e-ISSN:2602-2079

Volume 7
Issue 10
2023

JOURNAL of Surgery and Medicine

International Medical Journal

JOSAM

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Vol. 7 No. 10 (2023):

Published: 2023-10-31

Research Article

Case Report

ERCC8 related Cockayne syndrome type-1: A rare entity diagnosed in a Turkish boy

ERCC8 related Cockayne syndrome type-1

Sinem Kocagil, Ali Rıza Keklikci, Yusuf Aydemir, Oğuz Çilingir, Sabri Aynacı, Ebru Erzurumluoğlu Gökalp, Beyhan Durak Aras, Sevilhan Artan

719-721

J Surg Med. 2023;7(10):641-645.
DOI: 10.28982/josam.7903

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Evaluation of tension-free vaginal tape and transobturator tape surgery performed in one year in terms of mesh erosion

Elif Yıldız [1], Burcu Timur [2]

[1] Department of Obstetrics and Gynecology, University of Health Sciences Istanbul Gaziosmanpasa Training and Research Hospital, İstanbul, Turkey
[2] Department of Obstetrics and Gynecology, Ordu University Training and Research Hospital, Ordu, Turkey

ORCID ID of the author(s)

EY: 0000-0001-8396-5542
BT: 0000-0001-8769-5949

Corresponding Author
Elif Yıldız
University of Health Sciences Istanbul Gaziosmanpasa Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey
E-mail: elifsumer_@hotmail.com

Ethics Committee Approval
The study was approved by the clinical research ethics committee of the University of Health Sciences Istanbul Gaziosmanpasa Training and Research Hospital (Date: October 5, 2022, number: 126).
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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 3

Abstract

Background/Aim: Mesh erosion is one of the feared complications in surgeries performed using mesh, and its frequency is increasing as more and more of these surgeries are performed. This study aims to evaluate transobturator tape (TOT) and tension-free vaginal tape (TVT) surgeries performed in the surgical treatment of stress urinary incontinence (SUI) in our clinic in terms of clinical results and mesh erosion.
Methods: This study is a retrospective cohort study. The files of 50 patients who had SUI and underwent TOT and TVT surgery in our clinic between January 2022 and January 2023 were reviewed. Patients diagnosed with pure SUI and for whom surgery was performed were included in our study. The participants were divided into two groups: those who had TOT surgery and those who had TVT surgery. These groups were evaluated and compared in terms of mesh injury, mesh erosion, pelvic pain, dyspareunia symptoms, and urinary retention. The surgical data of patients, incidence of complications, pre- and postoperative incontinence impact questionnaires (IIQ-7) and the scores of the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) were recorded.
Results: The mean follow-up period of the participants was 8.96 (8.47) (range, 6-17 months). TVT surgery was performed on 13 participants and TOT surgery was performed on 37 patients. When the two groups were compared, there was no statistically significant difference in terms of age, body mass index (BMI), parity, menopausal status, duration of incontinence, preoperative IIQ-7 scores, and ICIQ-SF scores (P<0.05). There were no statistically significant differences between surgical durations, length of hospital stay, early surgical complications, postoperative 3rd month IIQ-7, and ICIQ-SF scores (P<0.05). Furthermore, no difference in the rates of mesh erosion and mesh-related complications between the two groups (P<0.05) was observed.
Conclusion: TOT and TVT surgeries seem to be quite safe in terms of complications, as well as being satisfactory in terms of patient satisfaction. Although mesh-related complications can be frightening, the rate of regression is low with appropriate management. Our results show that both operations are safe with an acceptable complication rate when performed by surgeons who have experience with anti-incontinence procedures.

Keywords: trans-obturatar tape, suburetral slings, stress urinary incontinance, tension-free vaginal tape

How to cite: Yıldız E, Timur B. Evaluation of tension-free vaginal tape and transobturator tape surgery performed in one year in terms of mesh erosion. J Surg Med. 2023;7(10):641-645.

Introduction

Stress urinary incontinence (SUI) defined as urinary incontinence while coughing and sneezing in women [1], is a health problem that affects women's quality of life by creating psychological, social, and sexual problems [2]. Hypermobility of the vesicoureteral segment due to pelvic floor insufficiency and failure to transmit intra-abdominal pressure to the bladder neck due to non-retropubic urethra are blamed as the formation mechanism. Its incidence is 22% during the reproductive ages, but it has been reported that it may increase as high as 73% with advanced age and the hypoestrogenemia caused by menopause [3].

SUI surgery aims to prevent involuntary urinary incontinence by supporting the bladder neck and urethra in the retropubic position [4]. Although there are many surgical treatment alternatives, after the clarification of this etiologic mechanism, mid-urethral sling surgery came to the fore. TVT and TOT surgery are the most frequently performed surgeries in urogynecology and urogynecology clinics in the treatment of SUI [5]. In both these surgeries, an attempt is made to support the urethra using mesh, which brings with it the risk of complications in addition to the risks of the surgery [6]. Although many patients undergoing mesh-enhanced vaginal repair recover uneventfully, based on the limited data currently available, there appears to be a small but significant group of patients who experience persistent and life-changing sequelae, including pain and dyspareunia, from the use of vaginal mesh. In the literature, infection, erosion, pelvic pain, dyspareunia, and organ injuries due to mesh erosion requiring resurgery have been described [7]. Concerns exist about the safety and efficacy of transvaginally inserted mesh [8].

In this study, we aimed to evaluate TOT and TVT surgeries in the treatment of SUI in line with the cases performed in our clinic during the last year, in terms of mesh erosion and other mesh complications, and in light of the literature.

Materials and methods

This is a retrospective cohort study. The files of 50 women who were diagnosed as having SUI or mixed-type urinary incontinence and underwent TOT and TVT surgery in our clinic between January 2022 and January 2023 were reviewed retrospectively. Ethical approval was obtained from the ethics committee of Gaziosmanpaşa Training and Research Hospital before starting the study (Date: October 5, 2022, No: 126).

Participans were those who were diagnosed as having SUI and for whom TOT or TVT surgery was performed. TVT surgery was performed in 13 women and TOT surgery was performed in 37 women. Surgery took place after all of the patients were informed in detail about the surgery they would undergo and provided informed consent.

Patients with neurological disease that would impair bladder function, pregnant women, and patients scheduled for surgery due to gynecologic malignancy, urinary system anomalies, and cystocele or rectocele were excluded from the study. Prior to the surgery, detailed anamnesis was taken from all patients and a voiding diary was maintained. A stress test was performed on all patients with urine constricted in the gynecologic examination position and standing, at rest, and under Valsalva. Q-tip testing was performed in the lithotomy position to assess urethral hypermobility. The preoperative stress test of all patients was positive. Bladder neck mobility was considered positive when the amount of angle change in the straining and resting states of the cotton swab was above 30 degrees. Upper urinary tract and post-micturition residue were evaluated through urinary ultrasonography. All patients underwent a simple neurologic examination.

The Turkish-validated versions of the IIQ-7 [9] and ICIQ-SF [10] tests were used to evaluate the symptoms of the patients and standardize them. Complete urinalysis, urine cultures, and post-void residual urine measurements were performed on the patients before the surgery. Those who were found to have an infection in the urine evaluation were treated with appropriate antibiotic therapy. The demographic characteristics of the patients, surgery information, early evaluations in the postoperative period, and surgical complications were recorded.

All surgeries were preferably performed under spinal anesthesia, and in cases where spinal anesthesia was not appropriate or spinal intervention was not accepted by the patient, general anesthesia was administered. Antibiotic prophylaxis was performed using 1 g of cefazolin before the surgery. The surgery was considered successful in patients with a negative post-operative stress test, a residual of less than 100 cc, and full continence. Surgery was considered unsuccessful in patients whose incontinence continued after the operation.

Surgical technique

TVT surgery: At the dorsal lithotomy position, the anterior vaginal wall was incised 1.5-2 cm below the urethra, approximately 2 cm, and the paraurethral areas were separated using sharp and blunt dissection and advanced to the underside of the symphysis pubis. The mesh (Betamix, Transobturatory set, 10 x 450 mm thickness) attached to the TVT needle from the created area was placed under the urethra somewhat laterally, passing it behind the symphysis pubis bone. The same procedure was performed on the other side. The suburethral distance was adjusted by inserting the scissors vertically between the urethra and the mesh. The bladder was evaluated for possible injuries using cystoscopy without any mesh being detected. After making sure that there was no perforation, excess mesh pieces in the suprapubic region were cut.

The vaginal mucosa was then sutured. The procedure was terminated after a tight tampon was placed.

TOT surgery: In the dorsal lithotomy position, the anterior vaginal wall was incised 1-2 cm below the urethra, approximately 2 cm. Paraurethral areas were separated in a sharp and blunt dissection, and the ischiopubic bone was reached with a finger. The skin was incised 1 cm lateral to the ischiopubic ramus on the line running parallel to the clitoris. Using the outside-in technique as described by Delorme [11] in 2001, bevelled needles were inserted through the skin close to the medial part of the obturator foramen, and the vagina was exited through the suburethral space with the help of a finger by passing the obturator membrane. Prolene mesh (Level SVT Helical Set, 10 x 450 mm thick) was attached to the end of the trocar and

pulled back. The same procedure was performed on the other side and the mesh was laid under the urethra. The suburethral distance was adjusted by inserting the scissors between the urethra and the mesh perpendicularly, and the excess mesh pieces were cut. The procedure was terminated after the vaginal mucosa was sutured and a tight pad was placed inside.

After discharge, the patients were seen for follow-ups on the tenth day, third month, and sixth month postoperatively. The symptoms of the patients were evaluated in terms of stress tests, quality of life scores, possible problems related to mesh, and other complications. In the case of mesh complications, the International Continence Society-International Urogynecological Association (ICS-IUGA) complication classification calculator, which is a classification system based on category, time and location, was used [12]. Surgical complications were classified according to the Clavien-Dindo system[13]. In cases diagnosed as vaginal erosion, prophylaxis with first-generation cephalosporin was administered. In cases with bacterial vaginosis, 2 x 500 mg metronidazole p.o. for 7 days was added. In postmenopausal cases, 25 µg/day of estradiol hemihydrate was given intravaginally as a topical estrogen for six weeks. In cases of erosion in the postoperative period or if mesh excision was required for any reason, the eroded mesh part was excised in vaginal erosions without infectious complications. After debriding and debriding the vaginal mucosa edges, suturing was done again.

Statistical analysis

Normality control of continuous variables was evaluated using the Shapiro-Wilk test. Non-parametric analyses were used for variables that were not parametric or conforming to the normal distribution. The independent sample t-test and Mann-Whitney U test were used for continuous variable comparisons between TVT and TOT groups. The Wilcoxon test was used for preop and post-op comparisons within the groups. To determine whether the changes according to time differed according to the groups, repeated measures of analysis of variance (ANOVA) (time x group interaction) were analyzed. Fisher's exact test was used in the analysis of categorical data. The analysis of the data was performed using the IBM SPSS 21 package program. A *P*-value of ≤0.05 was considered statistically significant.

Results

The mean age of the patients was 59.38 years in the TVT group and 61 years in the TOT group. When both groups were compared, no statistical difference was found between the groups in terms of age (*P*=0.527). Other demographic characteristics are shown in Table 1.

In the preoperative evaluation of the patients, their symptoms and durations were questioned, and their evaluations were made using the q test and cough test. The preoperative evaluation results of the patients are shown in Table 2.

