptom.

The primary endpoint of this study was defined as the rate of good anatomic responses in the 3rd month after 3 loading dose injections of Aflibercept and Ranibizumab.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn.21.0 software (SPSS Inc, Chicago, IL, USA). The visual acuity values were converted to the logarithmic value for minimum resolution (LogMAR) for statistical analysis. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. Numerical variables were stated as mean (standard deviation), and categorical variables, as number and percentage. For the comparison of three groups of numerical variables with normal distribution, One-Way variance analysis (ANOVA) was used for repeated measurements, and Bonferroni correction was applied if the result was significant. The Independent Samples t-test was used in the comparisons of numerical variables between two groups. The changes in BCVA and CMT from pre-treatment to 3 months were evaluated in each treatment group using the Dependent Samples t-test. Categorical variables were compared using the Chi-square test. A value of $P<0.05$ was considered statistically significant.

Results

Evaluation was made of 67 eyes of 54 patients, comprising 31 (57.4%) females and 23 (42.6%) males with a mean age of 62.7 (7.3) years (range, 46-78 years). IVA was applied to 33 (49.3%) eyes, and IVR to 34 (50.7%) eyes. The general characteristics of the groups are summarized in Table 1.

In both the IVA and IVR groups, a statistically significant increase was determined in mean BCVA at the end of 1 and 3 months compared to the baseline values ($P<0.001$ for all) (Table 2). The mean gain in BCVA at the end of the 3rd month was 3.6 in the IVA group and 3.1 in the IVR group. No statistically significant difference was determined between the groups with respect to the improvement in mean BCVA ($P=0.50$).

In both the IVA and IVR groups, a statistically significant decrease was determined in mean CMT at the end of 1 and 3 months compared to the baseline values ($P<0.001$ for all) (Table 2). The mean decrease in CMT at the end of the 3rd month was 86µm in the IVA group and 102µm in the IVR group ($P=0.92$).

A good response to treatment was determined in 24 eyes (72.7%) in the IVA group, and in 18 eyes (52.9%) in the IVR group, which were similar ($P=0.09$).

Among a total of 201 injections administered, no endophthalmitis was observed in any of the patients.

Table 1: General characteristics of the patients before the injections

	IVR	IVA	*P*-value *
Age (years)	63.8 (8.3)	61.1 (6.5)	0.300
Right/left	18/16	16/17	0.904
Preoperative BCVS (LogMAR)	0.71 (0.34)	0.75 (0.39)	0.548
Preoperative CMT (µm)	426 (92)	400 (82)	0.579

* Independent Student's t-test, Chi-square test, CMT: Central macular thickness, BCVA: Best corrected visual acuity

Table 2: Changes in the BCVA and CMT values of the patients from pre-treatment to 1 month and 3 months after the injections

	IVR				IVA			
	Pre-treatment	1 month	3 months	*P*-value *	Pre-treatment	1 month	3 months	*P*-value *
CMT (µm)	426 (92)	365 (74)	323 (60)	<0.001	400 (82)	349 (95)	313 (79)	<0.001
BCVA (LogMAR)	0.71 (0.34)	0.52 (0.34)	0.39 (0.30)	<0.001	0.75 (0.39)	0.53 (0.37)	0.38 (0.30)	<0.001

* repeated measures variance analysis, CMT: Central macular thickness, BCVA: Best corrected visual acuity

Discussion

Diabetic macular edema (DME) is the most common cause of sight loss in diabetic patients and is a leading cause of blindness in the working-age population in developed countries. Although DME can be seen at any stage of diabetic retinopathy (DR), as the duration of DM increases, so does the frequency of DME with advanced stages of DR [13]. However, corneal damage may occur in patients with DME [14].

For many years, focal and grid laser application was the gold standard in the treatment of DME [15]. However, as laser treatment does not increase visual acuity sufficiently and because of potential complications, new treatments have been researched. Compared to laser treatment, anti-VEGF agents are more successful in increasing visual acuity and reducing macular thickness and so have become the current standard treatment for DME [16].

Previous studies have found that VEGF is the main angiogenic factor responsible for the development of DR and DME, and a correlation has been shown between the VEGF level and retinopathy activity [17-19]. The VEGF family is formed of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor (PIGF). Ranibizumab is a humanized monoclonal antibody, which is produced by recombinant Eschericha coli, and is effective against all isoforms of VEGF-A. It was the first agent approved by the FDA for DME treatment. Aflibercept is a 115 kDa-weighted, recombinant fusion protein, formed with fusion of the Fc part of human immunoglobulin G1 and the extracellular parts of VEGFR-1 and VEGFR-2. VEGF-A binds to VEGF-B and PIGF with high affinity.

There are several studies in literature about the efficacy of IVA in DME treatment. In the DA VINCI, which was a phase II study, greater improvements were observed at the end of 24 weeks in the IVA groups than in the laser group [20]. In VIVID and VISTA, which were multicenter, randomized, double-blind phase 3 studies, the administration of IVA was statistically significantly superior to laser treatment in terms of anatomic and functional success [21]. Demir and Kutluturk [22] reported IVA is an effective and safe treatment agent for both improving BCVA and decreasing CMT in DME patients.

In a retrospective study by Erden et al. [23], BCVA changed from 0.54 (0.28) LogMAR pre-treatment to 0.32 (0.37) LogMAR after 3 months of 2mg IVA loading. The CMT of these patients decreased from 415 (88) µm pre-treatment to 277 (54) µm at the end of 3 months. According to these results, the administration of IVA was effective in the treatment of DME with a 3-month loading dose.

In the current study, similar results to those of previous studies were obtained in the IVA group with statistically significant improvements in BCVA and CMT after a 3-month loading dose.

There are several studies in literature showing that IVR administration is effective in the treatment of DME. In the phase II Resolve study, the administration of IVR was more effective than sham injection at the end of 1 year [24]. In the phase III Restore study, it was concluded that IVR treatment alone or combined with laser provided better results than laser treatment alone [25].

In a retrospective study by Erden et al. [23], BCVA improved from 0.58 (0.28) LogMAR pre-treatment to 0.32 (0.26) LogMAR at the end of 3 months as a result of 3 months of 0.5mg IVR loading. In these patients, CMT decreased from 406 (82) µm pre-treatment to 303 (60) µm at the end of 3 months. Nowacka et al. [26] applied 0.5mg IVR for 3 months to 17 eyes of 17 patients with DME, and reported BCVA as 0.62 (0.28) LogMAR pre-treatment and 0.4 (0.22) LogMAR after 3 months, and a decrease in CMT from 542 (136) µm pre-treatment to 325 (68) µm at the end of 3 months. According to these results, the administration of IVR was effective in the treatment of DME with a 3-month loading dose.

In the current study, similar results to those of previous studies were obtained in the IVR group with statistically significant improvements in BCVA and CMT after a 3-month loading dose.

In the DRCT-net protocol T study, which was designed to compare anti-VEGF drugs currently used in DME treatment, the efficacy and reliability of aflibercept, ranibizumab and bevacizumab were examined in the treatment of DME, which can lead to sight loss through involvement of the central retina. At the

end of one year, an increase in BCVA was determined with a mean of 13.3 letters in the patients treated with aflibercept, 11.2 letters with ranibizumab, and 9.7 letters with bevacizumab (aflibercept – bevacizumab $P<0.001$, aflibercept – ranibizumab $P=0.03$). When the first visual acuity score was ≥69 letters, the mean increase in BCVA score was 8.0 letters for aflibercept, 8.3 letters for ranibizumab, and 7.5 letters for bevacizumab, and no statistically significant difference was determined between the groups. However, when the first visual acuity score was <69 letters, the mean increase in BCVA score was 18.9 letters for aflibercept, 14.2 letters for ranibizumab, and 11.8 letters for bevacizumab. According to these results, in the group with lower initial visual acuity, aflibercept treatment was significantly more successful in the first year than ranibizumab and bevacizumab [12].

When the 2-year results of the Protocol T study were examined, the BCVA increase was determined as 12.8 letters for aflibercept, 12.3 letters for ranibizumab, and 10 letters for bevacizumab (aflibercept - bevacizumab: $P=0.02$, aflibercept - ranibizumab: $P=0.47$, ranibizumab - bevacizumab: $P=0.11$). From these results it was seen that at the end of 2 years, ranibizumab treatment was able to reach the same treatment results as aflibercept, but bevacizumab did not show the same success. When the patients were separated into groups according to the initial visual acuity, there was no statistically significant difference between the drugs in the patient group with BCVA ≥69 letters, while for those with a score of <69 letters, no difference was determined between aflibercept and ranibizumab. However, aflibercept treatment was significantly more successful than bevacizumab [10].

In a study by Erden et al. [23], treatment-naive DME patients were separated into two groups and IVA was applied to one group and IVR to the other. At the end of 3 months, there was no statistically significant difference between IVA and IVR in terms of both BCVA gain and CMT decrease. In a prospective study by Fouda et al. [27], 70 patients were separated into two groups, and received 2mg/0.05 ml IVA per month or 0.5mg/0.05ml IVR per month. At the end of 3 months, the improvement in BCVA on the Snellen chart was 1.8 rows in the IVA group and 1.5 rows in the IVR group. The decrease in CMT at the end of 3 months was reported as 95µm in the IVA group and 77µm in the IVR group. In this study, no significant difference was found between the two groups in terms of efficiency in the short term.

In current study, similar results were obtained with previous studies. No statistically significant difference was found between the two groups in terms of BCVA gain and CMT decrease with the 3-month loading dose.

Limitations

The limitations of our study include its retrospective and single-centered nature, and small number of patients.

Conclusion

The results of this study demonstrated that both visual and anatomic success can be achieved with a 3-month loading dose of both IVA and IVR. No statistically significant superiority was determined of one drug over the other in the 3-month period. Although the rate of patients with a good response to treatment was higher in the IVA group than in the IVR group, the difference was not statistically significant.

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Difficulties experienced by geriatric patients regarding respiratory devices and access to health services: A cross-sectional study

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Abstract

Background/Aim: In the treatment of chronic respiratory failure, long-term oxygen therapy at home (LTOT) and domiciliary noninvasive mechanical ventilation (NIV) are important components of home care. The aim was to evaluate the compliance of geriatric patients with LTOT/NIV at home and their access to health services in the last year.