In this study, mesh-related complications were observed in eight women from a group of 50 participants. Three were in the TVT group, and the remaining five were in the TOT group. In one patient, during the cystoscopy performed during the TVT surgery, it was noticed that the bladder mucosa was perforated when the mesh was passed through, and TOT surgery was performed on the patient by removing the mesh. In the postoperative six-month follow-up, only one patient had inguinal pain after TVT surgery; no inguinal pain was observed in the group that underwent TOT surgery. Vaginal mesh erosion-exposure (greater than 2 cm) that required excision was observed in one patient after TVT surgery and one patient after TOT surgery. The mesh of both patients was excised under general anesthesia and the mucosa was repaired. After the TOT surgery, approximately 0.5 cm of mesh erosion was observed in another patient; the mesh was treated with local estrogen therapy for six weeks without excision, and it was completely epithelialized over the mesh. Dyspareunia developed in three patients who underwent TOT surgery, but only one required mesh excision. Although excision was recommended for one patient, it was not performed, because the patient rejected the procedure. Mesh excision was determined for six of eight patients who developed complications, but five of them were treated by excision of the mesh. One patient with erosion did not accept excision and the mucosal repair was renewed with local anesthesia. Considering the regression with treatment in post-op symptoms, only one patient who underwent TOT reported intense pain in the mesh area, and the pain did not regress despite the removal of the mesh. The symptoms of the other seven patients disappeared with appropriate management. The classification of patients with complications according to the ICS-IUAG classification is shown in detail in Table 3. When looking at the Clavien-Dindo stages, only one patient was found to be stage 3, one patient was stage 2, and the remaining six patients were stage 1.

Table 1: Demographic characteristics of the patients

		TVT			TOT			
		Mean (SD)	**Median [IQR]**	**Min-Max**	**Mean (SD)**	**Median [IQR]**	**Min-Max**	***P-value***
Age (years)		59.38 (7.22)	58 [53.5-65]	49-72	61 (8.07)	61 [55-66.5]	46-78	0.527[a]
BMI (kg/m^2)		30.24 (6.22)	27.4 [25.8-34.76]	21.9-44.1	27.83 (5.82)	27.56 [23.34-30.93]	17.72-42.31	0.214[a]
Parity (n)		2.38 (0.96)	2 [2-3]	1-4	2.46 (1.02)	2 [2-3]	1-5	0.799 [b]
Vaginal birth (n)		1.62 (1.33)	2 [0-2.5]	0-4	1.89 (1.26)	2 [1-3]	0-5	0.539 [b]
		n	**%**		**n**	**%**		***P-value***
Mena-pause	No	11	84.6		33	89.2		0.643
	Yes	2	15.4		4	10.8		
Hrt usage	No	12	92.3		34	91.9		1.000
	Yes	1	7.7		3	8.1		
Smoke	No	11	84.6		33	89.2		0.643
	Yes	2	15.4		4	10.8		
Vaginal birth	No	4	30.8		6	16.2		0.420
	Yes	9	69.2		31	83.8		
Cesarean	No	10	76.9		30	81.1		0.707
	Yes	3	23.1		7	18.9		
Previous surgery	No	10	76.9		32	86.5		0.413
	Yes	3	23.1		5	13.5		

[a]: Independent Sample t-test, [b]: Mann-Whitney U test, P2: Fisher's Exact test

Table 2: Preoperative evaluations of the patients

		TVT			TOT			
		Mean (SD)	**Median [IQR]**	**Min-Max**	**Mean (SD)**	**Median [IQR]**	**Min-Max**	***P1*-value**
Duration of incontinence (years)		3.92 (1.75)	4 [2.5-5]	1-7	2.19 (1.47)	2 [1-3]	1-6	0.22
		n	**%**		**n**	**%**		***P2*-value**
Q test	No	4	30.8		12	32.4		1.000
	Yes	9	69.2		25	67.6		
Cough test	No	1	7.7		2	5.4		1.000
	Yes	12	92.3		35	94.6		
Nocturia	No	11	84.6		31	83.8		1.000
	Yes	2	15.4		6	16.2		
Pelvic organ prolapse	No	11	84.6		32	86.5		1.000
	Yes	2	15.4		5	13.5		

P1: Mann-Whitney U test, *P2*: Fisher's Exact test

Table 3: Early and late complication information of the patients

		TVT			TOT			
		Mean (SD)	**Median [IQR]**	**Min-Max**	**Mean (SD)**	**Median [IQR]**	**Min-Max**	***P1*-value**
Urinary catheter stay (hours)		26.46 (4.77)	24 [24-28]	24-36	26.38 (6.14)	24 [24-24]	24-48	0.632
Hospital stay (hours)		1.23 (0.44)	1 [1-1.5]	1-2	1.11 (0.31)	1 [1-1]	1-2	0.278
		n	**%**		**n**	**%**		***P2*-value**
Intraoperative bladder injury	No	12	92.3		37	100.0		0.260
	Yes	1	7.7		0	0.0		
Hematoma	No	13	100.0		37	100.0		-
Pelvic pain	No	12	92.3		37	100.0		0.260
	Yes	1	7.7		0	0.0		
Mesh erosion	No	12	92.3		35	94.6		1.000
	Yes	1	7.7		2	5,4		
Pain in the mesh area	No	13	100.0		35	94.6		1.000
	Yes	0	0.0		2	5.4		
Dyspareunia	No	13	100.0		34	91.9		0.558
	Yes	0	0.0		3	8.1		
Mesh removal patient	No	11	84.6		33	89.2		0.643
	Yes	2	15.4		4	10.8		
Denova urge incotinance	No	11	84.6		35	94.6		0.275
	Yes	2	15.4		2	5.4		
Improvement in postoperative symptoms after treatment	No	3	%35		5	%65		0.357
	Yes	3	%100		4	%80		

P1: Mann Whitney U test, *P2*: Fisher Exact test

Table 4: Preoperative and postoperative survey results of the patients

	TVT			TOT				
	Mean (SD)	**Median [IQR]**	**Min-Max**	**Mean (SD)**	**Median [IQR]**	**Min-Max**	***P*$_{group}$-value**	***P*$_{all}$-value**
ICIQ-SF Score Preop	12.92 (1.44)	13 [11.5-14]	11-15	12.9 (1.31)	13 [12-14]	11-15	0.964	0.941
ICIQ-SF Postop	1.85 (1.41)	2 [1-3]	0-5	1.92 (1.62)	2 [1-3]	0-5	0.982	
***P*$_{time}$-value**	0.001			<0.001				
IIQ-7 Preop	15.54 (1.27)	15 [14.5-16.5]	14-18	15.46 (1.14)	15 [14.5-16]	14-18	0.891	0.612
IIQ-7 Postop	0.77 (0.93)	1 [0-1]	0-3	0.95 (0.97)	1 [0-1]	0-3	0.553	
***P*$_{time}$-value**	0.001			<0.001				

P_{group}: Mann Whitney U test, P_{time}: Wilcoxon test, P_{all}: Repeated Measures ANOVA (timexgroup interaction)

Pre/postoperative IIQ-7 and ICIQ-SF questionnaires results are given in Table 4. In both tests, statistically significant improvement was found in postoperative data compared to preoperative scores. These results showed that there was a positive change in the quality of life of the patients with both surgeries, independent of complications. The variation of ICIQ-SF scores and IIQ-7 scores over time did not differ between the groups (P>0.05).

Discussion

SUI surgery is a frequently performed treatment in urogynecology clinics because of the increasing quality of life expectation of women, the awareness that this is not a destiny based on the effects of training and social media, and the effective treatment options with high success rates. In addition to potential general surgical problems, each surgery carries its own risks of complications. Besides general surgical complications in TOT and TVT surgeries, there are some concerns about the use of mesh. In July 2011, the United States Food and Drug Administration (FDA) issued a safety statement titled "Update on Serious Complications Associated with Transvaginal Surgical Mesh Placement for Pelvic Organ Prolapse." As a warning, the purpose of this paper was to invite healthcare providers and patients to be more selective because important complications with the placement of this mesh were not uncommon, and it was not clear if these repairs were more effective than meshless repairs. Many countries, considering this warning, concluded that it was necessary to reconsider the use of mesh and decided not to use it as much due to serious complications [14]. When we look at the literature, there are many case reports about mesh-related complications and articles on their management. Contrary to Richter et al. [15], who argued that post-operative groin and leg pain, which can be permanent, was more common in TOT surgery than in TVT, in our study, there was one patient with groin and leg pain in the TVT group, but no leg pain was observed in the TOT group. This result needs to be confirmed by studies with a larger number of participants. In all surgeries using mesh, the most feared complication is mesh-related erosion. These can be small or present as the opening of a fairly large area. The general tendency is to provide an environment for the repair of the mucosal area on the mesh with sexual abstinence and local estrogen treatment of small erosion areas [16,17]. In larger erosion areas where the mesh is infected, and in small erosion areas that do not regress despite local treatment, the mesh should be removed locally or totally [18]. In our study, mesh erosion developed in a total of four women, one from the TVT group and three from the TOT group; because one of them was very small, it was followed up with local estrogen therapy

and sexual abstinence, and spontaneous closure was ensured requiring no excision. In one case, due to the accompanying severe inguinal pain, excision was performed even though the mesh erosion area was small. In all four patients, the symptoms completely regressed after excision and treatment were provided.

In a case presented by O'kane et al. [19], intravesical mesh erosion occurred in a patient after TVT was detected during routine follow-up in which the patient had no symptoms. Although excision was suggested, it was rejected by the patient, and prophylactic weekly 1 g antibiotic prophylaxis was started to prevent stone formation and possible infective processes in the bladder; routine follow-up was performed using cystoscopy. The authors did not indicate a negative process related to the patient in their article in which they reported a follow-up of about three years. This case highlights the importance of subsequent follow-up in preventing complications. Patients should be informed in detail about the potential complications of this surgery, which include a foreign material being inserted into the body, and they should be motivated to adhere to their routine follow-ups.

In our study, eight (16%) patients who developed complications were treated with an appropriate approach and full recovery was achieved in seven (88.8%) patients. In one patient (2%), persistent inguinal pain developed despite the excision of the mesh. In the literature, the incidence of erosion due to mesh has been reported as a rare complication ranging from 0.2% to 22% [20,21]. Considering our results, the complication rate is at an acceptable level and is compatible with the literature.

Limitations

There are some limitations to our study. The menopausal status of the patients, whether they used HRT, the duration of treatment, the presence of vaginal mucosal atrophy, and wound healing can be affected in the presence of additional diseases such as diabetes. It is known that this reduces surgical success, and we could not exclude these factors. Because our study was retrospective, we could only reach a limited patient group, and some records were incomplete or insufficient. There is a need for studies with more stringent exclusion criteria related to additional diseases and conditions, and thıs may be the focus of other studıes. Another important limitation is that causality cannot be determined because cross-sectional data are analyzed. Health status and reproductive variables were self-reported. This national study evaluates only non-institutionalized adults and this may limit the generalizability of these results to other groups.

Conclusion

When the results of our study are evaluated together with the literature, neither TOT nor TVT surgery seems to have an advantage over the other in terms of mesh-related complications. TOT and TVT surgeries seem to be quite safe in terms of complications, as well as acceptable in terms of patient satisfaction. Although mesh-related complications can be frightening, the rate of regression is high with appropriate management.This means that in SUI treatment the surgeon can choose either of the two methods, based on his/her experience and the patient’s compatibility.

Acknowledgements

We would like to thank Asena Ayça Özdemir for the statistical analysis of the study. Also, many thanks to Mr. David F. Chapman for editing the English of the article.

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J Surg Med. 2023;7(10):646-650.
DOI: 10.28982/josam.7972

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Predictors of mortality in elderly patients in emergency abdominal surgery: A retrospective single-center study

Mustafa Altınay, Sibel Oba

Department of Anesthesiology, Sisli Hamidiye Etfal Training and Research Hospital, University of Health Sciences, Istanbul, Turkey

ORCID ID of the author(s)

MA: 0000-0002-2036-048X
SO: 0000-0002-5466-1715

Corresponding Author
Mustafa Altınay
Sisli Hamidiye Etfal Training and Resource Hospital, University of Health Sciences
34371 Sisli, Istanbul, Turkey
E-mail: m_altinay@yahoo.com

Ethics Committee Approval
The study was approved by Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee (date: August 1, 2023, approval number: 4,025). 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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 4

Abstract

Background/Aim: Advancements in medical technologies and prolonged life expectancy have increased the number of surgical interventions for elderly patients. Despite this however, emergency surgical interventions remain associated with a high mortality rate. Managing an emergency abdominal surgery in elderly patients poses great challenges for both the surgeon and the anesthesiologist. However, knowing the risk factors that increase mortality may offer advantages to the clinician managing the treatment process. There are studies in the literature examining the mortality of emergency surgeries in elderly patients. However, there are very few studies that work with a specific patient group such as abdominal surgery and then analyze laboratory test results. Here, we aimed to identify the risk factors that can be used to predict mortality in elderly patients undergoing emergency abdominal surgery.

Methods: The study was designed retrospectively in a single center; 100 patients over the age of 80 who underwent emergency abdominal surgery were included in the study. The patients were divided into two groups as survivor and non-survivor. Demographic, surgical, and anesthetic characteristics, laboratory tests, American Society of Anesthesiologists (ASA) physical status scores, postoperative intensive care needs, and treatments of the groups were compared using the chi-squared and Mann Whitney U-test. Determining factors were investigated with logistic regression analysis.

Results: In multivariate analysis, ASA 3 and major surgery significantly increased mortality (P=0.041, P=0.011). Receiver operating characteristic (ROC) curve analysis showed that C-reactive protein with a cut-off value of >84 mg/L had a sensitivity of 58.8% and a specificity of 71.2% (AUC=0.636, P=0.004), while lactate with a cut-off value of >3.6 mmol/L had a sensitivity of 50% and a specificity of 95.5% in predicting mortality (AUC=0.776, P<0.001).

Conclusion: The magnitude of surgery and the ASA score were the best predictors of mortality in elderly patients undergoing emergency abdominal surgery.

Keywords: emergency abdominal surgery, mortality, lactate, c-reactive protein, elderly

How to cite: Altınay M, Oba S. Predictors of mortality in elderly patients in emergency abdominal surgery: A retrospective single-center study. J Surg Med. 2023;7(10):646-650.

Introduction

The rise in life expectancy and advancements in medical technology in recent years has significantly increased the number of surgical procedures performed on elderly patients. In the United States, individuals over the age of 65 account for 15% of its population, which is expected to rise to 25% by 2060 [1]. Over 40% of all surgeries performed in the United States were on patients over the age of 65 [2].

Multicenter studies reported that patients who underwent emergency general surgery have a significantly higher risk of mortality and complications than patients undergoing elective general surgery [3]. Factoring in age, the risk of mortality and morbidity increases even more due to the frailty of elderly patients. Frailty is a modern concept in geriatric medicine and is defined by Campell et al. [4] as a medical syndrome characterized by decreased strength and endurance and reduced functional reserve of multiple organ systems, which increases an individual's susceptibility to injury and death.

Emergency surgical procedures for the frail elderly over 80 years of age poses enormous challenges for both the surgeon and the anesthesiologist, and thus a multidisciplinary approach is necessary for quickly planning perioperative procedures and postoperative treatment and care services. Risk factors as well as the surgical and anesthetic procedures must be assessed during planning. While several studies have evaluated the risk factors for emergency surgical procedures in geriatric patients [5,6], specific studies analyzing both emergency abdominal surgery and laboratory test results are limited [7,8].

Here, we evaluated the effects of demography, comorbidity, laboratory tests, surgical, and anesthesia procedures, and postoperative intensive care unit (ICU) treatments on the mortality of elderly patients (aged over 80 years) who underwent emergency abdominal surgery.

Materials and methods

This retrospective observational study was approved by Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee (date: August 1, 2023, approval number: 4,025). All procedures were performed in accordance with the ethical standards of the Helsinki Declaration (2008) and the STROBE guidelines for reported retrospective cohort studies [9].

Emergency department records between 2015 and 2023 were screened from the hospital information recording system. Patients aged over 80 years who presented to the emergency department and underwent emergency abdominal surgery were included. Patients treated 24 hours after admission, those with missing data, those who do not have a life expectancy of more than 24 hours, and trauma patients were excluded.

Data on age, gender, comorbidity, and American Society of Anesthesiologists (ASA) physical status classification system scores were recorded. Comorbidities included hypertension, diabetes mellitus (DM), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), heart failure, Alzheimer's disease, dementia, malignancy, hepatic cirrhosis, chronic renal failure (CRF), and cerebrovascular stroke (CVS). The laboratory test results of the first blood samples taken after the emergency room admission were screened for hemoglobin (Hgb), white blood cells (WBC), C-reactive protein (CRP), glucose, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), Ph, partial carbon dioxide pressure (pCO_2), bicarbonate (HCO_3) and lactate levels.

The following characteristics related to the surgery were collected: the surgical diagnosis, time from admission to surgery, magnitude of surgery, and anesthesia method used (general anesthesia or neuraxial anesthesia). Procedures performed in the first 12 hours were defined as early surgery, and those performed between 12 and 24 hours were defined as late surgery. The magnitude of surgery classification was performed based on the magnitude of surgery samples included in the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) scoring system [10]. According to this scoring, surgical procedures were categorized as minor, intermediate, major, and major+ (Table 1).

Table 1: The magnitude of general surgery

Minor	Intermediate	Major	Major+
hernia	open cholecystectomy	laparotomy and small-bowel resection	abdominoperineal excision of rectum
varicose vein	laparoscopic cholecystectomy	colonic resection or anterior resection	aortic surgery
minor perianal surgery	appendectomy	major amputation	Whipple resection
scrotal surgery	excision of lesion requiring grafting or minor excision	nonaortic vascular surgery	radical total gastrectomy
minor transurethral resection of tumor	minor amputation	cholecystectomy and exploration of bile duct	
excision of large subcutaneous lesion	thyroid lobectomy	total thyroidectomy	

Patients' postoperative intensive care needs, need for mechanical ventilation (MV), hemodiafiltration (HDF), vasopressor support (VPS), and 90-day mortality were recorded. Patients were categorized by mortality into non-survivor and survivor groups, and all recorded data were compared. Univariate and multivariate regression analyses were performed on the significant data.

The primary outcome of the study was to analyze the effects of demographics, comorbidities, laboratory tests, surgical, and anesthesia procedures, and postoperative ICU treatments on mortality in patients over 80 years of age undergoing emergency abdominal surgery. The secondary outcome of the study was to describe the characteristics of the patients and the surgical and anesthesia procedures.

Statistical analysis

SPSS 15.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for statistical analysis. Descriptive statistics were given in terms of number and percentage for the categorical variables and in terms of median and interquartile range for the numeric variables. The rates in groups were compared via the chi-squared test. Comparisons of two independent groups were made with the Mann-Whitney U-test because the numerical variables did not follow the normal distribution condition. The prognosis power of the inflammatory parameters to predict mortality was assessed based on the analysis of the receiver operating characteristic (ROC) curve. Determining factors were investigated with logistic regression analysis. The alpha significance level was defined at *P*-value <0.05.

Results

Baseline characteristics

Between 2015 and 2023, 173 patients over the age of 80 underwent emergency abdominal surgery. Of these, 100 patients (68% female) were included in the study because they met the study criteria. The mortality rate in the study population was 34%. Details are presented in Table 2. The non-survivor and survivor groups comprised 34 and 66 patients, respectively. ASA 4 was found to be statistically significantly higher in the non-survivor group (P<0.001). LDH, CRP, and lactate were significantly higher, and Ph was significantly lower in the non-survivor group (P=0.05, P=0.026, P<0.001, P=0.010) (Table 3). In the cut-off value examinations with ROC curve analysis for CRP and lactate levels in predicting mortality, a cut-off value of >84 mg/L with 58.8% sensitivity and 71.2% specificity was found for CRP (AUC=0.636, P=0.004) and >3.6 mmol/L with 50% sensitivity and 95.5% specificity for lactate (AUC=0.776, P<0.001) (Figure 1, Table 4).

Table 2: Demographic and clinical characteristics of the patient cohort

		Total (n=100)	Survivor (66%)	Non-survivor (34%)	*P*-value
Age (Median (IQR)		84 (82-88)	84 (82-87.25)	85 (81.75-88)	0.773*
Sex n (%)	Male	32 (32.0%)	22 (33.3%)	10 (29.4%)	0.690#
	Female	68 (68.0%)	44 (66.7%)	24 (70.6%)	
ASA n (%)					
1		1 (1.0%)	1 (1.5%)	0 (0.0%)	<0.001#
2		38 (38.0%)	32 (48.5%)	6 (17.6%)	
3		38 (38.0%)	26 (39.4%)	12 (35.3%)	
4		23 (23.0%)	7 (10.6%)	16 (47.1%)	
Hypertension		83 (83.0%)	53 (80.3%)	30 (88.2%)	0.317#
Diabetes mellitus		35 (35.0%)	24 (36.4%)	11 (32.4%)	0.690#
CAD		10 (10.0%)	6 (9.1%)	4 (11.8%)	0.731#
COPD		12 (12.0%)	8 (12.1%)	4 (11.8%)	1.000#
Cardiac failure		12 (12.0%)	8 (12.1%)	4 (11.8%)	1.000#
Alzheimer's		12 (12.0%)	11 (16.7%)	1 (2.9%)	0.054#
Dementia		2 (2.0%)	2 (3.0%)	0 (0.0%)	0.547#
Malignancy		14 (14.0%)	9 (13.6%)	5 (14.7%)	1.000#
Cirrhosis		3 (3.0%)	3 (4.5%)	0 (0.0%)	0.549#
CRF		4 (4.0%)	2 (3.0%)	2 (5.9%)	0.603#
CVS		15 (15.0%)	8 (12.1%)	7 (20.6%)	0.261#
Others		26 (26.0%)	15 (22.7%)	11 (32.4%)	0.299

#Chi Square Test, *Mann Whitney U Test

Table 3: Laboratory tests of the patient cohort

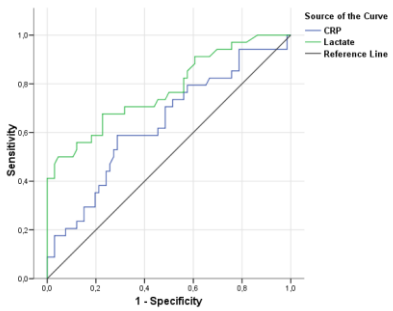
	Total (n=100)	Survivor (66%)	Non-survivor (34%)	*P*-value
CRP	53.47 (14-155.545)	29.8 (12.125-124)	106.37 (22.275-199)	0.026*
Hgb	12.35 (10.5-13.85)	12.1 (10.5-13.8)	13.1 (10.35-14.95)	0.189*
WBC	10.93 (8.33-16.68)	10.555 (8.58-16.6)	11.75 (7.33-17.18)	0.977*
Glucose	140 (115-176.5)	137.5 (112.5-172)	142.5 (118.75-186)	0.541*
Urea	57.5 (38.5-78)	49 (36.5-77)	72 (40.5-92)	0.062*
Creatinine	1.05 (0.76-1.485)	0.975 (0.74-1.26)	1.175 (0.78-1.85)	0.130*
Ph	7.4 (7.35-7.46)	7.42 (7.37-7.46)	7.35 (7.23-7.45)	0.010*
PCO_2	40 (32.15-42.975)	40 (32.25-42.35)	39.45 (31.43-45.65)	0.968*
HCO_3	23.35 (20.55-26.7)	23.85 (21.4-26.7)	21.15 (16.925-26.675)	0.032*
ALT	13 (10-21)	13 (9-21.25)	14 (10.75-21)	0.821*
AST	22 (16.25-33.9)	21 (16-30.5)	25 (19-40)	0.112*
LDH	234 (196.75-321.75)	218 (179-288.75)	266.5 (223.75-363.25)	0.005*
Lactate	1.98 (1.325-3.4)	1.795 (1.18-2.57)	3.53 (1.76-5.5)	<0.001*

#Chi Square Test, *Mann Whitney U Test

Table 4: Areas under the ROC curve (AUC) obtained for cut-off value analysis in detecting the mortality.