Methods: Screening of 669 patients who were hospitalized in our pulmonary intensive care unit between 30.09.2019 and 30.09.2020 revealed a total of 109 patients over 80 years of age with chronic respiratory failure. Among them, 70 died after discharge. Six of the 39 surviving cases were excluded from the study because they were discharged without any LTOT and/or NIV devices, and the COVID-19 PCR tests of 4 patients were positive after discharge. The remaining 29 patients over 80 years of age were enrolled in the study. After questioning the patient's care status, caregivers were asked whether the patients were compliant with NIV and/or LTOT devices at home and their usage in terms of hours during the day and nighttime. In non-compliant patients, the reasons were acquired, and the answers were noted. They were asked whether they gave up on healthcare services and scheduled check-ups, had difficulties in getting a doctor's appointment, and whether they were incompliant with the appointments they made. If the answers were yes, they asked about their reasons for each question.

Results: The median age was 85 (80-96) years, and 65.5% (n=19) of the cases were female. The diagnosis which led to hospitalization in 86.2% (n=25) of the patients was hypercapnic respiratory failure. Fifteen patients (51.7%) with LTOT and 9 patients (81.8%) with NIV did not use their devices as recommended. The patients' caregivers expressed that 22 patients (75.8%) could not meet their basic needs and 17 patients (77.2%) did not receive home care services provided by the Ministry of Health. Although the need arose in the post-discharge period, it was observed that 24 patients (82.7%) were not taken to the doctor and 20 patients (68.9%) did not schedule doctor visits after discharge. All caregivers stated that they were afraid of the COVID-19 pandemic and catching the COVID-19 disease from the emergency rooms and outpatient clinics.

Conclusions: Our patients' compliance with the LTOT device was poor and 51.7% of the patients used the device less than recommended. Moreover, the patients were mostly incompliant with domiciliary NIV treatment. Receiving nonspecific home care services did not have any effect on LTOT and/or NIV compliance. It was observed that disruption in doctor visits and patient admissions leads to the decreased compliance with LTOT and/or NIV devices and loss of motivation to use these devices. The cases in this study avoided all kinds of admissions to the hospital due to the COVID-19 pandemic. In such conditions, structured and specific home care services for geriatric respiratory failure patients become more important. Continuing education and motivation at home will increase the quality of life of the patients and improve compliance.

Keywords: Long-term oxygen therapy, Domiciliary noninvasive mechanical ventilation, Very elderly, Geriatric patients, Compliance, Home care

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Introduction

In the treatment of chronic respiratory failure, domiciliary long-term oxygen support (LTOT) and noninvasive mechanical ventilation (NIV) are important components of home care. The use of LTOT/NIV has increased in the last 20-30 years [1].

Domiciliary NIV is used in the treatment of chronic diseases such as chronic obstructive pulmonary disease (COPD), obesity hypoventilation syndrome, neuromuscular diseases, and restrictive chest wall disorders [2]. In a study from Turkey, NIV's main indications were COPD (75%), OHS (10%) of COPD and OHS overlap (10%), and restrictive lung disorders (5%) [3].

Age has not been reported as a criterion in indications for use of NIV at home. Available data show that the NIV usage rate increases in the elderly population (74-85 years and ≥85 years). The decline in respiratory reserve and comorbidities due to aging, and very advanced age resulted in a decrease in quality of life, as well as an increase in hospital admissions and healthcare costs [1].

The efficacy, safety, and benefits of domiciliary LTOT and NIV have been demonstrated in elderly patients. However, in the same patient group, difficulty in compliance with treatment and treatment failure were also emphasized [4-7].

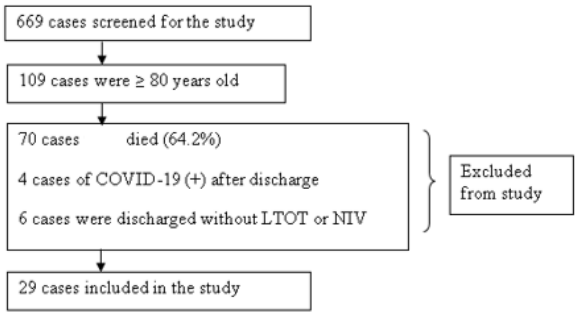
In this context, compliance of patients aged 80 years and over with LTOT/NIV was evaluated with a remote interview in patients who were treated in our pulmonary intensive care unit. It was noted whether these elderly patients had difficulties in accessing health services due to pandemic conditions within the last year.

Materials and methods

A total of 669 patients were hospitalized in our pulmonary intensive care unit of tertiary chest diseases hospital between 30.09.2019 and 30.09.2020. A total of 109 patients over 80 years old were identified. COVID-19 PCR positivity or suspicion was excluded in all 109 patients before hospitalization to our pulmonary intensive care unit (ICU). It was seen that 70 of 109 patients died after discharge. Six of the 39 surviving cases were excluded from the study because they were discharged without any LTOT and/or NIV devices, and 4 cases were found to be COVID-19 positive after discharge. During hospitalization, all patients were routinely asked for permission to use their anonymous medical data for clinical studies, and twenty-nine cases who gave their consent were included in the study (Figure 1). After retrospective data were collected, the caregivers of all cases were interviewed, and their verbal consents were obtained. For open-ended questions, their own words were recorded on the registration form without any bias. Retrospective analyses require no ethics board approval; however, our study was approved by the Ethics Board of Atatürk Chest Diseases and Chest Surgery Training and Research Hospital (Date: 07.01.2021, Number: 708)

The patients' compliance with the LTOT and/or NIV devices were questioned after three months following discharge from the hospital. The study was conducted in January 2021. After questioning the patient's care status, caregivers were asked six closed and six open-ended questions based on their answers. They were asked whether they used the NIV and/or LTOT device at home, and for how many hours during the day and night, whether they gave up on healthcare services and scheduled check-ups, had difficulties in getting a doctor's appointment, and whether they were incompliant with the appointments they made. If the answers were yes, they asked about their reasons for each question. The responses of the caregiver to the open-ended questions were recorded word for word. At the end of the interview, patients are invited for a control examination.

Figure 1: Flow-diagram



Statistical analysis

Statistical analyses were performed with SPSS version 22. Categorical data were presented as number and percentage, non-normally distributed ordinal or numerical data were given as median, min and max values, and normally distributed numerical data, as mean (SD). Categorical data were evaluated with Chi-square or Fisher tests, and numerical data were assessed with Student t-test or Mann-Whitney U test. A value of $P<0.05$ was considered statistically significant.

Results

This study consisted of geriatric patients who were hospitalized in a tertiary chest diseases training and research hospital. Four of twenty-nine patients had a history of intubation-extubation, and a total of twenty-one patients were transferred from the anesthesia intensive care unit to our intensive care unit. In our intensive care unit, the mean duration of hospitalization was 10.9 (6.3) days. After their treatment and LTOT and/or NIV device training, 28 patients were discharged directly to their home, and one case was transferred to an inpatient service and discharged later.

The median age was 85 (80-96) years, 65.5% (n=19) of the cases were female and 58.6% (n=17) were illiterate. Demographic data are shown in Table 1. Before hospitalization, 19 patients had LTOT devices, and 5 patients had NIV devices at home. LTOT device was prescribed to 10 patients and NIV device was prescribed to 6 patients according to social security institution reimbursement conditions, and their use was reevaluated for indications at discharge. The patient's own and newly prescribed devices were routinely brought to our clinic by caregivers or relatives. A routine follow-up was made with their own devices for 24 hours before discharge. Device training was repeated and recorded for caregivers and patients during their stay. Necessary training was repeated during the last follow-up day. Once stable, the patients were discharged with their own devices.

The diagnosis which led to hospitalization was hypercapnic respiratory failure in 86.2% (n=25) and COPD in 82.8% (n=24). Diabetes mellitus (31%) and congestive heart failure (41.4%) were the most common comorbidities. Four or more comorbidities were observed in 86.2% of all patients (Table 2).

Table 1: Demographic and basic characteristics

Characteristics	n (%)
Age median (min-max)	85 (80-96)
Gender	
Male	10 (34.5)
Female	19 (65.5)
Education status	
Illiterate	17 (58.6)
Literate	5 (17.2)
Primary school	4 (13.8)
Middle School	1 (3.4)
High school	2 (6.9)
College	0 (0)
Need for home care	
Yes	22 (75.9)
No	7 (24.1)
Receiving home care service	
Taking	5 (17.2)
Not receiving	24 (82.8)
Caregiver	
First-degree relative	21 (95.5)
Professional caregiver	1 (4.5)
The clinic where they came from	
Emergency	7 (24.1)
Inpatient clinics	1 (3.4)
Level 3 intensive care unit	21 (72.4)
Place of discharge	
Home	28 (96.6)
Inpatient clinics	1 (3.4)

Table 2: Comorbidity status

Comorbidity	n (%)
Hypercapnic respiratory failure	25 (86.2)
Chronic obstructive pulmonary disease	24 (82.8)
Hypertension	20 (69.0)
Congestive heart failure	12 (41.4)
Diabetes mellitus	9 (31.0)
Coronary artery disease	4 (13.8)
Hypoxic respiratory failure	3 (10.3)
Heart rhythm disorder	3 (10.3)
Alzheimer	3 (10.3)
Chronic renal failure	3 (10.3)
Cancer	2 (6.9)
Hyperthyroid	1 (3.4)
Parkinson	1 (3.4)
Comorbidity number	
3 and less	4 (13.8)
4 and more	25 (86.2)

The caregivers expressed that twenty-two patients (75.8%) could not meet their basic needs (eating, drinking, using drugs, using LTOT and/or NIV, and toilet needs on their own). The caregivers of twenty-one of these twenty-two cases were first-degree relatives. Seventeen (77.2%) of twenty-two patients did not receive home care services provided by the Ministry of Health.

It was observed that the number of patients who applied for the control examination planned after discharge was only three. Twenty-six patients had not applied for recommended and planned follow-up examinations after discharge.

All patients (n=29) had an LTOT devices, and 11 patients had NIV devices at home. Fifteen patients (51.7%) with LTOT and 9 patients (81.8%) with NIV did not use their devices as recommended; they were considered non-compliant (Table 3).

Table 3: Treatment compliance status

	Compliant n (%)	Non-compliant n (%)
Long-term oxygen therapy	14 (48.3)	15 (51.7)
Noninvasive mechanical ventilation	2 (18.1)	9 (81.9)

After questioning their compliance with LTOT and/or NIV and care status, caregivers were asked six closed and six open-ended questions, and their answers were evaluated. Although the need arose in the post-discharge period, it was observed that twenty-four patients (82.7%) were not taken to the doctor. When asked about the reason without any inducements, all caregivers stated that they were afraid of the coronavirus disease-19 (COVID-19) pandemic and catching the COVID-19 disease in emergency rooms and outpatient clinics. Twenty patients (68.9%) who did not come for planned doctor check-ups after discharge stated the same reasons.

Discussion

Out of 109 patients hospitalized in the second-level chest diseases intensive care unit within the specified 1-year period, twenty-nine patients who met the inclusion criteria comprised the study group.

The mortality rate among those aged 80 years and over within the last 15 months was 64.2% (n=70), regardless of whether they died in or out of the hospital. These cases were excluded from the study due to the design, and no further analysis was performed. However, this result is quite surprising and constitutes important data for further studies on survival after respiratory intensive care unit admission in the elderly/geriatric group. Cirik et al. [8] reported that the 30-day mortality rate was 46% in the geriatric patient group in the third level anesthesia intensive care unit.

In this sample group, we found that only 5 of 22 patients received regular home care services, despite being in need. Respiratory diseases negatively affect the quality of life of individuals with their life-long treatment and symptoms. They change patients' lifestyles and require home care after discharge from the hospital. The purpose of home care in respiratory system diseases is preventing the progression of the disease and decline in functions, reducing symptoms and complications, preventing and/or treating recurrent acute attacks, protecting respiratory functions, increasing exercise capacity, and protecting and increasing the quality of life [9].

In a study conducted in Canada in 2015, it was found that the home care needs of slightly more than one-third of adults in the community are not met [10]. The home care system offers a wide variety of services designed to help geriatric patients improve their symptoms and functionality, and manage their illness [11, 12]. Home care can reduce hospital costs [13]. Studies suggest that home care services are more cost-effective than outpatient services [7]. Almost all caregivers of the patients in our study were first-degree relatives. Studies show that caregiving imposes significant physical, psychological, and financial burden on caregivers [14].

Home care services are extremely useful when elderly patients have difficulties in access to health services such as under pandemic conditions, socioeconomic deficiencies, burnout of caregivers, or diseases that cause immobilization. It has been reported that home care in respiratory patients reduces 1-year mortality, increases the health-related quality of life, decreases admission to hospital and emergency services, and decreases complications associated with recurrent hospitalizations [7].

NIV is an effective treatment for the elderly. It has been shown that NIV reduces the intubation and mortality rates in very elderly patients with acute hypercapnic respiratory failure [6]. It improves arterial blood gases and nocturnal desaturations, reduces hospitalizations, and is associated with long-term survival. Therefore, elder age should not be considered an exclusion criterion for prescribing NIV. It has been reported that NIV compliance is good in the elderly and they have similar usage rates with other age groups [4,5]. However, in this study, it was found that patients who must use NIV treatment at home were mostly non-compliant. Receiving nonspecific home care service did not have any effect on NIV compliance.

Studies have shown that LTOT treatment has a survival benefit in COPD and chronic hypoxemia. However, when 30-60%

of the patients with LTOT indication at the beginning were checked 1-3 months later, the indication had disappeared. For this reason, it is recommended that patients with LTOT be checked after 90 days. Although Chest Diseases specialists meet the correct criteria while prescribing LTOT, patients do not use the devices at home as recommended and exaggerate the duration of use when asked. The reasons for non-compliance included difficulty in managing the equipment, the absence of shortness of breath, limited range of motion, fear that treatment would not work "when it was needed", and feelings of embarrassment [7].

In this study, it was stated that the patients' compliance with the LTOT device was poor and 51.7% of the patients used the device less than recommended. Receiving nonspecific home care services did not have any effect on LTOT compliance. Studies indicate that compliance with domiciliary LTOT is suboptimal, and behavioral and psychological interventions are required to improve compliance [15]. The indication for LTOT needs to be better demonstrated in elderly patients with COPD. It has been suggested that after a few days of treatment in the hospital due to exacerbation of hypoxemia in elderly patients with COPD, future LTOT indication cannot be evaluated. If the oxygen saturation is 85%, oxygen deprivation test can be performed safely after 5-7 days of treatment and should be performed after 1 month of oxygen therapy [16].

We observed that five patients who received nonspecific home care services had poor device compliance, like other patients. Although it is concluded that receiving home care services does not affect compliance with NIV and LTOT devices, this finding should be evaluated with a large number of patients. Home care can identify problems, improve the usage of LTOT and allow interventions when needed. It is stated that smoking cessation, LTOT device maintenance and cleaning, use of a humidifier, and adjusting the length of the connector hose are the most common interventions. They may be beneficial in patients with LTOT noncompliance [17].

The cases in this study avoided all kinds of admissions to the hospital because of the COVID-19 pandemic. This can significantly worsen the general health status of geriatric patients.

Limitations

Our study comprises a very elderly population (≥80 years). Due to high rates of death in very elderly populations, the number of study participants was lower than expected. We could not monitor 70 patients' compliance to devices until they died. This can be regarded as a bias for our study because we only enrolled surviving patients. Also, the effects of home care on NIV and LTOT compliance should be assessed with a large number of patients.

Conclusion

Disruption in doctor visits and patient admissions leads to incompliance with LTOT and/or NIV devices and loss of motivation for their use. In pandemic conditions where patient admissions may be interrupted and morbidity and mortality risks increase, structured and specific home care services for respiratory failure patients become more important. Continuing education and motivation at home and providing on-site psychosocial support to caregivers for patients to use their devices regularly will increase the quality of life of patients and decrease the disease burden. We emphasize the importance of turning geriatric patients' staying at home into an advantage.

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Research article

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Astaxanthin and Coenzyme Q10 are not synergistic against oxidative damage in cerulein-induced acute pancreatitis

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Ethics Committee Approval
All experimental protocols were approved by Marmara University Animal Care and Use Committee (63.2018.mar) according to Turkish law on the use of animals in experiments and New York Academy of Sciences guidelines.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The anti-inflammatory effects of Astaxanthin (ATX) and Coenzyme Q10 (Ubiquinone) are studied in different inflammation models. The study aims to investigate the synergistic effect of astaxanthin and Coenzyme Q10 in a rat model of acute pancreatitis.
Methods: Twenty-four female Wistar rats were grouped as control (C), vehicle-treated control (AP), astaxanthin-treated (ATX; 40 mg/kg), astaxanthin+coenzyme Q10- treated (ATX+Q10; 40 mg/kg and 1 gr/kg) groups. Cerulein was administered (50 µg/kg) twice, one hour apart. Seven hours after the first cerulein injection, the rats were sacrificed. Pancreatic oxidative damage was evaluated with an increase in the serum activity of lipase and amylase, tissue levels of myeloperoxidase activity (MPO), malondialdehyde (MDA), luminol and lucigenin and decrease of glutathione.
Results: In all AP groups, MDA and MPO increased while GSH decreased ($P<0.001$). ATX and ATX+Q10 both decreased MDA and MPO ($P<0.001$) and increased GSH ($P<0.01$). Both therapies significantly increased luminol levels ($P<0.001$, and $P<0.01$, respectively). Lucigenin markedly decreased in the ATX+Q10 group ($P<0.01$).
Conclusion: Antioxidant combination therapy does not alleviate oxidative damage in pancreatic tissue better than astaxanthin alone.

Keywords: Astaxanthin, Coenzyme Q10, Oxidative damage, Acute pancreatitis

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Introduction

Acute pancreatitis (AP) is an inflammatory condition which develops with interstitial pancreatic edema [1]. Oxidative stress has a well-known role in the pathophysiology of acute pancreatitis. Many reports revealed that while lipid peroxidation products increase, glutathione decreases in accordance with the severity of the disease.[2]

Epidemiologic data show an increase in the incidence of AP worldwide with significant morbidity and mortality [3]. The disease ranges from mild to severe, and patients with severe disease have a 30 % mortality rate.

Evidence-based data show an association between acute pancreatitis and oxidative stress. Based on these findings and experimental studies, antioxidants are beneficial in the management of acute pancreatitis [5,6].

Astaxanthin (ATX) is a naturally reddish carotenoid pigment derived mostly from marine environment. *Haematococcus pluvialis* is used as a dietary supplement [7]. Astaxanthin is ten times more effective than the other carotenoids such as zeaxanthin, lutein, and canthaxanthin [8,9]. Experimental studies also support its powerful antioxidant effect, which is due to the chain breaking role in free radical reaction [10,11].

Coenzyme Q (CoQ) a naturally occurring vitamin-like essential compound predominant in humans, is biosynthesized from a quinone structure [12]. It has antioxidant activity and a beneficial role in experimental models are reported [13-15]. It is also preferred as a dietary supplement worldwide as an antiaging agent because its levels decrease by age [16].

To the best of our knowledge, there is limited data regarding the role of astaxanthin and CoenzymeQ10 in pancreatitis. Recent studies revealed that astaxanthin may have a beneficial effect in acute pancreatitis. In the present study, we investigated the therapeutic activity of naturally occurring antioxidants, astaxanthin and CoQ10, in a rat model of acute pancreatitis.

Materials and methods

Animals

Twenty-four female Wistar rats (4-6 months old) were obtained from Marmara University Experimental Animals Research and Implementation Centre (DEHAMER) (Istanbul, Turkey). Animals were kept under standard conditions of humidity (65-70 %), temperature (22 ± 2°C) and constant light/dark (12 h/12 h) cycles and fed pellets and water *ad libitum*. All experimental protocols were approved by Marmara University Animal Care and Use Committee (63.2018.mar) according to Turkish law on the use of animals in experiments and guidelines of the New York Academy of Sciences.

Experimental design

The rats were divided randomly as control (C, n=6) and acute pancreatitis (AP, n=24) groups. The AP groups were subsequently divided into 3 subgroups as vehicle-treated (AP), astaxanthin (Sigma-Aldrich Co. LLC, Germany)-treated (ATX) and astaxanthin+ CoenzymeQ10 (Sigma-Aldrich Co. LLC, Germany) treated (ATX+Q10) group.