Area Under the Curve			
Test result variable(s)	Area	Asymptotic 95% Confidence Interval	
CRP	0.636	0.520	0.753
Lactate	0.776	0.675	0.877

Figure 1: CRP and lactate in ROC curve



Surgical characteristics

When the surgical characteristics were examined in all patients, ileus (29%), hernia (37%), and acute abdomen (18%) were the most common surgical diagnoses. Here, 34 (34%) were considered intermediate, 61 (61%) major, and 5 (5%) major+ according to surgery magnitude. General anesthesia was performed on 76 (76%) patients and spinal anesthesia on 24 (24%). When we look at the magnitude of surgery, major surgery was found to be statistically significantly higher in the non-survivor group (P<0.001). All details of the surgical characteristics are given in Table 5.

Postoperative characteristics

Seventy-six (76%) of the patients were transferred to the ICU in the postoperative period. The need for ICU, MV, HDF, and VP support was statistically higher in the non-survivor group (P<0.001, P<0.001, P=0.006, P<0.001) (Table 5).

In univariate analysis, ASA 4, CRP, lactate, LDH, Ph, major and major+, IMV, HDF, and VPS significantly increased mortality (P=0.006, P=0.021, P<0.001, P=0.017, P=0.004, P=0.001, P=0.004, P<0.001, P=0.017, P<0.001) (Table 6). In multivariate analysis, only ASA 4 and major surgery were significant in predicting mortality (P=0.041, P=0.011) (Table 7).

Table 5: Surgery and postoperative characteristics of the patient cohort

	Total (n=100)	Survivor (66%)	Non-survivor (34%)	*P*-value
Time from admission to surgery (Hour) Median (IQR)	6 (4-10)	5 (4-8)	7 (4-11)	0.133*
Surgery Timing n (%)				
Early (0-12)	83 (83.0%)	55 (83.3%)	28 (82.4%)	0.902#
Late (13-24)	17 (17.0%)	11 (16.7%)	6 (17.6%)	
Magnitude of Surgery n (%)				
intermediate	34 (34.0%)	33 (50.0%)	1 (2.9%)	<0.001#
Major	61 (61.0%)	31 (47.0%)	30 (88.2%)	
major+	5 (5.0%)	2 (3.0%)	3 (8.8%)	
Anesthesia n (%)				
General Anesthesia	96 (96.0%)	63 (95.5%)	33 (97.1%)	1.000#
Neuraxial Anesthesia	4 (4.0%)	3 (4.5%)	1 (2.9%)	
Postoperative ICU Need n (%)	76 (76.0%)	42 (63.6%)	34 (100%)	<0.001#
IMV n (%)	37 (37.0%)	9 (13.6%)	28 (82.4%)	<0.001#
HDF n (%)	7 (7.0%)	1 (1.5%)	6 (17.6%)	0.006#
VPS n (%)	34 (34.0%)	7 (10.6%)	27 (79.4%)	<0.001#

#Chi Square Test, *Mann Whitney U Test

Table 6: Mortality risk factors - univariate logistic regression analysis

	P-value	OR	%95 CI	
ASA (Ref:1-2)	0.002			
3	0.099	2.538	0.839	7.676
4	0.009	12.571	3.626	4.58
CRP	0.021	1.004	1.001	1.007
CRP (Ref: <84) >84	0.004	3.534	1.486	8.403
PH	0.004	0.003	0.000	0.163
LDH	0.017	1.006	1.001	1.011
Lactate	<0.001	2.091	1.438	3.039
Lactate (Ref: <3.6). >3.6	<0.001	21.00	5.503	80.13
Magnitude of Surgery, Ref:intermediatae	0.003			
major	0.001	31.935	4.104	248.516
major+	0.004	49.500	3.409	718.826
IMV	<0.001	29.556	9.570	91.282
HDF	0.017	13.929	1.602	121.123
VPS	<0.001	32.510	10.373	101.890

Ref: reference

Table 7: Mortality risk factors - multivariate logistic regression analysis

	P-value	OR	95% CI	
ASA Ref:1-2	0.052			
3	0.624	1.88	0.15	23.54
4	0.041	18.67	1.12	310.51
CRP	0.421	1.00	1.00	1.01
LDH	0.965	1.00	0.99	1.01
Lactate	0.102	1.88	0.88	4.00
Magnitude of Surgery, Ref: intermediate	0.038			
major	0.011	44.92	2.36	855.14
major+	0.070	77.24	0.70	8545.11
IMV	0.111	7.74	0.62	96.07
HDF	0.175	12.05	0.33	438.73
VPS	0.127	5.65	0.61	52.27

Hosmer and Lemeshow Test Chi-square: 6.991 P=0.538 Cox & Snell R Square 0.587, Ref: Reference

Discussion

We investigated the effects of demographics, comorbidities, laboratory, diagnostic, surgical, and postoperative treatments on mortality in patients over 80 years of age who underwent emergency abdominal surgery. The mortality rate of the study group seems to be high. However, some studies have reported mortality rates up to 50% [10,11]. Based on our results, ASA 4 and major surgery may be predictors of mortality.

Comorbidities that increase with age are an issue that should be meticulously investigated before all surgeries. In the present study, hypertension was as high as 83%, which may be associated with geography and dietary habits. However, none of the comorbidities we analyzed posed a risk for mortality on their own. Although comorbidity by itself is not significant as a risk factor, the number of these comorbidities, whether they are under control or not, affect the perioperative process along with many other similar risk factors. The scoring systems used to determine these risks in the perioperative period include the American Society of Anesthesiologists (ASA) Physical Status Classification, Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM), and Estimation of Physiologic Ability and Surgical Stress (E-PASS) [12-14]. However, these scoring systems are not specifically structured for elderly patients and are used for all ages and patient groups. In our study, we used the ASA Physical Status Classification System and Operative Severity Score—one of the sub-parameters of POSSUM scoring. We found that ASA 4 and major surgery increased mortality. Merani et al. [15] investigated a similar patient group and reported that ASA 3 and 4 increased mortality rates, which is consistent with our findings. Although there are studies on POSSUM in the literature, we did not find any studies focusing on the magnitude of surgery.

The increase in surgical interventions in elderly patients has resulted in an increase in clinical studies and published articles in this field. Although surgical characteristics, comorbidities, and postoperative complications are common in the literature, very few studies focused on the baseline laboratory results of patients, and only the baseline Hgb and WBC were included [8,16]. Bolger et al. [16] reported that anemia and WBC >10,000 values did not affect mortality, while Duron et al. [8] reported that anemia and WBC >10,000 could pose a risk for mortality. Here, we analyzed the hemogram, biochemistry, and blood gas of the patients and found that mortality rate was not affected by Hgb and WBC values but was impacted by increased lactate, CRP, and LDH levels as well as decreased Ph values. Lactate is the product of pyruvate metabolism in an anaerobic environment [17]. In patients with circulatory disorders, blood lactate levels are therefore increased. Infection due to perforation, sepsis, or primary cardiac pathologies may explain this situation in our patient cohort. The association of high lactate levels with mortality is not a new result. However, in a patient presenting with high lactate levels, the time to surgery may be informative in terms of intervening variables such as surgical methods and postoperative treatments.

C-reactive protein is a plasma protein increased in inflammation [18]. It is not surprising that all surgical indications in this study were elevated due to peritoneal inflammation. However, the fact that the sensitivity of CRP in predicting mortality in patients should be considered. We did not find any studies examining the predictive value of lactate and CRP for mortality in similar patient groups in our literature search.

The literature shows that the need for postoperative ICU in elderly patients undergoing abdominal surgery varies over a wide range. [8,19]. These disparate ratios may be associated with the experience of clinicians and the standard of care in hospital ward rooms. In some hospitals, inadequate and poor ward conditions require postoperative ICU follow-up. However, these frail patients do need postoperative ICU care after all emergency surgeries regardless of the conditions of the ward rooms. In our study, we found that treatments administered in the ICU had a significant association with mortality in univariate analysis, although it was not significant in multivariate analysis. While treatments such as failed surgery, sepsis, or multiple organ failure are all common to increased mortality, it is difficult for clinicians to select the appropriate treatment modalities and explain them to patients and their relatives—especially for patients with very low life expectancy. An urgent need for surgery can lead to a high survival expectancy for the patient and their relatives after surgery regardless of the patient's age and comorbidities. However, for patients who have no chance of survival despite surgery, quality of life should be prioritized in the selection of treatments, and relatives should be included in this process.

Limitations

Our study does have some limitations. First, changes in the hospital information management systems over time allowed us to only review the last eight years in retrospect. In addition, certain parameters could not be analyzed due to the small sample size. Furthermore, medical developments in recent years were not evenly distributed across all patients, and this could have disrupted the homogeneity of the study group. However, it is controversial to say that this is a research advantage. Second, sample surgery tables were used instead of blood loss, contamination, and presence of malignancy when calculating the magnitude of surgery in the POSSUM system due to a lack of data. The most important reason for such limitations is that they are based on retrospective data. Future prospective observational studies will make greater contributions to the literature.

Conclusion

Despite advancements in medical technology, the mortality rate for elderly patients who undergo emergency abdominal surgery remains very high. The risk factors that increase mortality should be identified when making surgical and medical treatment decisions. The magnitude of surgery and ASA score are the best predictors of mortality for this patient group.

In addition, the sensitivity of high lactate levels in predicting mortality should be considered. Prospective studies focusing on laboratory results will make significant contributions to the literature in this field.

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J Surg Med. 2023;7(10):651-655.
DOI: 10.28982/josam.7977

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Performance of artificial intelligence chatbot as a source of patient information on anti-rheumatic drug use in pregnancy

Nurdan Oruçoğlu, Elif Altunel Kılınç

Department of Rheumatology, Mersin University Faculty of Medicine, Mersin, Turkey

ORCID ID of the author(s)

NO: 0000-0002-8613-5373
EAK: 0000-0003-2501-2473

Corresponding Author
Nurdan Orucoglu
Department of Internal Medicine, Division of Rheumatology, Mersin University Faculty of Medicine, Mersin, TR-33343, Turkey
E-mail: nurdanorucoglu@yahoo.com

Ethics Committee Approval
This study did not require ethics committee approval because neither human nor animal data were used.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 4

Abstract

Background/Aim: Women with rheumatic and musculoskeletal disorders often discontinue using their medications prior to conception or during the few early weeks of pregnancy because drug use during pregnancy frequently results in anxiety. Pregnant women have reported seeking out health-related information from a variety of sources, particularly the Internet, in an attempt to ease their concerns about the use of such medications during pregnancy. The objective of this study was to evaluate the accuracy and completeness of health-related information concerning the use of anti-rheumatic medications during pregnancy as provided by Open Artificial Intelligence (AI's) Chat Generative Pre-trained Transformer (ChatGPT) versions 3.5 and 4, which are widely known AI tools.

Methods: In this prospective cross-sectional study, the performances of OpenAI's ChatGPT versions 3.5 and 4 were assessed regarding health information concerning anti-rheumatic drugs during pregnancy using the 2016 European Union of Associations for Rheumatology (EULAR) guidelines as a reference. Fourteen queries from the guidelines were entered into both AI models. Responses were evaluated independently and rated by two evaluators using a predefined 6-point Likert-like scale (1 – completely incorrect to 6 – completely correct) and for completeness using a 3-point Likert-like scale (1 – incomplete to 3 – complete). Inter-rater reliability was evaluated using Cohen's kappa statistic, and the differences in scores across ChatGPT versions were compared using the Mann–Whitney U test.

Results: No statistically significant difference between the mean accuracy scores of GPT versions 3.5 and 4 (5 [1.17] versus 5.07 [1.26]; *P*=0.769), indicating the resulting scores were between nearly all accurate and correct for both models. Additionally, no statistically significant difference in the mean completeness scores of GPT 3.5 and GPT 4 (2.5 [0.51] vs 2.64 [0.49], *P*=0.541**)** was found**,** indicating scores between adequate and comprehensive for both models. Both models had similar total mean accuracy and completeness scores (3.75 [1.55] versus 3.86 [1.57]; *P*=0.717). In the GPT 3.5 model, hydroxychloroquine and Leflunomide received the highest full scores for both accuracy and completeness, while methotrexate, Sulfasalazine, Cyclophosphamide, Mycophenolate mofetil, and Tofacitinib received the highest total scores in the GPT 4 model. Nevertheless, for both models, one of the 14 drugs was scored as more incorrect than correct.

Conclusions: When considering the safety and compatibility of anti-rheumatic medications during pregnancy, both ChatGPT versions 3.5 and 4 demonstrated satisfactory accuracy and completeness. On the other hand, the research revealed that the responses generated by ChatGPT also contained inaccurate information. Despite its good performance, ChatGPT should not be used as a standalone tool to make decisions about taking medications during pregnancy due to this AI tool's limitations.

Keywords: anti-rheumatic drugs, artificial intelligence, ChatGPT, pregnancy

How to cite: Oruçoğlu N, Altunel Kılınç E. Performance of artificial intelligence chatbot as a source of patient information on anti-rheumatic drug use in pregnancy. J Surg Med. 2023;7(10):651-655.

Introduction

A significant number of individuals with rheumatic disorders (RMD) receive their diagnoses during the reproductive stages of their lives [1]. Drug usage during pregnancy can frequently cause anxiety; thus, many women with RMDs discontinue medications before pregnancy or during the early stages of their pregnancies [2]. Pregnant women tend to seek health-related information from a variety of sources, as their information needs increase during pregnancy [3]. It has been determined that pregnant women utilize the Internet as a source of information concerning their pregnancies and medications more frequently than they consult medical professionals [4]. Incorrect information obtained from the Internet can increase the tendency of highly worried pregnant women to discontinue their medicine thus leading to exacerbation of the disorder and an increase in the risk of pregnancy-related problems [5]. For this reason, it is very important for patients to have access to accurate information sources during pregnancy. However, some doubts regarding the accuracy and quality of health-related content on the internet exist.

In recent years, the area of computer science known as artificial intelligence (AI) has exhibited substantial development. The language-learning model (LLM) is a natural language processing artificial intelligence (AI) tool that is trained on excessive amounts of datasets and is capable of understanding and generating human-like responses [6]. LLMs and the OpenAI tool "Chat Generative Pre-trained Transformer," or "ChatGPT," in particular, have attracted great interest in medical science lately due to their high performance. One of the most popular, ChatGPT, is a natural language processing (NLP) system developed by OpenAI (OpenAI, L.L.C., San Francisco, CA, USA). Currently, two versions are available: (1) GPT-3.5, which is the fastest and is free to use and (2) GPT-4.0, which has a fee but is regarded as the most powerful version [7]. This version offers several advantages, including more efficiency, higher precision, and cost savings. It has several difficulties, however, including safety issues and limited performance [8]. Furthermore, insufficient evidence concerning the accuracy, reliability, and quality of medical information provided by Chatbots is available.

This study aimed to evaluate the accuracy and completeness of chatbots, including ChatGPT versions GPT 3.5 (free) and 4 (fee for use) in the framework of digital health-related information regarding the use of anti-rheumatic drugs before and during pregnancy.

Materials and methods

In this prospective, cross-sectional study, OpenAI's chatbots ChatGPT versions 3.5 and 4 were used to evaluate the performance of the LLM-based AI for health-related information concerning anti-rheumatic drug use during pregnancy. The reference source for this study was the 2016 European Union of Associations for Rheumatology (EULAR) guidelines entitled "The EULAR points to consider for use of antirheumatic medicines before pregnancy and during pregnancy" [9]. Fourteen queries in this guideline containing information about expert opinions on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressive drugs during pregnancy were used to generate responses.

On September 16, 2023, all domain items were entered as questions into two versions of OpenAI models (GPT-3.5 and -4, August version). English was used as the chat language. Responses obtained from each AI model were analyzed separately by two rheumatology specialists. A single rater submitted questions to the AI programs and recorded the answers. To reduce bias, the other rater had no information about which AI programs generated the answers. In case of disagreement between the scores presented by the raters, the answer was reviewed, and the decision was made by consensus. This final score was utilized for the analysis.

Johnson et al.'s [10] scoring system, which was determined for the ChatGPT study, was used for the accuracy and completeness of the content. The rating of accuracy for each response was assessed using a six-point Likert scale: (1) completely incorrect, (2) more incorrect than correct, (3) Approximately equal correct and incorrect, (4) more correct than incorrect, (5) nearly all correct, and (6) correct.

The completeness scale is based on a 3-point Likert scale: (1) incomplete, missing essential details or information, only partially answering the question; (2) adequate, covering all bases and providing the minimum amount of information required to be considered complete; and (3) comprehensive, covers all areas of the query, and offers more details than what was expected.

The study did not require ethical approval as it did not involve human or animal participants.

Statistical analysis

Data analysis was performed using SPSS software (IBM SPSS Statistics v. 22.0 for Windows; Armonk, NY: IBM Corp). Numbers, percentages, and median (interquartile range) values were used to represent descriptive data. The Shapiro–Wilk test was used to determine normality of the data. Inter-rater reliability and overall agreement between raters were assessed using Cohen's kappa statistic. According to intra-class correlation coefficient results, positive values ranging from 0 to 0.2 indicated poor agreement, 0.2 to 0.4 indicated fair agreement, 0.4 to 0.6 indicated moderate agreement, 0.6 to 0.8 indicated good agreement, and 0.8 to 1 indicated very good agreement. Differences observed in the scores across ChatGPT versions were compared using the Mann–Whitney U test. Significance was evaluated at the level of $P < 0.05$.

Results

The mean accuracy scores for GPT 3.5 were 5 (1.17) and 5.07 (1.26) for GPT 4 with no statistically significant difference between scores (P=0.769). The mean completeness scores for GPT 3.5 were 2.5 (0.51) and 2.64 (0.49) for GPT 4 with no statistically significant difference between the two versions (P=0.541). Both models had similar mean accuracy and completeness scores (3.75 [1.55] versus 3.86 [1.57)]; P=0.717). Table 1 presents the accuracy and completeness scores regarding the medicine.

Table 1: Accuracy and completeness of responses generated by Chat Generative Pre-trained Transformer (ChatGPT) versions 3.5 and 4 to the questions regarding the use of NSAIDs, synthetic DMARDs, and immunosuppressive medicines in pregnancy

		GPT 3.5	GPT 4	*P*-value
Methotrexate	Accuracy Completeness	6 2	6 3	
Leflunomide	Accuracy Completeness	6 3	6 3	
Sulfasalazine	Accuracy Completeness	6 2	6 3	
Hydroxychloroquine	Accuracy Completeness	6 3	6 3	
Azathioprine	Accuracy Completeness	2 2	4 2	
Cyclophosphamide	Accuracy Completeness	6 2	6 3	
Ciclosporin	Accuracy Completeness	4 2	2 2	
Mycophenolate mofetil	Accuracy Completeness	6 2	6 3	
Prednisone	Accuracy Completeness	4 3	4 3	
NSAIDs	Accuracy Completeness	4 3	4 3	
Colchicine	Accuracy Completeness	5 3	4 2	
Tofacitinib	Accuracy Completeness	5 3	6 3	
Tacrolimus	Accuracy Completeness	5 3	5 2	
IVIG	Accuracy Completeness	5 2	6 2	
Total mean (SD)	Accuracy Completeness	5 (1.17) 2.5 (0.51)	5.07 (1.26) 2.64 (0.49)	*P1*=0.769¶ *P2*=0.541¶
Total scores of all items	Mean (SD) Median (IQR)	3.75 (1.55) 3 (4)	3.86 (1.57) 3 (4)	*P*=0.717¶

GPT: Generative Pre-trained Transformer; NSAID: non-steroidal anti-inflammatory drug; IVIG: intravenous immunoglobulin; SD: Standard deviation, IQR: Interquartile range; *P*1: *P*-value of accuracy scores, *P*2: *P*-value of completeness scores; *P*<0.05 was considered statistically significant. ¶: Mann–Whitney U test

The frequency of the accuracy and completeness scores of answers generated by two GPT versions were evaluated. For accuracy, GPT 4 yielded scores of 7.1% (n=1) more incorrect than correct, 28.6% (n=4) more correct than incorrect, 7.1% (n=1) nearly all correct, and 57.1% (n=8) correct. GPT 3.5 yielded scores of 7.1% (n=1) more incorrect than correct, 21.4% (n=3) more correct than incorrect, 28.6% (n=4) nearly all correct, and 42.9% (n=6) as shown in Figure 1. For completeness, GPT 4 yielded scores of 64.3% (n=9) comprehensive and 35.7% (n=5) adequate, and no incomplete score was noted. GPT 3.5 yielded scores of 50.0% (n=7) comprehensive and 50.0% (n=7) as adequate, and no incomplete score was noted (Figure 2).