Acute pancreatitis was induced by the injection of cerulein (Sigma-Aldrich Co. LLC, Germany; 50 µg/kg) intraperitoneally twice, one hour apart. After the first cerulein injection the AP group was treated with vehicle olive oil, ATX group received 40 mg/kg astaxanthin, and ATX+ Q10 group (40 mg/kg astaxanthin + 1 gr/kg CoQ10) by orogastric gavage.

At the 6th hour following the final injection, the rats were sacrificed with cardiac puncture under anesthesia by thiopental sodium (50 mg/kg/ip). The pancreas tissue was removed for tissue analyses. Serum samples were collected for blood biochemical analyses.

Biochemical analyses

Serum amylase, lipase

Collected blood was centrifuged at 3,000g for 10 min at 4 °C. The serum amylase and lipase levels were determined using enzyme-linked immunosorbent assay (ELISA) kits (eLabscience, San Diego, CA, USA) in accordance with the manufacturer's instructions and guidelines.

Malondialdehyde (MDA) and Glutathione (GSH) Levels

MDA level is a significant marker of lipid peroxidation. It is measured by a spectrophotometer at 532 nm by monitoring thiobarbituric acid reactive substance formation as previously described and expressed as nmol/g [17]. GSH was also measured by a spectrophotometric method via modification of the Ellman procedure [18], and a coefficient of 1.36 x 104 M-1 cm- was used to calculate GSH levels, which were expressed as µmol GSH/g tissue.

Myeloperoxidase activity

A heme protein, myeloperoxidase, is found predominantly in azurophilic granules and expressed by phagocytic cells. Tissue MPO activity is utilized to predict tissue PMN accumulation specially in inflamed tissues and correlates with the number of PMN determined histologically. By measuring the H2O2-dependent oxidation of o-dianizidine·2 HCl MPO activity is calculated. The activity of the enzyme was set as the amount of MPO that caused a change in absorbance tested at 460 nm by the spectrophotometric method. MPO activity was expressed as U/g tissue [19].

Chemiluminescence assay

To show reactive oxygen species (ROS) in the pancreatic tissue, we performed the chemiluminescence (CL) assay. It directly measures ROS where luminol and lucigenin can be used as enhancers. CL levels were tested with a Junior LB 9509 luminometer (EG&G Berthold, Germany). The results were calculated by the area under the curve and adjusted to the wet tissue weight. All results are expressed as relative light unit/ mg tissue (rlu / mg) [20].

Statistical analysis

Statistical analysis was performed using analysis of variance (ANOVA post hoc Tukey test) with GraphPad Prism 6.0. Differences were considered significant if $P<0.05$. Values are expressed as mean ± SEM.

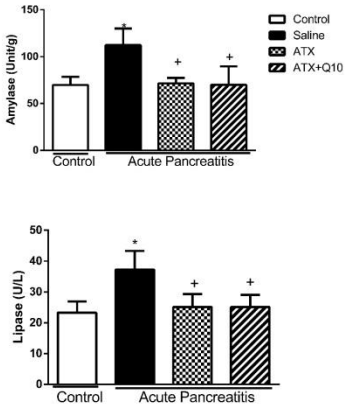
Results

Effect of compounds on serum amylase and lipase levels

When compared with the control group, serum lipase and amylase levels were higher in the vehicle-treated group ($P<0.05$),

and lower in the ATX and ATX+Q10 groups compared to the vehicle-treated group (P<0.05) (Figure 1).

Figure 1: Lipase and amylase levels in sera (Lipase (A)- and Amylase (B) levels in the pancreatic tissues of the control and vehicle, ATX and ATX+CoQ10 treated acute pancreatitis groups (n=6 per groups). Data are expressed as mean ± SEM; n=6 rats/group; **P<0.01 vs control group; +P<0.05 vs vehicle-treated group)



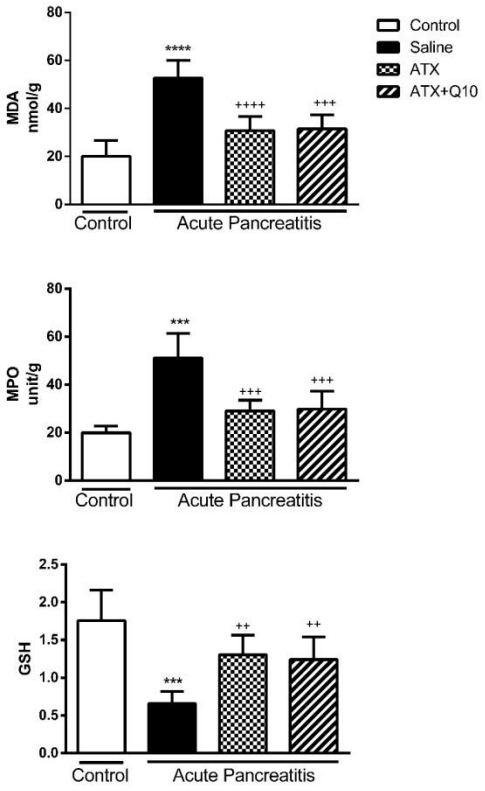
Effect of compounds on MPO activity and MDA level.

MPO activity and MDA level are elevated significantly in vehicle-treated group compared to the control group (P<0.001) (Figure 2a, b). Increased MPO activity and MDA levels were reduced by both treatments (P<0.001). The reduction amounts were similar between the two groups, and with the control group.

Effect of compounds on GSH level

When compared with the control group, GSH level decreased significantly in the vehicle-treated group (P<0.001). Depressed GSH level was elevated with ATX and ATX+Q10 treatments (P<0.01 for both) (Figure 2c).

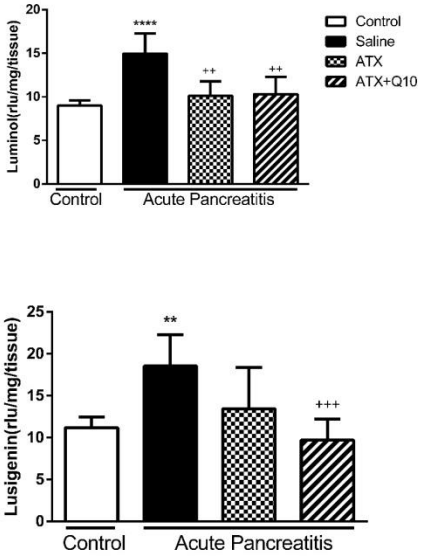
Figure 2: Pancreatic tissue, Malondialdehyde (MDA), Myeloperoxidase activity (MPO) and Glutathione (GSH) levels (Data are expressed as mean ± SEM; n=6 rats /group; **P<0.01, ***P<0.001 vs control group; +P<0.05, ++P<0.01 vs vehicle-treated group.)



Effect of Astaxanthin on CL values

Both luminol and lucigenin levels were elevated in the saline-treated group compared with the control group (P<0.001 and P<0.01, Figure 3). While elevated levels of luminol were reduced significantly (P<0.01), the decrease in lucigenin was not significant in ATX group. Significant decrease in luminol and lucigenin were observed in the Q10 group (P<0.01) compared to the AP group.

Figure 3: Pancreatic luminol-enhanced (A)- and lucigenin-enhanced (B) tissue chemiluminescence (CL) levels (Data are expressed as mean ± SEM; n=6 rats/group; *P<0.05, **P<0.01 vs control group; +P<0.05, ++P<0.01 vs vehicle-treated group.)



Discussion

Acute pancreatitis affects 13-45/100.000 individuals per year [21] and supportive treatment is the mainstay of management. We investigated the effect of astaxanthin and astaxanthin+Q10 combination, both of which are lipid soluble antioxidants, on a cerulein-induced rat acute pancreatitis model.

Serum lipase or amylase activities are the most used serum biochemical markers of AP. Our findings point out to a significant reduction in amylase and lipase levels in both groups. Similar to our results, a recent study reported a significant decrease on rising serum amylase and lipase with Q10 treatment [22].

Since the role of oxidative damage is defined in acute pancreatitis, scavenging efficiency of many natural products on ROS were evaluated [10, 23]. However, the antioxidant effect of plant-derived natural products on ROS species is still controversial [7-9, 24, 25]. A study reported that plant derived antioxidants affect free radicals [26]. ATX is a lipid soluble carotenoid [27] which inhibits cyclooxygenase 2 (COX2) and autoimmune reactions and activates T-cells [28]. Similar to ATX, coenzyme Q10 is a lipid soluble endogenous compound with antioxidant properties which is used to treat many diseases [29-32]. The role of Q10 in inhibition of ROS production is the blockage of NF-κB at the mitochondrial level [33, 34]. However, its antioxidant capacity is 800 times less than that of ATX.

Many studies showed synergistic effects of antioxidants by inhibition of lipid peroxidation [35]. Elevation in reactive oxygen species (ROS) and reduced antioxidant activity markedly influence inflammation [3, 4]. In this study, we investigated ATX's antioxidant capacity with or without coenzyme Q10. Our

results confirmed increased reactive oxygen species and decreased antioxidants in the cerulein-induced acute pancreatitis model, similar to previous reports. Our model reflects the early stage of acute pancreatitis, and as expected, MDA levels and MPO activity were increased while GSH was decreased [5, 10, 36-39]. GSH levels were later increased by ATX [36, 40]. However, Q10 addition was not effective, parallel with the data of the above-mentioned study [22].

Chemiluminescence is an assay for detecting reactive oxygen species. The luminol probe of this technique detects OH^-, H_2O_2, hypochlorite, peroxynitrite, and lipid peroxyl radicals, while lucigenin is specific for superoxide radicals. In conformity with the previous reports, our results showed an increased pancreatic production of reactive oxygen species. ATX decreased the luminol and lucigenin levels in acute pancreatitis just like in other inflammatory diseases [14]. Interestingly, while lucigenin decreased in ATX group, significant decrease was achieved in the ATX+CoQ10 group.

Limitations

These results must be considered in the context of the study limitations. First, although our results showed significant differences in the ATX+Q10 group, and the lack of Q10 group made it difficult to generalize our results. Moreover, we did not evaluate the underlying physiological mechanisms against acute inflammation. Despite these limitations, a strength of this study is that it compared inflammatory markers, enzymes, and reactive oxygen species indicators between the groups.

Conclusion

This study shows that antioxidant combination does not inhibit oxidative damage better than astaxanthin alone in a cerulein-induced rat model of acute pancreatitis. Astaxanthin, a carotenoid, ameliorates increased oxidative stress markers, and addition of Q10 is ineffective in this regard. It is probably a result of Q10's weak antioxidant capacity. Thus, astaxanthin can be used as a valuable therapeutic pharmacological agent in the treatment of acute pancreatitis.

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Evaluation of nitric oxide metabolism and malondialdehyde levels as an indicator of oxidant stress in malign and parapneumonic pleural effusion

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Ethics Committee Approval
This study was approved by the Ethics Committee of Ankara University Medical Faculty (25 - 487, 28 February 2011).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Pleural effusion is an important pathology which usually develops comorbid to varying diseases and negatively affects the quality of life. Studies to understand the etiopathogenesis of the disease are important. Although there are some studies in the literature about the arginine-NO metabolism in pleural diseases, there is not another study including all patient groups and the parameters examined in this study. Pleural fluid arginase and NOS (nitric oxide synthase) activities as well as NO (nitric oxide) and MDA (malondialdehyde) levels of patients were determined. The aim of our study was to investigate the possible relationship between these parameters and the mechanism of pleural fluid accumulation.

Methods: In this study, pleural fluid arginase and NOS (nitric oxide synthase) activities as well as NO (nitric oxide) and MDA (malondialdehyde) levels of patients with malignancy, pneumonia and CHF (congestive heart failure) were determined. Our study was a cross-sectional descriptive research and our study groups consisted of patients with pneumonia (n=28), malignancy (n=28) and CHF (n=24). NO and MDA level with arginase and NOS activity were determined spectrophotometrically. Results were expressed as mean (standard deviation).

Results: Pleural fluid arginase activity in CHF patients was significantly lower than in the malignancy and pneumonia groups (P=0.003). The pleural NO level and NOS activity were higher in the malignancy group than in the other groups (P<0.001). Compared to the other groups, MDA level was significantly increased in the pneumonia group. (P<0.001).

Conclusion: In the light of these results, it may be concluded that the arginase- NO metabolism and MDA formation are involved in the pathogenesis of pleural effusions.

Keywords: Arginase, Malondialdehyde, Nitric oxide, Nitric oxide synthase, Pleural effusion

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Introduction

Arginase is an important hydrolytic enzyme involved in arginine degradation. Arginine is also used by NOS to produce NO, and NOS and arginase may compete to utilize that common substrate. The main task of arginase in tissues is to regulate the intracellular arginine concentration to diminish NO production by NOS [1].

NO is a short- lived polyfunctional signaling molecule and a well-known free radical [2]. There are three isoforms of NOS in the human body, and all are identified in the respiratory system. One of the three isoforms of NOS is iNOS (inducible NOS) which is expressed in response to bacteria and proinflammatory stimuli and produces large amounts of NO for a longer period [3]. All three isoforms (endothelial, inducible and neuronal NOS) participate in the regulation of respiratory physiology by cooperative production of NO. Any change in the activities of these enzymes may affect the NO level and play a role in pathogenesis of many respiratory diseases [4].

It is known that free radicals play a role in the development of cancer, inflammation damage and chemical toxicity and elevated levels of NO are associated with free radical production. NO may act both as an inhibitor and activator of lipid peroxidation under different conditions [5]. That is why we aimed to investigate the possible complex relationship between arginase, NOS/NO and MDA as a product of lipid peroxidation.

Pleural effusion is a common clinical problem in routine practice and is often seen as a complication of a systemic pathology or other organ diseases. The most common causes of pleural effusion include CHF, malignancy, pneumonia, and tuberculosis.

Various markers of oxidative stress can be detected in different biological specimens such as blood, sputum, bronchoalveolar lavage (BAL) fluid, pleural fluid, and exhalation air in lung diseases. These samples demonstrate both local and systemic effects of oxidative stress. However, the role of free radicals in pleural diseases is not yet fully known. Free radicals may occur as a byproduct of normal metabolism, as well as by the effects of infections, inflammation, carcinogenesis, drugs, and other harmful chemical substances. Therefore, in this study, the levels of NO, MDA and the activity of NOS and arginase in pleural fluid were examined in three groups of patients with heart failure, lung cancer and pneumonia, and the possible relationship between these parameters and etiopathogenesis of the diseases were investigated.

Materials and methods

Study population and protocol

This study was approved by the Ethics Committee of Ankara University Medical Faculty (25 - 487, 28 February 2011). Informed consents were obtained from all patients. The samples of pleural fluid were collected by thoracentesis from the patients in Ankara Atatürk Chest Diseases and Chest Surgery Training and Research Hospital. Patients with pleural effusions whose pleural collections were sampled for diagnostic and /or therapeutic purposes were included in the study. Patients were divided into three groups based on their final diagnoses. Similar numbers of patients to those in the literature were included in each group. We tried to reach the maximum number of patients within the planned research period. The first group of 28 patients had pneumonia with parapneumonic effusion (PPE). This group consisted of 21 males and 7 females. The mean age of the patients was 56.4 (18.0) years. Diagnosis of PPE was established based on the measurement of the pH, glucose and LDH (lactate dehydrogenase) levels of the pleural fluid using the Light criteria [6]. Also, inflammatory cells were seen in the cytopathological examination of the effusion, which was called "parapneumonic fluid". The second group consisted of 24 patients, 19 males and 5 females who had CHF related transudative effusion that was diagnosed by the presence of clinical and radiologic findings suggestive of cardiac dysfunction. Ejection fraction was <40% based on echoes performed on these patients and a diagnosis of heart failure was made. Patients in this group also had massive fluid accumulation in their lungs. Examination of these fluids showed that it is a transudate due to CHF. The mean age of the patients in this group was 70.8 (10.8) years.

The third group comprised 28 patients, 20 males and 8 females with malignancy. Their mean age was 60.9 (11.9). Malignant effusion was diagnosed by the presence of cytologic and /or histopathologic evidence of malignancy in pleural fluid or bronchoscopic specimens.

Pleural fluid specimens were stored at -80ºC until the day of biochemical analysis. All analyses were performed in the research laboratory of Department of Medical Biochemistry, Ankara University Faculty of Medicine.

Measurement of NO, NOS, MDA, and arginase: The pleural fluid supernatant was obtained after the centrifugation of primary tube at 3000 rpm for 15 minutes at room temperature and NO, NOS, MDA, and arginase values were determined by spectrophotometric methods. Arginase activity was measured using the method described by Chinard [7]. One unit of arginase activity was defined as 1 µmole liberated ornithine per minute at 37 ° C. Arginase activity was expressed as IU/L.

Measurement of the NO pool (consisting of $NO\cdot + NO\neg^{2}$) is based on a chemical reaction in which NO ($NO\cdot$) to a greater extent, and nitrite anion ($NO\neg^{2}$) to a lesser extent, gives a diazotization reaction with sulfanilic acid. The absorbance of complexone formed with N-(1-naphthyl-ethylene diamine) reflects the sum of $NO\cdot$ and $NO\neg^{2}$ levels in the reaction medium, termed the NO pool. NO pool values were given as mM. In this method, sodium nitroprusside was used as the chemical standard and the reaction scheme described by Durak et al. [8] was followed. NOS activity which is known to produce NO by catalyzing a five-electron oxidation of guanidino nitrogen of L-arginine was measured at the same time and expressed as IU/mL [9].

MDA, an end product of fatty acid peroxidation, reacts with thiobarbituric acid to form a colored complex that has maximum absorbance at 532 nm [10]. Results were expressed as nmol/mL. Absorbances were read using a Unicam HeλIOS-α UV-VIS spectrophotometer (Unicam, Cambridge, UK). All chemicals were purchased from Sigma and Merck Chemical Companies (St. Louis, MO).

Statistical analysis

Data analysis was performed by using SPSS for Windows, version 15. Values in the groups did not show normal

distribution. Therefore, nonparametric Kruskal Wallis test was used for comparison of multiple groups. All data were expressed as mean (SD) and median. For all statistical calculations, $P<0.05$ was considered statistically significant. When there was a significant difference between the three groups, post hoc multiple comparison test was used to determine the groups from which the difference originated. In addition, Spearman correlation analysis was performed separately for the three groups participating in the study. Possible relationships between the parameters examined in the groups were investigated.

Results

As seen in Table 1, there were significant differences between all three groups in terms of all parameters. Pleural fluid arginase activity in CHF patients was significantly lower than in the malignancy and pneumonia groups ($P=0.003$), and similar between the pneumonia and malignant groups ($P=0,983$). Pleural NO level and NOS activity were higher in the malignancy group than in the other groups ($P<0.001$), and similar between the pneumonia and CHF groups ($P=0.987$, $P=0.921$). MDA level was significantly increased in the pneumonia group compared to the other groups ($P<0.001$), and similar between the CHF and malignant groups ($P= 0.865$).

Table 1: NO and MDA levels and NOS and arginase activities of groups

	Pneumonia (n=28) Mean (SD) Median (min-max)	Malignancy (n=28) Mean (SD) Median (min-max)	CHF (n=24) Mean (SD) Median (min-max)	*P*-value All groups Pneumonia vs. Malignancy	*P*-value Pneumonia vs. CHF Malignancy vs. CHF
Arginase (IU/L)	198.6 (65.8) 53.8 (16.5-1643.0)	78.4 (2.0) 78.7 (57.9 – 95.0)	90.7 (36.9) 16.6 (2.0 - 848.8)	0.003 0.983	0.027 0.003
NO (mM)	15.8 (1.6) 14.7 (8.7 - 56.7)	45.5 (2.2) 48.2 (23.7 - 61.7)	14.5 (1.2) 13.0 (8.7 - 39.7)	<0.001 <0.001	0.897 <0.001
NOS (IU/ml)	6.9 (0.2) 6.3 (5.4 - 9.1)	10.9 (0.3) 10.9 (5.5 - 14.1)	6.0 (0.4) 6.5 (2.9 - 9.6)	<0.001 <0.001	0.921 <0.001
MDA (nmol/ml)	2.5 (0.3) 1.9 (1.2 - 8.1)	1.5 (0.2) 1.1 (0.5 – 5.0)	1.4 (0.2) 1.3 (0.4 - 5.4)	<0.001 <0.001	<0.001 0.865

Min: Minimum, max: maximum, SD: Standard Deviation

According to correlation analysis, only arginase and MDA levels in the pneumonia group were positively correlated ($P=0.002$).