Figure 1: Distribution of the accuracy scores for Chat Generative Pre-trained Transformer (ChatGPT) versions 3.5 and 4

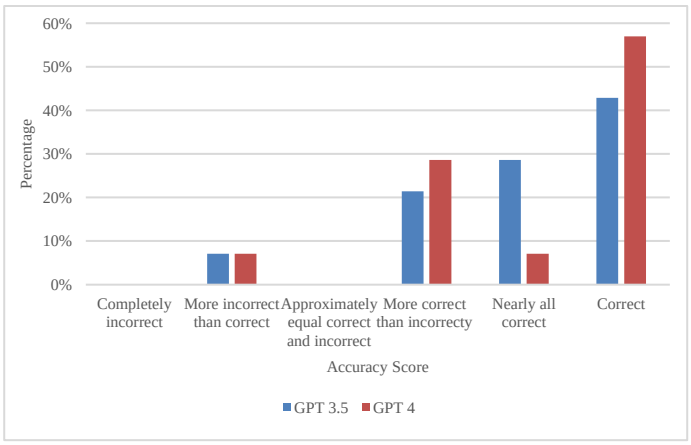
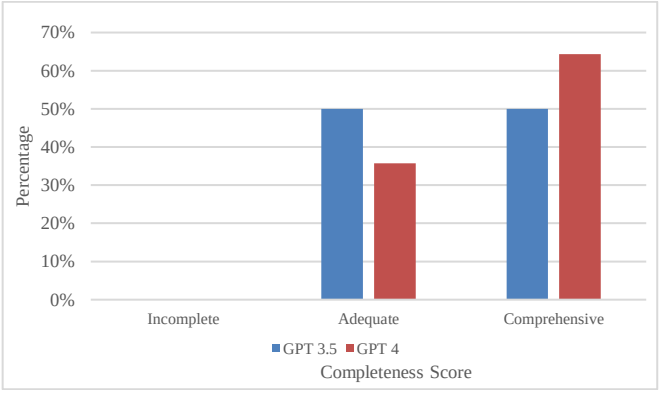


Figure 2: Distribution of the completeness scores for ChatGPT versions 3.5 and 4.



The inter-rater reliability as assessed by Cohen's kappa coefficient demonstrated a level of agreement ranging from good to very good. The agreement of the accuracy scores for GPT versions 3.5 and 4 were 0.794 (*P*<0.001) and 0.763 (*P*<0.001), respectively. The agreement of the completeness scores for GPT 3.5 and GPT 4 were 0.714 (*P*=0.008) and 0.851 (*P*=0.001), respectively.

In the GPT 3.5 model, hydroxychloroquine and Leflunomide received the highest full scores for both accuracy and completeness, while methotrexate, Sulfasalazine, Cyclophosphamide, Mycophenolate mofetil, and Tofacitinib received the highest total scores in the GPT 4 model. Azathioprine received the lowest accuracy and completeness scores for the GPT 3.5 model and Ciclosporin for the GPT 4 model.

Discussion

The popularity of AI use, particularly ChatGPT, in the field of healthcare is increasing. However, data concerning its reliability and adequacy are still not entirely sufficient. This study aimed to evaluate the accuracy and completeness of ChatGPT version 3.5 (free) and version 4 (fee for use) in the context of digital health-related information on the use of anti-rheumatic medicines in pregnancy. Based on the results of our research, the answers generated by ChatGPT versions 3.5 and 4 to inquiries about the safety and compatibility of rheumatological medications during pregnancy demonstrate a satisfactory level of accuracy and completeness. The outcomes of both versions exhibited similarities and did not demonstrate superiority over one another. To the best of our knowledge, our study is the first study in which ChatGPT versions 3.5 and 4 were evaluated in terms of the use of anti-rheumatic medicines in pregnancy, and no similar study was found in the literature. From the patient's perspective, pregnancy while using rheumatological medicines is a subject that involves a high level of anxiety and motivates patients to investigate this issue. Our study is important in terms of evaluating whether patients have access to accurate and sufficient information other than their physicians.

Since the potential teratogenic effect of many medicines has not yet been demonstrated, the use of medicines in pregnancy should be approached carefully [11]. It has been reported that only 5% of 213 new medicines approved by the United States Food and Drug Administration (USFDA) between 2003 and 2012 can be used safely in pregnancy, and information on whether many medicines can be used safely in pregnancy is still limited [12,13]. This situation causes anxiety in pregnant

women who have chronic diseases, such as rheumatological diseases, and need to continue pharmacological therapy during pregnancy. Therefore, easily accessible sources of information come into play at this stage and are used to help patients find answers to their questions. Studies show that the rate of pregnant women's use of Internet resources related to medicine use reaches as high as 76%, and the Internet plays an essential role in pregnant women's access to health information and decision-making [14,15].

To what extent can the information about medicine and health found on the internet be deemed accurate? Which application or website provides the most accurate and trustworthy data? The proliferation of the Internet in the healthcare industry has prompted these questions. ChatGPT is a popular and generally trustworthy model of artificial intelligence. Sabry Abdel-Messih et al. [16] investigated the capabilities of ChatGPT to respond to questions regarding a specific case of acute organophosphate poisoning in their research. That study's findings demonstrated that the model effectively addressed all questions posed. Both the initial and reconstructed responses obtained from ChatGPT were deemed to be highly satisfactory. They stated that as ChatGPT evolves and its application in medicine becomes more refined, AI could be useful for addressing rare clinical cases, which are sometimes overlooked by experts, as opposed to replacing healthcare professionals. Similarly, it has been reported to be a useful tool in many medical areas, such as cirrhosis and hepatocellular carcinoma, dental applications, drafting, and plastic surgery [17–19].

In addition to the data supporting the reliability and adequacy of ChatGPT versions, studies claiming the opposite have also been published. In the study by Jeblick et al. [20] in which radiology reports were evaluated, potentially harmful errors, such as missing important medical findings, were identified, and they emphasized the need for manual checking of these automated reports. In the discharge summary example provided in a study by Patel [20], ChatGPT added extra information to the summary that was not included in the prompts [21]. In a study by Alkaissi et al., questions about homocysteine were asked to ChatGPT, and although they received mostly correct answers, they also received irrelevant answers. When asked to provide references on this subject, the ChatGPT provided article titles that did not exist. The PubMed IDs he provided for these articles were for completely different and unrelated articles [22]. So, how does ChatGPT provide information that does not exist? As far as we know, chatbots respond to pre-programmed datasets. However, generative models, such as ChatGPT, can generate new information that is not real. Alkaissi et al. [22] called this condition an "artificial hallucination". This artificial condition raises concerns about the level of ChatGPT's reliability.

One important finding of our study is that ChatGPT generally performed better with medications, such as methotrexate and Leflunomide, which are contraindicated in pregnancy and whose association with malformations is well-established. Although other drugs generally did not reach full accuracy and completeness scores, it was emphasized that decisions should be made according to the condition of the patient and his/her disease status in addition to the benefit/risk ratio obtained from the ChatGPT. Additionally, it was stated that healthcare professionals should be consulted before deciding whether (or not) to use such a tool.

Limitations

This study has some limitations. First, this study was designed to evaluate the existing versions of ChatGPT. The database used to train ChatGPT only contains information through 2021. Due to this limitation, the information that is provided in the study may not be current. The study is conducted solely in English, which may not fully represent the AI's capabilities in other languages or the global diversity of users seeking information on anti-rheumatic drugs during pregnancy. The subjective nature of Likert-type scales and self-reported scores may result in bias. Additionally, previous experiences or preconceived notions of the investigators regarding the use of anti-rheumatic drugs during pregnancy may influence their evaluation and lead to bias.

Further research is needed to better investigate ChatGPT's reliability and comprehensiveness across different medical fields. Additionally, more comprehensive studies should be done to evaluate whether this tool produces the same results in other languages.

Conclusion

In conclusion, while ChatGPT versions 3.5 and 4 offer a substantial amount of reliable information, the prevailing research indicates the necessity of acknowledging the limitations inherent in the information derived from these models. This study demonstrated that the AI chatbots, GPT versions 3.5 and 4 provide accurate and comprehensive information to patients in the setting of anti-rheumatic drug use during pregnancy. On the other hand, information generated by ChatGPT must be validated, and patients should be cautioned about the potential of receiving misinformation on health-related issues. Evaluation and advancement of these tools are essential steps for assuring the accuracy and quality of the information generated. Due to ChatGPT's limitations, it cannot serve as a stand-alone decision-making tool for such a sensitive issue, such as the use of medication during pregnancy. ChatGPT lacks access to and cannot analyze a patient's laboratory parameters, prior pregnancy complications, and the internal dynamics of the patient. The information acquired from ChatGPT necessitates verification. While both iterations of ChatGPT offer valuable insights, it is crucial to keep in mind that ChatGPT does not possess the expertise of a medical professional. Further research is required to investigate and develop its potential for use in treating a variety of medical conditions.

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J Surg Med. 2023;7(10):656-659.
DOI: 10.28982/josam.7980

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Evaluation of inferior mesenteric vein drainage patterns in the Turkish population: A multidetector computed tomography study

Hakan Yılmaz

Department of Radiology, VM Medicalpark Hospital, Kocaeli, Turkey

ORCID ID of the author(s)
HY: 0000-0002-4710-7927

Corresponding Author
Hakan Yılmaz
Department of Radiology, VM Medicalpark Hospital, Kocaeli, Turkey
E-mail: dr_hyilmaz@hotmail.com

Ethics Committee Approval
The study was approved by the local ethics committee of Kocaeli Health and Technology University (no:2023-54, date: August 2, 2023). 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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 6

Abstract

Background/Aim: The inferior mesenteric vein (IMV) plays a crucial role in the venous system as it joins the superior mesenteric vein (SMV) and splenic vein to form the portal vein. The widespread adoption of multidetector computed tomography (MDCT) has greatly enhanced our ability to assess abdominal vascular structures. This study aimed to investigate the IMV drainage patterns in a Turkish population using MDCT.

Methods: This descriptive, single-center, retrospective study included patients who had undergone abdominal computed tomography (CT) in the portal phase at our hospital for various clinical indications. Excluded from the study were patients who did not undergo imaging in the portal venous phase, those with incomplete evaluation of all IMV segments, and individuals who had undergone pancreaticoduodenal or intestinal surgery for any reason. We retrospectively analyzed a total of 877 contrast-enhanced MDCT examinations performed at our hospital between March 2022 and March 2023. Patients were classified based on their IMV drainage patterns into the following categories: type 1 (drainage into the splenic vein), type 2 (drainage into the SMV), type 3 (drainage at the junction level), type 4 (drainage into the branches of the SMV), and type 5 (patients in whom IMV assessment was not possible).

Results: The mean age of the patients was 48.7 years (range: 24–92 years), with 449 (51.2%) being male and 428 (48.8%) female. The distribution of patients according to IMV drainage patterns was as follows: type 1, n=379 (43.2%); type 2, n=398 (45.4%); type 3, n=71 (8.1%); type 4, n=15 (1.7%); and type 5, n=14 (1.6%).

Conclusion: Our study findings indicate that in the Turkish population, the IMV predominantly drains into the SMV before joining the splenic vein. This disparity from certain studies in the literature underscores the variability in IMV drainage patterns, emphasizing the importance of individualized patient evaluation in this regard.

Keywords: inferior mesenteric vein, computed tomography, variation

How to cite: Yılmaz K. Evaluation of inferior mesenteric vein drainage patterns in the Turkish population: A multidetector computed tomography study. J Surg Med. 2023;7(10):656-659.

Introduction

The inferior mesenteric vein (IMV) is a significant venous structure that combines with the superior mesenteric vein (SMV) and splenic vein (SpV) to create the portal vein (PV). The IMV is responsible for draining the superior rectum, sigmoid colon, and descending colon, but its venous drainage pattern exhibits variability. Anatomical references related to PV structures primarily focus on the SMV and SpV, offering limited information about the IMV, except for its common drainage into the SpV [1]. Nevertheless, recent studies have revealed that the IMV can also merge and discharge into the SMV, the junction between the SpV and SMV, or other mesenteric venous drainage regions [2,3].