Discussion

The accumulation of fluid in the pleural space, usually due to an underlying disease, is called pleural effusion [11]. We have very little knowledge about the immunological and molecular mechanisms that play a role in pleural diseases and effusions. A large number of mediators and proteins released by the mesothelial cells play role in inflammation processes. One of these mediators is NO [12]. Experimental studies have shown that during an inflammatory process, pleural mesothelial cells increase NO synthesis by inducing cytokine and lipopolysaccharide. These proinflammatory cytokines increase nitrite/nitrate production [13].

In animal experiments, nitrite/nitrate levels were high in exudative pleural effusion which is generated by carrageenan injection to normal mice. In the same study, it was observed that in mice with iNOS gene loss, the inflammatory response was decreased compared to the pleurisy occurring in normal mice. Nitrite / nitrate levels were also lower in the pleural fluids of mice with iNOS gene loss [14]. The inflammatory reaction was reduced in the exudate formed by the administration of a NOS inhibitor. Regnault et al. [15] reported that NO production was higher in exudate pleural effusions which were induced by an inflammatory reaction. In our study, we found a significant difference between all groups for NO and mean NO levels were higher in exudate groups compared to transudate CHF group. Similar results were found for NOS activity. According to these findings, we may suggest that NO is a possible mediator playing a role in the development of exudates.

Arginase is a potent immune system inhibitor and has an inhibitory effect on lymphocyte proliferation [16]. In many different studies, serum arginase activity was investigated especially in patient groups with different malignancies. Two isoforms of arginase are present in the respiratory system [4]. Thus, in our study, we also aimed to evaluate the changes in arginase activity in pleural diseases and its relation to NO and NOS. Arginase median values of patients with CHF were lower than those of patients in the pneumonia and malignant groups, and similar between the latter two. Furthermore, as to the mean levels of arginase in the study groups, the malignancy group with the lowest mean activity also had the highest NO and NOS averages. This result may further support the supposed relationship between NOS and arginase sharing the common substrate [17]. High NOS activity may be the cause of decreased arginase activity in this group.

Free radicals and peroxides are involved in the pathogenesis of various inflammatory and malignant diseases. Most lipid-containing biological systems such as plasma membranes, organs, and cell membranes utilize the measurement of malondialdehyde in assessing lipid damage because of oxidative stress. Diseases related to the pleural cavity such as malignancy, tuberculosis or pneumonia may cause exudate and theoretically contribute to oxidative stress production. Conversely, transudative pleural effusions are not associated with local pleural pathology and are due to imbalance between hydrostatic and oncotic pressure. So, transudate is not expected to lead to the formation of reactive oxygen derivatives.

Various studies have been carried out to reveal the importance of free radicals in pleural diseases. In a study by Hammouda and colleagues [18] who measured pleural fluid MDA levels, MDA levels were significantly elevated in exudative fluids relative to transudative fluids. Kostikas and colleagues [19] found that oxidative stress was high in the exudative pleural effusion. According to the obtained values, MDA level measurement was a useful method that could be used to differentiate between transudative-exudative fluids.

We compared the pleural fluid MDA levels of three groups of patients as an oxidative stress indicator. We observed a significant difference between the three groups. In bilateral comparisons, the pneumonia group had significantly higher levels compared to malignancy and CHF groups. There was no significant difference between the malignancy and CHF groups. High MDA values in the pneumonia group were supportive of other studies [20], however, MDA levels in the malignancy group were not significantly different from the transudate CHF group.

Limitations and strengths

The pleural effusion sample used in our study is difficult to obtain and requires an invasive procedure. Therefore, the small number of samples constitutes a limitation in our study. However, we examined more than one parameter in three different disease groups, which was the strength of our work.

Conclusion

Considering our results, we think that arginine-NO metabolism may play a role in the etiopathogenesis of pleural effusions caused by different lung diseases. MDA seems to be involved in the pathophysiology of pneumonia as an indicator of lipid peroxidation.

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Evaluation of the effects of ultrasound-guided infraclavicular nerve block on postoperative pain in pediatric supracondylar fracture surgery

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Ethics Committee Approval
Ethical approval was obtained from Selcuk University, Medical School Ethics Committee (Ref no: 2017/201).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Abstract

Background/Aim: Ultrasound-guided upper and lower extremity nerve blocks offer significant advantages in adult patients. However, the effectiveness of these advantages in children is being investigated. The aim of this study was to evaluate postoperative pain scores of single-injection infraclavicular nerve block in pediatric patients who underwent supracondylar surgery.

Methods: Forty-one patients who underwent supracondylar surgery between December 2016 and December 2017, with either general anesthesia (GA, n=19) or ultrasound-guided infraclavicular block (ICB, n=22) were included in this retrospective cohort study. Postoperative visual analogue scale (VAS) pain scores at the 30th min, 2nd, 6th, 12th, and 24th hours, the total amount of pethidine and paracetamol administered, and time until the first analgesia requirement were evaluated.

Results: The demographic characteristics of the patients were similar ($p>0.05$). The VAS scores and total amount of consumed pethidine and paracetamol were lower in the ICB group in the first 12 hours than in the GA group, but the opposite was true at the 24th hour ($P<0.001$). The first analgesia requirement time was much longer in the ICB group than in the GA group ($P<0.001$). The two groups were similar in terms of complications ($P<0.05$).

Conclusion: Ultrasound-guided infraclavicular block could be a useful option for postoperative analgesia control in patients undergoing supracondylar surgery.

Keywords: Supracondylar surgery, Infraclavicular nerve block, General anesthesia, Ultrasonography, Visual analogue score

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Introduction

Supracondylar fracture of the humerus requires approximately 85% surgical intervention in pediatric orthopedic practice, accounting for more than half of all elbow fractures and roughly 33% of all pediatric limb fractures [1]. Although surgical procedures generally require general anesthesia in children, regional anesthesia is used more frequently. In recent years, brachial plexus anesthesia has become a valuable option in the surgical treatment of the upper extremity in children. In pediatric regional anesthesia practice, the use of ultrasonography (USG) has various reported effects such as shortening the time to onset of the block, high rates of block success, and postoperative analgesia [2]. In addition, USG-guided pediatric regional anesthesia decreases the amount of intraoperative anesthetic and systemic narcotic drugs, it can be used in pediatric trauma surgery where general anesthesia can be dangerous due to the high risk of gastric aspiration, and more importantly, it helps control postoperative pain [3-5].

In this study, it was aimed to evaluate postoperative pain scores of single injection infraclavicular nerve block in pediatric patients who underwent supracondylar surgery.

Materials and methods

This retrospective clinical study was approved by the Ethics Committee of Selcuk University, Faculty of Medicine (Ref no: 2017/201). From all patients admitted from December 2016 to December 2017, anesthesia data of 41 patients aged between 5-12 years who were American Society of Anesthesiologists (ASA) risk group I/III and scheduled for surgery due to supracondylar humerus fracture were included. The information of the patients was collected from the hospital automation database. The patients included in the study were evaluated; those who received general anesthesia comprised the GA group (n=19), and those who underwent infraclavicular nerve block were assigned to the ICB group (n=22).

All patients received a standard GA protocol. Anesthesia induction was performed with 2 mg kg^{-1} propofol, 2 mg kg^{-1} fentanyl, and 0.6 mg kg^{-1} rocuronium at the onset of GA induction in the GA group. Anesthesia continued with 1-2% sevoflurane, 40% O_2, and 0.1 mcg kg min^{-1} remifentanil infusion at regular intervals and muscle relaxants. Intravenous paracetamol (15 $mg.kg^{-1}$) was administered to all patients prior to any surgical incision for the purpose of preemptive analgesia.

Patients in group ICB were also lying in the supine position after routine GA induction and intubation, and the patient's head was turned to the opposite side of where the block was performed. The skin on the infraclavicular block area and its surroundings were sterilized using 10% povidone iodine. The block applications were performed using an Esaote MyLab 30 US (Florence, Italy) device with a broadband, and multifrequency linear probe (10-18 MHz). After aseptic preparation, the USG linear probe was placed perpendicularly to the proposed region (the point where the clavicle and coracoid protrusion intersect) to apply infraclavicular block through the lateral-sagittal technique proposed by Klaastad et al. [6]. When the cords (lateral, medial, and posterior) of the axillary artery, vein, and brachial plexus were visualized, 22-G nerve stimulation needle (Stimuplex, Braun®, Gemany) USG probe was directed towards the 3-6-9 alignment relative to the artery. As a local anesthetic, 0.3 $mg.kg^{-1}$ of 0.25% bupivacaine (Bustesin® 0.5%, Istanbul, Turkey) was administered in divided doses, with intermittent negative aspiration to avoid intravascular injection. It was observed with USG that the local anesthetic brachial plexus spread around all three cords in a "U" shape.

Postoperative VAS-3 levels were considered painful for group GA and group ICB and 10 $mg.kg^{-1}$ paracetamol was administered orally. If VAS-3 pain values did not decrease after 15 min, 1 $mg.kg^{-1}$ pethidine IM was given.

Clinical evaluation

Sociodemographic and clinical data were recorded in the preoperative period. Age, sex, weight, height, ASA status, operation side, and anesthesia and surgical time were evaluated. VAS pain scores at the postoperative 30th minute, and 2nd, 6th, 12th, and 24th hours, total amount of paracetamol and pethidine, first opioid analgesia requirement time, and complications were evaluated.

Statistical analysis

The statistical analyses of the study were performed with the SPSS 20.0 software. Descriptive measures of continuous and categorical variables were extracted and are presented as tables and graphs. Continuous variables are presented in the form of mean (standard deviation or error) and the frequencies and percentages of categorical variables are given. The Kolmogorov-Smirnov normality test was used for continuous variables. Group comparisons of the variables that showed normal distribution were performed using one-way analysis of variance (ANOVA). Mann-Whitney U variance analysis was used for discrete numeric variables that did not show normal distribution. Relationships between the categorical variables were determined by preparing crosstabs and using the Chi-square (χ^2) test. In all analyses, $P<0.05$ was considered statistically significant.

Results

Data were obtained from hospital anesthesia records from December 2016 to December 2017. A total of 41 pediatric patients who underwent surgery for supracondylar humerus fractures were included. Two patients were excluded from the analysis due to data loss. Accordingly, 17 patients in the GA group and 22 patients in the ICB group were included in the final analysis. The patients' demographic characteristics, ASA status, operation side, and duration of surgery and anesthesia were similar ($P>0.05$) (Table 1).

Table 1: Patient characteristics and clinical data

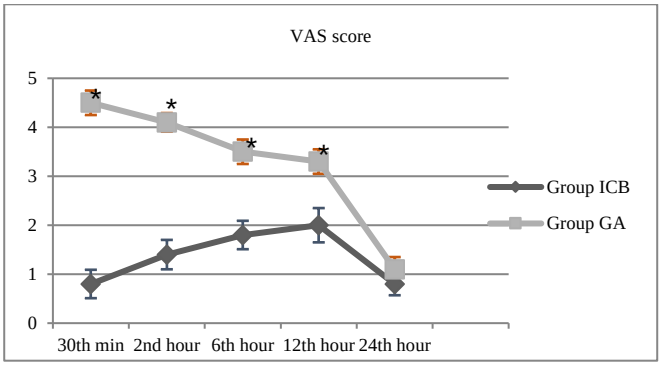
	Group ICB n=22	Group GA n=17	*P*-value
Gender, M/ F	13/9	11/6	0.512
Age, years	8 (3.3)	7.8 (4.6)	0.867
Weight, kg	25.1 (9.7)	26.5 (8.3)	0.789
Height, cm	114.2 (13.9)	111.9 (15.0)	0.811
ASA I / II	21/1	17/0	0.504
Anesthesia time, min	99.2 (15.6)	102.8 (12.3)	0.622
Surgical time, min	89.5 (14.7)	93.0 (12.4)	0.432
Side of surgery, R / L	13/11	10/7	0.247

Values are presented as mean (standard error) or number of patients. ICB: infraclavicular nerve block, GA: general anesthesia, ASA: American Society of Anesthesiologists, F/M: female/male, R/L: right/left

Within the first 24 hours postoperatively, there was a significant difference between the VAS scores of the GA and ICB groups ($P<0.001$). VAS pain scores (at 30th min, and 2nd, 6th, and 12th hours) were significantly lower in group ICB than in group

GA at all measurement points, except for the 24th hour (P<0.001, P<0.001, P=0.018, P=0.033, and P=0.416, respectively) (Figure 1).

Figure 1: Comparison of postoperative visual analogue scale (VAS) scores between the two groups



* VAS scores significantly differed except at the 24th hour (P<0.001, P<0.001, P=0.018 P=0.033 and P=0.416, respectively)

A total of 550 (82.6) mg and 1240.2 (110.8) mg paracetamol and 0 mg and 10.5 (9.3) mg of pethidine were consumed in the ICB and GA groups, respectively (P<0.001 for both) (Table 2).

Table 2: Time that elapsed until first requirement for analgesia and the total amount of pethidine and paracetamol consumed over the first 24 hours after surgery

	Group ICB n=22	Group GA n=17	P-value
Time that elapsed until first requirement for analgesia (hours)	13.2 (2.2)	6.3 (3.8)	0.021
Total amounts pethidine consumed (mg)	0	10.5 (9.3)	<0.001
Total amounts paracetamol consumed (mg)	550.5 (82.6)	1240.2 (110.8)	<0.001

Values are presented as mean (standard error). ICB: infraclavicular nerve block, GA: general anesthesia

The time until first analgesia requirement was 13.2 (2.2) and 6.3 (3.8) hours in groups ICB and GA, respectively (P=0.013) (Table 2). There was no significant difference between the two groups in terms of postoperative complications (P<0.05).

Discussion

The analgesic effect of ICB, which was added to GA in supracondylar humeral fracture surgery, was superior to the GA group in the first 12 postoperative hours. In addition, compared with the GA group, the time until first opioid analgesia administration increased in the ICB group, while the total amount of paracetamol and pethidine consumed decreased.

It has been stated that single-injection infraclavicular nerve block is safe and provides sufficient sensory and motor blockade in children [7]. Studies on infraclavicular brachial plexus block regard its comparison with other brachial nerve blocks or block formation times of different approaches of the infraclavicular block. Studies on the postoperative analgesia of infraclavicular block are relatively few.

Hadzic et al. [8] showed that analgesia scores were better in brachial plexus block compared with GA in daily hand surgery attempts. The brachial plexus block group was discharged earlier, there was no need for additional analgesia, and it was superior in terms of adverse effects. In a prospective randomized study, Aboobacker et al. [9] showed that the continuous infraclavicular block performed with USG provided better postoperative pain scores, less narcotic use and complications, and better sleep satisfaction. In our study, ICB provided superior analgesia, and less and later use of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.

There are some important problems that can be seen in ICB plexus block. First, the complications that can arise from the block: Horner syndrome, hematoma, nerve damage, arterial puncture, and pneumothorax; second, local anesthetic toxicity can develop as a result of the high amount of local anesthetic injection during the block [10]; and third, compartment syndrome [11]. The advantages of USG guidance lie in the imaging of the anatomic structures and needle during the intervention, thus avoiding nerve damage, pneumothorax, and vascular perforation. Another is the possibility to directly visualize the distribution of the local anesthetic and control the distribution [12]. De José et al. [13] reported that USG-guided supraclavicular and ICB applications might reduce existing risks in pediatric patients. In our ICB application, we think that we have achieved high success rates and low complication rates in postoperative analgesia because we performed it with the lateral sagittal ICB technique described by Klaastad et al. [9].

Limitations

Our study has some limitations. First, this is a retrospective study and including limited number of cases. Second, when evaluating VAS scores, it was not determined at what time the difference between the 12th and 24th postoperative hours disappeared. Third, the ICBs were performed by more than one anesthesiologist.

Conclusion

Single-injection infraclavicular nerve block accompanied by USG was more advantageous than systemic analgesia with superior VAS values in postoperative pain control, less opioid and paracetamol use, and prolonged first analgesia requirement time. However, we believe that stronger prospective studies are also needed.

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Gynecological surgical approach to a patient with Sneddon's syndrome

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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Abstract

In this case report, the management of a patient with Sneddon's syndrome who underwent laparoscopic hysterectomy for menometrorrhagia and multiple leiomyoma uteri is discussed. The clinical management of Sneddon's syndrome is based on four distinct aspects: Neurological, hematological, dermatological, and psychiatric. Their analysis can be a valuable tool in the preoperative and postoperative monitoring of these patients.

Keywords: Sneddon's syndrome, Menorrhagia, Laparoscopy

Introduction

Sneddon's syndrome, a non-inflammatory thrombotic vasculopathy which involves small and medium diameter arteries, manifests with Livedo reticularis and cerebrovascular diseases. The relationship between livedo reticularis and cerebrovascular symptoms was first defined by Kimming in 1959. Sneddon named this as a syndrome in 1965 with the reporting of 6 patients showing all the characteristics of a syndrome. The primary underlying event in the pathogenesis of the disease is a reduction in blood flow to the brain and skin, caused by small and medium diameter arterial occlusions. With an incidence of 4/1,000,000, it is usually observed in middle-aged females [1-3].

The etiopathogenesis of Sneddon's syndrome is unknown. Anti-cardiolipin antibodies (ACA) have drawn the most attention. In some reports, ACAs, especially IgG, were high in Sneddon's syndrome patients. Therefore, it is thought that ACAs could play a role in the pathogenesis of the disease [4-9]. Findings similar to those of antiphospholipid antibody syndrome, such as recurrent, low thrombocytopenia, have also been observed in various cases with Sneddon's syndrome [5, 10, 11]. In numerous reports, Sneddon's syndrome is evaluated under the main heading of antiphospholipid antibody syndrome [2]. However, the ACA levels of many Sneddon's syndrome patients remain normal, and elevated ACA levels are not deemed necessary for diagnosis [1, 12, 13]. This subject remains a matter of debate.

Livedo reticularis lesions, which are a characteristic finding of Sneddon's syndrome, have the appearance of a persistent, blue-purple colored, irregular mesh. They extend particularly from the trunk (gluteal region, and the lower lumbar region) towards the extremities (thighs, dorsal surface of the arms). Livedo reticularis generally emerges a few years or even a few decades before the onset of central nervous system (CNS) symptoms. As diagnosis is usually made after CNS symptoms, the age at diagnosis is the fifth decade. These lesions are progressive and exacerbated in the acute phase of a neurological attack [6, 14-16].

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Cerebrovascular symptoms usually occur secondary to ischemic attacks. In approximately 77% of patients, headache, seizures, hemiparesis, sight disorders and psychiatric disorders such as depression may be seen. The common CNS pathology in patients include temporary ischemic attack (TIA) and/or ischemic stroke. Despite widespread lesions in the CNS, clinical findings are not very severe due to the involvement of small and medium diameter arteries. In approximately 75% of patients, the symptoms are recurrent, generally in a similar form to the first symptoms [1, 10-14]. The first symptoms in Sneddon's syndrome generally occur in the reproductive years and disease activity tends to stabilize with menopause. The use of oral contraceptives can increase the disease. As Sneddon's syndrome is usually seen in females, female reproductive hormones are thought to play a role in the pathogenesis of the disease. It has also been reported that hypertension, observed in some patients with Sneddon's syndrome, may have a triggering role in the development of symptoms [1-6]. No effective definitive treatment has yet been defined. The use of oral anticoagulants, such as warfarin and clopidogrel, is widely accepted in the treatment of the disease [17-19].

We herein present the management of a patient with Sneddon's syndrome.