A thorough comprehension of portal venous drainage is crucial for preventing bleeding and postoperative gastric congestion in procedures concerning the pancreaticoduodenal region. It is also vital for assessing the intestinal segments that may be affected in cases of mesenteric venous thrombosis. The study of IMV changes through cadaveric investigations is hampered by the scarcity of cases, limiting the ability to conduct comprehensive evaluations on a larger scale. However, the widespread adoption of multidetector computed tomography (MDCT) has greatly facilitated the assessment of abdominal vascular structures [4].

This study aimed to assess the IMV drainage patterns within the Turkish population using MDCT.

Materials and methods

The descriptive study received approval from the local ethics committee of Kocaeli Health and Technology University (Approval Number: 2023-54, Date: August 2, 2023). Prior to commencing the study, a minimum sample size of 774 was determined through power analysis, ensuring a power of 0.8 and a significance level of 0.05.

Retrospectively, a total of 877 contrast-enhanced MDCT examinations conducted at our hospital between March 2022 and March 2023 were assessed. The study included patients who underwent abdominal computed tomography (CT) in the portal phase for any medical indication at our hospital. Patients who did not undergo imaging in the portal venous phase, cases where evaluation of all segments of the IMV was not feasible, and individuals who had undergone pancreaticoduodenal or intestinal surgery for any reason were excluded from the study.

All participants in the study shared Turkish ancestry. Data regarding the age and gender of each patient were meticulously documented. The assessment of IMV drainage involved a comprehensive evaluation of all segments of this structure within abdominal CT images.

Based on their respective IMV drainage patterns, the patients were categorized into the following groups: Type 1: Drainage into the splenic vein (Figure 1); Type 2: Drainage into the SMV (Figure 2); Type 3: Drainage occurring at the junction between the splenic vein (SpV) and SMV (Figure 3); Type 4: Drainage into the branches of the SMV.

Furthermore, cases where assessment was possible for the distal segments of the IMV while the proximal segments remained unassessable, as well as instances where IMV evaluation was unachievable despite the availability of a portal phase, were classified as type 5.

Figure 1: Curved planar reformatted multiplanar reconstruction multidetector computed tomography image of a 45-year-old male patient, showing that the inferior mesenteric vein drains into the splenic vein, consistent with type 1 drainage pattern (arrow).

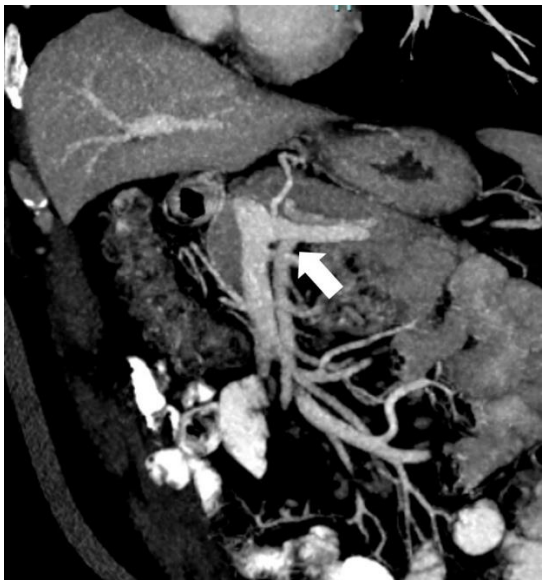


Figure 2: Curved planar reformatted multiplanar reconstruction multidetector computed tomography image of a 52-year-old female patient, showing that the inferior mesenteric vein drains into the superior mesenteric vein, consistent with type 2 drainage pattern (arrow).

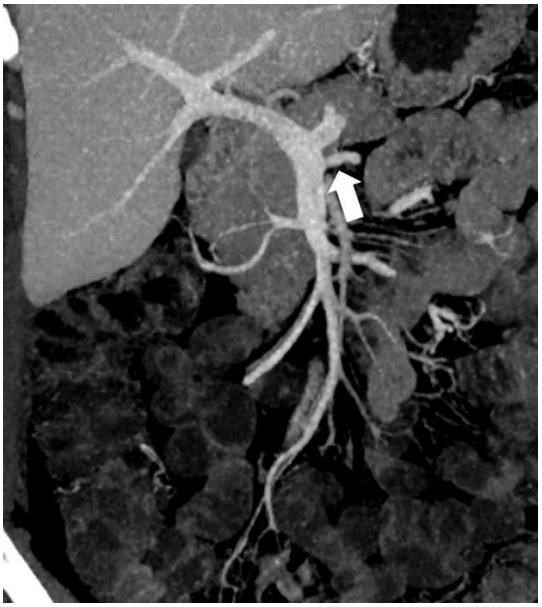
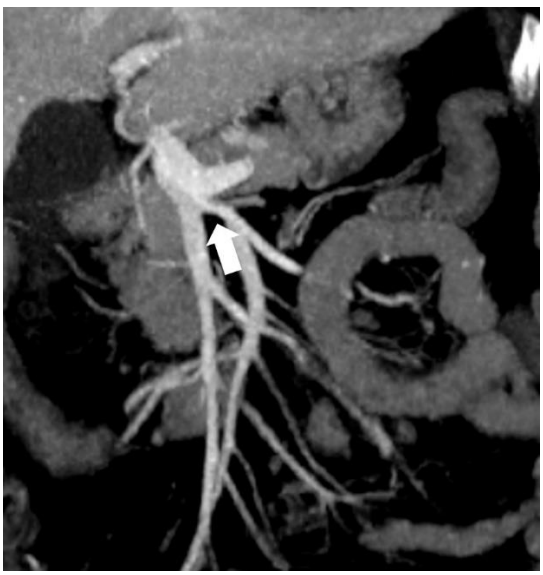


Figure 3: Curved planar reformatted multiplanar reconstruction multidetector computed tomography image of a 37-year-old female patient, showing that the inferior mesenteric vein drains at the junction level, consistent with type 3 drainage pattern (arrow).



Images were acquired utilizing a Siemens Somatom Definition 128-MDCT device based in Erlangen, Germany. All examinations were conducted with a detector configuration of 128x0.6 mm, employing a tube potential of 120 kVp. Additionally, automatic tube current modulation (CARE Dose, Siemens) was activated to optimize radiation exposure.

A contrast-enhanced triphasic examination, encompassing arterial, portal, and venous phases, was administered to all patients. For contrast injection, a 21-G intravenous line was inserted via the medial cubital vein. The MDCT examination scope was precisely adjusted to encompass the region from the liver to the pelvic inlet.

Non-ionic iodinated contrast material (300 mg I/mL, Omnipol, Polifarma, Istanbul, Turkey) was administered using an auto-injector (Medrad Stellant CT Injection System, Bayer HealthCare, The Netherlands). The arterial phase was initiated with the bolus tracking method when a threshold of 200 Hounsfield units was reached at the level of the abdominal aorta. The time interval between the initiation of contrast material injection and the commencement of the arterial phase was 25 s. Subsequently, the portal phase and venous phase were triggered 15 s and 30 s after the initiation of the arterial phase, respectively.

The imaging data were transferred to a dedicated workstation (Syngo.via, Siemens, Erlangen, Germany). Multiplanar reconstruction (MPR) images were generated from the portal phase images, and the drainage pattern of the IMV was identified on these reconstructed images.

Statistical analysis

Statistical analysis was conducted using MedCalc (version 12, Ostend, Belgium). Descriptive statistics were presented as the mean (standard deviation), while categorical variables were expressed as frequencies and percentages.

Results

The study included CT images from a total of 877 patients. The mean age of these patients was 48.7 years (SD=24). Out of the patients, 449 (51.2%) were male, while 428 (48.8%) were female. The distribution of patients based on their IMV drainage patterns was as follows: type 1, n=379 (43.2%); type 2, n=398 (45.4%); type 3, n=71 (8.1%); type 4, n=15 (1.7%); and type 5, n=14 (1.6%). A convergence of the IMV with the SMV and its branches (type 2 and type 4 junction) was observed in 413 (47.1%) patients (Table 1).

Table 1: Distribution of patients according to their inferior mesenteric vein drainage patterns.

	n	%
Type 1	379	43.2
Type 2	398	45.4
Type 3	71	8.1
Type 4	15	1.7
Type 5	14	1.6

Discussion

The most significant outcome of our study reveals that the IMV most commonly drained into the SMV within the Turkish population. In a study conducted by Krumm et al. [5] involving 916 patients, they reported that the IMV drained into the splenic vein (SpV) in roughly 40% of the cases, into the portal junction in approximately 30%, and into the SMV in about 20%. Another study by Graf et al. [6], which assessed mesenteric venous anatomical variations in a total of 54 patients, revealed that the IMV drained into the SpV in 56% of the cases and into the SMV in 26%. In a separate investigation, Sakaguchi et al. [4] examined mesenteric venous patterns in 102 patients, reporting that the IMV converged with the SpV in 68.5% of cases, with the SMV in 18.5% and with the SMV in 18.5%. In a study involving 66 patients, Arimoto et al. [7] observed that the IMV drained into the SpV in 48.5% of cases and into the SMV in 40.9%, a finding that closely mirrors our own. These variations in results among these studies can be attributed to the diverse populations on which the studies were conducted.

The MDCT technique plays a pivotal role in assessing the IMV. Our MDCT protocol entails imaging 70 s after the administration of 150 ml (300 mg/dl) of iodinated contrast material, facilitated by an auto-injector (3–5 ml/h). Curved multiplanar reconstruction (MPR) images prove particularly valuable for IMV evaluation, given the considerable variability in its course and the challenges associated with visualizing the entire structure in thin coronal reformatted Minimum Intensity Projection (MIP) images. We recommend a slice thickness of less than 10 mm for MPR images, while a range of 10-35 mm is employed for thin MIP images. Volumetrically processed images offer valuable insights, especially in cases involving the premature filling of the IMV, such as those associated with inflammation or arteriovenous fistulas [8]. In our study, we also utilized curved planar MPR images.

Alternative modalities for IMV visualization include Digital Subtraction Angiography (DSA) and Magnetic Resonance Angiography (MRA). DSA boasts the distinct advantage of dynamic and high-resolution IMV visualization. However, it lacks the capability for three-dimensional and cross-sectional imaging. Conversely, MRA, while radiation-free, comes with certain limitations, including extended examination times and the potential for artifacts [9]. The chief advantage of MDCT lies in its ability to meticulously depict anatomy during a standard abdominal CT examination, all accomplished within a remarkably brief timeframe [10,11].

In recent years, mounting evidence has underscored the oncological benefits of complete mesocolic excision coupled with central vascular ligation and lymphadenectomy. This surgical approach, which can also be conducted laparoscopically, has exhibited superior outcomes compared to traditional colonic resections, manifesting in a lower five-year local recurrence rate and enhanced overall survival rates [12]. The effectiveness of laparoscopic surgery has been substantiated through evidence attesting to its surgical safety, improved perioperative results, and comparable long-term oncological outcomes [13]. However, it is important to note that these surgical procedures are technically demanding and carry a heightened risk of intraoperative organ injuries and severe non-surgical complications [14]. A comprehensive grasp of the intricate three-dimensional anatomy of the IMV is crucial in mitigating iatrogenic injuries, especially during contemporary radical resections performed for colon cancer [15].