Case presentation

A 41-year old female presented with complaints of irregular menstruation and intermittent bleeding. She was diagnosed with Sneddon's syndrome priorly, and there had been several miscarriages associated with this disease (Gravidity:10, Abortus:9, Parity:1). While investigating the neurological findings of the patient, livedo reticularis lesions were noticed on the lower extremities, and the diagnosis had been previously made because of skin biopsies obtained from these lesions (Figure 1) and neurological findings. The patient was taking warfarin 5 mg once a day. Physical examination revealed livedo reticularis lesions on the whole trunk, gluteal region, and hands (Figure 2). The second toe on the right foot was amputated from the middle of the proximal phalanx (Figure 3), due to an arterial circulation disorder when the patient stopped taking warfarin for a lengthy period. In pelvic examination, there was passive bleeding, the cervix was of nulliparity type and normal. Transvaginal ultrasound examination revealed that the uterus was larger than normal. There was a subserous myoma of 8 cm in the fundus, extending 3 cm intramurally, which was compressing the cavity, along with numerous myoma. The patient was admitted for a planned laparoscopic hysterectomy. In routine tests, Hemoglobin was 6.7 g/dL, platelet count was $135x10^3/mm^3$ INR was 2.6, and blood pressure was normal. Erythrocyte suspension was transfused preoperatively for anemia. INR was checked daily to assess bleeding risk; warfarin was terminated, and enoxaparin treatment of 2 x 0.6 ml was started.

To reduce the risk of intraoperative bleeding to a minimum, INR was expected to fall to below 1.5. However, after starting the enoxaparin treatment, a progressive decrease was observed in thrombocytes as a side-effect. In addition, during this period when warfarin was terminated, the patient showed psychiatric problems such as insomnia and anxiety. Headaches became more frequent and the skin lesions became more evident. The planned operation was scheduled earlier due to the exacerbation of the syndrome. With Hb 11.8 g/dL and platelet count $46x10^3/mm^3$, three units of thrombocyte suspension were transfused, and the patient was admitted for surgery. Laparoscopic hysterectomy was performed because of the lower morbidity taking into consideration potential problems which could be experienced in the postoperative period (wound site problems, thrombosis caused by late mobilization). No complication developed intraoperatively.

Figure 1: Skin biopsy from livedo reticularis lesion of the patient (HEx100)

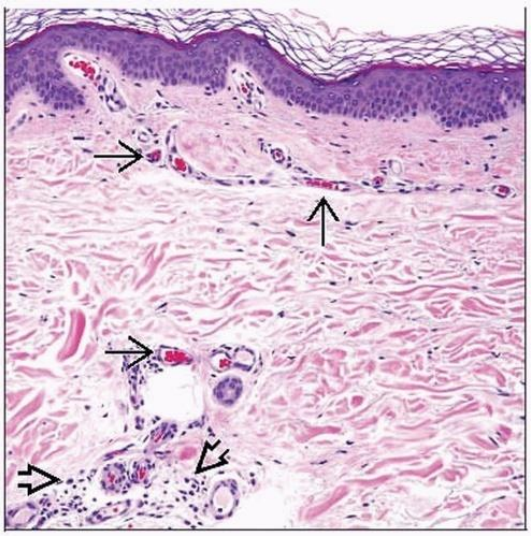


Figure 2: Livedo reticularis lesions on the patient's hand

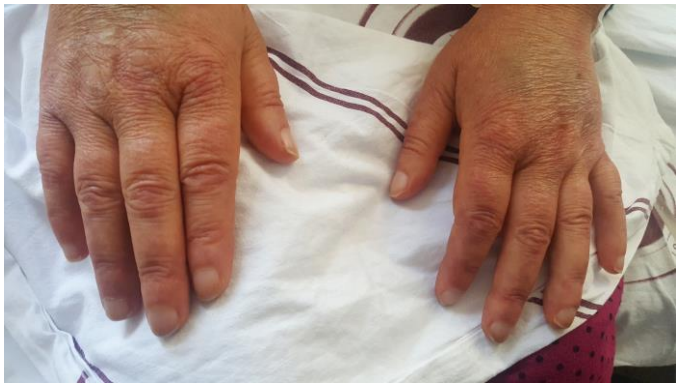
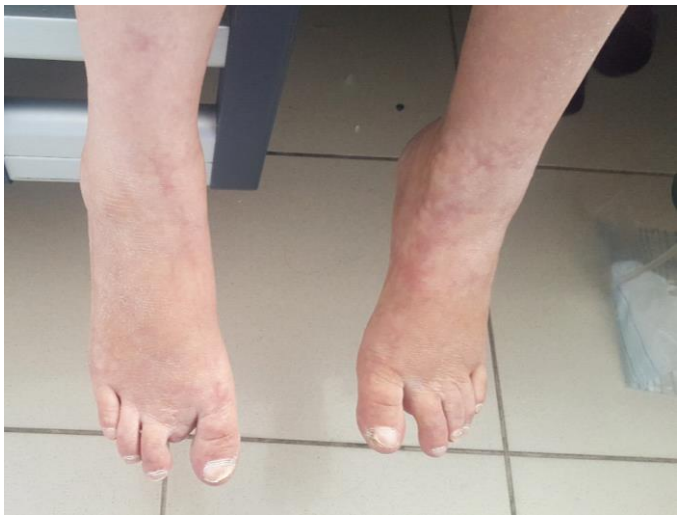


Figure 3: The second toe on the right foot was amputated from the middle of the proximal phalanx.



In the postoperative period, 200 milliliters of hemorrhagic drainage was observed in intra-abdominal drain in the first 24 hours. At 8 hours postoperatively, enoxaparin was

started and continued at 2 x 0.6 ml. Despite thrombocyte transfusion, platelet count was $33x10^3$ /mm^3, which necessitated six more units of thrombocyte suspension transfusion. The follow up PLT count was $27x10^3$/mm^3. Precautions of frequent mobilization and anti-embolism stockings were taken, and as bleeding control had not been achieved, enoxaparin was terminated, and warfarin was re-started. For the purposes of immunosuppression, 100 mg dexamethasone was administered. The vital signs of the patient were closely monitored, which revealed a sudden increase in blood pressure. Systolic blood pressure was 170 mmHg, and nifedipine 60 mg twice a day was started, after which the blood pressure decreased and stabilized. A short time after the addition of nifedipine to the treatment, the color of the livedo reticularis lesions on the hands and feet of the patient was observed to fade. The patient was monitored for 5 days without the administration of enoxaparin and warfarin. Blood tests obtained after terminating enoxaparin revealed a progressive elevation in thrombocytes. During this period of observation without enoxaparin, the patient reported double vision. Neurological examination and cranial magnetic resonance imaging **(**MRI) were performed, which revealed no neurological pathologies. Crying episodes started to accompany the complaints of insomnia and anxiety which had begun preoperatively. Thinking that this could be a psychiatric and cognitive symptom related to the syndrome, the Psychiatry Department was consulted. As the patient stated that she saw insects on the walls, especially at night, delirium was suspected, and 2 x 1 drops of haloperidol was administered daily. In the evaluation made after 2 days of haloperidol use, the complaints of the patient had receded. After ensuring that bleeding control had been obtained, warfarin was re-started. Blood follow-up was continued until the INR returned to the desired level. When thrombocyte value reached 129,000 and the INR value was 1.8, the patient was discharged with recommendations.

Discussion

Sneddon's syndrome is rare with clinical manifestations of various systems and well-defined clinical and laboratory findings. Based on our experience in this patient, the symptomatology is based on neurological, hematological, dermatological, and psychiatric aspects, as defined in literature. Therefore, essential points requiring special attention in the clinical and surgical management of a patient with Sneddon's syndrome were noted.

Anticoagulants are included in the treatment of Sneddon's syndrome [17-19]. In the adjustment of the INR level to reduce the risk of intraoperative bleeding, warfarin used in the treatment of the syndrome must be terminated preoperatively. In the current case, warfarin was terminated by checking INR daily. To reduce the risk of intraoperative bleeding to a minimum, we waited until the INR fell to below 1.5.

Low molecular weight heparin (LMWH) should be initiated to protect the patient against thrombosis when warfarin is stopped [1-3]. In the current patient, 2 x 0.6 ml enoxaparin was started when warfarin was terminated.

After starting enoxaparin, a progressive drop was observed in thrombocyte count as a side-effect. Appropriate blood products were prepared preoperatively as a precaution against the possibility of bleeding. It must not be forgotten that thrombocytopenia could develop in patients as a complication of LMWH, so platelet levels must be closely monitored with blood tests and blood products should be prepared preoperatively.

Before ceasing warfarin treatment, the lesion borders must be marked for more accurate monitoring of the lesions. In the current patient, there was no change in the size of the lesions, but they became more evident than before.

Taking into consideration wound site problems that may develop and the risk of thrombosis when the patient is immobile, the operation process should be accelerated and if possible, laparoscopy should be preferred [1-3]. With the consideration of potential problems that may be experienced postoperatively, a laparoscopic hysterectomy was performed in our patient for lower morbidity.

We placed one intra-abdominal drain during the operation and monitored it for postoperative bleeding. Within the first 24 postoperative hours, 200 milliliters of hemorrhagic content drained. Taking a history of warfarin use and the risk of thrombocytopenia into consideration, the drain should be placed intraoperatively for the purpose of monitoring intra-abdominal bleeding.

Vital signs must be closely monitored for a hypertensive status that can occur with the combination of the nephrological effects of the syndrome and the effects of the anesthetic substances administered intraoperatively [1]. We observed a sudden increase in blood pressure in our patient. As systolic blood pressure was around 170 mmHg, 60 mg of nifedipine was administered twice a day, after which regulation of blood pressure was achieved. A brief time after the addition of nifedipine to the treatment, the livedo reticularis lesions on the hands and feet began to fade.

The psychiatric leg of the syndrome must not be forgotten, and if necessary, psychiatric consultation should be requested [1, 10, 11]. In the current patient, crying attacks started to accompany the complaints of insomnia and anxiety which had begun preoperatively. During the psychiatric interview, the patient stated that she saw insects walking up the wall, especially at night, which led to the diagnosis of delirium and appropriate treatment was administered.

To avoid missing neurological problems, frequent neurological examinations should be performed [12-14]. On the seventh postoperative day, our patient reported double vision. She was evaluated with neurological examination and MRI, which revealed no neurological pathologies.

Conclusion

The results obtained from close clinical monitoring of the current patient in the preoperative and postoperative periods will be of guidance for the management of other patients with Sneddon syndrome. Nevertheless, there is a need for examination of a greater number of patients to confirm the data obtained.

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