Our study stands out for several key features. It represents a novel undertaking as the first investigation conducted within the Turkish population in this specific domain.

Furthermore, it boasts the distinction of including the largest patient cohort among the existing body of literature.

Limitations

Our study is subject to several limitations. First, the sample size was relatively small. Second, the study was conducted retrospectively and was centered at a single institution. Third, the lack of clinical and laboratory data prevented the execution of relevant statistical analyses. Fourth, the assessment of CT images was performed by a single radiologist, thus rendering it impossible to assess interobserver variations. Lastly, the MDCT findings were not corroborated with the gold standard method, DSA. In the future, more comprehensive prospective studies, potentially incorporating DSA, can be envisioned to address these limitations.

Conclusion

Based on our study, it is observed that within the Turkish population, the IMV predominantly drains into the SMV before converging with the splenic vein. The variance in this finding compared to certain studies in the literature underscores the variability in IMV drainage patterns. In this regard, a patient-specific assessment holds significant importance.

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J Surg Med. 2023;7(10):660-664.
DOI: 10.28982/josam.7952

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Non-obstetric surgery and anesthesia during pregnancy. Five-year single-center retrospective analysis

Mustafa Altınay, Ayşe Surhan Çınar

Department of Anesthesiology, Sisli Hamidiye Etfal Training and Research Hospital, University of Health Sciences, Istanbul, Turkey

ORCID ID of the author(s)

MA: 0000-0002-2036-048X
ASÇ: 0000-0003-2247-9764

Abstract

Background/Aim: Surgical procedures during pregnancy incur great difficulties for both the surgeon and the anesthesiologist. Changing maternal and fetal physiology changes both the pharmacodynamics and pharmacodynamics of the anesthetic drugs administered. In this study, the researcher aimed to determine the risk factors of non-obstetric surgery or anesthesia that cause preterm labor and/or low birth weight.

Methods: Our study was planned as a single-center retrospective study and was carried out by scanning the data of 52 pregnant patients between 2015 and 2020. Preterm labor and low birth weight were defined as adverse events. The patients were divided into two groups: those who developed adverse events and those who did not. The effects of age, parity, type of surgery and anesthesia, duration of surgery, gestational age, mode of delivery, and birth weight on mortality have been investigated.

Results: Comparing the patient groups with and without adverse events, no statistically significant difference was found between their general characteristics, anesthesia, and surgical characteristics (P>0.05).

Conclusion: In the study, the researcher analyzed the surgical and anesthesia factors of non-obstetric surgery. It was concluded that neither surgical nor anesthetic factors independently increased the risk of preterm labor or low birth weight.

Keywords: non-obstetric surgery, preterm labor, low birth weight

Corresponding Author
Mustafa Altınay
Sisli Hamidiye Etfal Training and Resource Hospital, University of Health Sciences, 34371 Sisli, Istanbul, Turkey
E-mail: m_altinay@yahoo.com

Ethics Committee Approval
The study was approved by Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee with the number 2363 on June 13, 2023. 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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 5

How to cite: Altınay M, Çınar AS. Non-obstetric surgery and anesthesia during pregnancy: Five-year single-center retrospective analysis. J Surg Med. 2023;7(10):660-664.

Introduction

Surgical procedures during pregnancy are a serious source of concern for both the surgeon and the anesthesiologist. Therefore, the tendency in pathologies requiring surgery is to postpone the procedure after pregnancy. Nonetheless, indications such as acute appendicitis, trauma-related orthopedic surgery, or maternal malignancy necessitate surgery during pregnancy. The need for non-obstetric surgery during pregnancy varies between 0.75% and 2% [1].

Acute appendicitis ranks first among the indications that constitute the need for this surgery, followed by acute cholecystitis and maternal trauma [2]. Data on both non-obstetric surgery and anesthesia methods and timing to be applied during pregnancy are contradictory. Although a clinical study conducted with retrospective analysis of data on 6.5 million pregnancies in the UK showed that fetal complications of non-obstetric surgery are low and non-obstetric surgery is safe during pregnancy, it was reported in other studies that non-obstetric surgery progressed with increased fetal and maternal complications [3–6]. Reviewing these complications, preterm labor, low birth weight, and pregnancy loss take the first place.

In this study, the researcher aimed to determine the risk factors of non-obstetric surgery or anesthesia that cause preterm labor and low birth weight.

Materials and methods

For the retrospective observational study, approval was obtained from the Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee of our hospital on 13/06/2023 with number 2363. All procedures were carried out in accordance with the ethical standards specified in the Declaration of Helsinki (2008). Data analysis was performed by two anesthesiologists, and while reviewing the diagnoses of the patients, The International Classification of Diseases, 10th Revision (ICD-10) diagnostic codes were used. It was planned to list all patients who had been diagnosed with pregnancy with Z33 and Z32.1 codes between 2015 and 2020 by scanning the data processing system of our hospital. Patients who underwent non-obstetric surgery during pregnancy were included in the study. Patients who did not undergo non-obstetric surgery, whose antenatal follow-up and delivery were not performed in our hospital after surgery, who underwent non-obstetric surgery in the same session as cesarean section, who were operated under local anesthesia, or whose data were incomplete were not included in the study.

Non-obstetric surgery was defined as the surgery performed during pregnancy other than fetal surgery, cesarean section, uterine surgery, cervical circulation, tubo-ovarian surgery, and dilatation curettage. Non-obstetric surgical procedures were scanned by extracting the cesarean code in the operating room module of the hospital data processing system, considering the multitude of possible diagnostic codes. The type of surgery, duration of the surgery, and the gestational week in which it was performed were recorded. Non-obstetric surgical procedures applied were grouped under the headings of gastrointestinal surgery, urinary system surgery, and others. The gestational week in which the surgery was performed was also grouped under 1st, 2nd, and 3rd trimester headings.

In our hospital, the American Society of Anesthesiologists guide is taken into consideration in the application of obstetric surgery anesthesia [7]. In our hospital, for the last 10 years, general anesthesia induction for non-obstetric surgery has been routinely performed with propofol, fentanyl, and rocuronium, followed by sevoflurane, intermittent fentanyl, or remifentanil infusion. Bupivacaine is used in neuraxial anesthesia and peripheral nerve blocks. Anesthesia type was grouped under general anesthesia, neuraxial anesthesia, sedation, and regional anesthesia headings. The type and duration of anesthesia were recorded.

Among the listed patients who had non-obstetric surgery, age, parity, cesarean and vaginal delivery, gestational time of birth, birth weight, preterm labor, and abortion diagnoses were manually scanned and recorded.

Preterm labor and low birth weight were defined as adverse events. The patients were divided into two groups: those with and without adverse events. The primary finding of the study is to determine the risk factors related to anesthesia and surgical procedures that may cause adverse events. The secondary finding is to define the general characteristics of non-obstetric surgeries performed in our hospital.

Statistical analysis

For statistical analysis, the SPSS 15.0 program (SPSS Inc., Chicago, IL, USA) for Windows was used. The descriptive statistics were considered as number and percentage for categorical variables, and mean, standard deviation, minimum, and maximum values for numerical variables. Ratios in the groups were compared with the Chi-Square Test. Comparisons of numerical variables between two independent groups were made with the Student's T-Test when the normal distribution condition was met, and the Mann-Whitney U test when the condition was not met. Risk factors were examined by Logistic Regression Analysis. The alpha significance level was accepted as P-value <0.05.

Results

A total of 8,053 pregnant subjects were screened between 2015 and 2020. From these, 91 (1.13%) underwent non-obstetric surgery. Among them, 18 patients had concurrent cesarean, and 21 were missing in the follow-up. The remaining 52 patients were included in the final analysis. Characteristics of the patients analyzed are presented in Table 1. Gastrointestinal and urinary surgery were performed on the majority of the patients (19 patients each, 38 patients [73%] total). Double-J ureteral stenting (n=19) and appendectomy (n=15) were the leading causes for these surgeries. Details of the surgeries are presented in the Supplemental Table 1.

Adverse events of any type occurred in 13 (25%) patients. Of these, 5 had low birth weight alone, 2 had preterm labor alone, and 6 had both preterm labor and low birth weight. Most of the patients underwent sedation (n=22) and general anesthesia (n=19).

The type of surgery or type of anesthesia did not affect the outcome of having any adverse events upon the birth. Also, parity and the trimester in which the surgery was performed did

Table 1: Comparison of patient groups with and without adverse events.

			Adverse events		
		Total N=52	**Yes n=13 (%25)**	**No n=39 (%75)**	***P*-value**
Demography					
Age (yrs.)		27.5 (4.9) (19-37)	27.0 (3.9) (20-34)	27.7 (5.2) (19-37)	0.674*
Parity	Nulliparae	20 (38.5)	7 (53.8)	13 (33.3)	0.399#
	Primipara	13 (25.0)	3 (23.1)	10 (25.6)	
	Multipara	19 (36.5)	3 (23.1)	16 (41.0)	
Surgical Features					
Surgical type	Gastrointestinal Surgery	19 (36.5)	6 (46.2)	13 (33.3)	0.521#
	Urinary Surgery	19 (36.5)	3 (23.1)	16 (41.0)	
	Others	14 (27)	4 (30.8)	10 (25.6)	
Anesthesia type	General Anesthesia	19 (36.5)	6 (46.2)	13 (33.3)	0.166#
	Neuraxial anesthesia	10 (19.2)	3 (23.1)	7 (17.9)	
	Sedation	22 (42.3)	3 (23.1)	19 (48.7)	
	Regional anesthesia	1 (1.9)	1 (7.7)	0 (0.0)	
Trimester	1st Trimester	8 (15.4)	1 (7.7)	7 (17.9)	0.457#
	2nd Trimester	28 (53.8)	6 (46.2)	22 (56.4)	
	3rd Trimester	16 (30.8)	6 (46.2)	10 (25.6)	
Gestational age		23.1 (7.8) (5-36)	25.9 (7.9) (6-35)	22.1 (7.6) (5-36)	0.082£
Surgical Duration (hrs.)		70.4 (51.0) (25-290)	63.5 (37.9) (30-155)	72.7 (54.9) (25-290)	0.907£
Anesthesia Duration (hrs.)		87.9 (59.1) (35-330)	81.9 (42.9) (40-180)	89.9 (63.9) (35-330)	0.807£
Delivery Features					
Delivery type	Vaginal delivery	11 (21.2)	4 (30.8)	7 (17.9)	0.435#
	Cesarean	41 (78.8)	9 (69.2)	32 (82.1)	

* Student's T-Test £Mann-Whitney U test # Chi-Square Test

Table 2: Adverse events risk factors univariate and multivariate logistic regression analysis

	Univariate				**Multivariate**			
	P	**OR**	**95% C.I.**		***P***	**OR**	**95% C.I.**	
Age	0.667	0.972	0.852	1.108	0.767	0.970	0.791	1.188
Parity (Ref: Nulliparae)	0.390				0.146			
Primipara	0.469	0.557	0.114	2.716	0.132	0.156	0.014	1.746
Multipara	0.179	0.348	0.075	1.621	0.077	0.077	0.004	1.317
Surgery Type (Ref: Gast. Surgery)	0.509				0.258			
Urinary Surgery	0.260	0.406	0.085	1.947	0.682	0.459	0.011	19.130
Others	0.853	0.867	0.191	3.923	0.234	5.893	0.318	109.238
Anesthesia Type (Ref: General Anesthesia)	0.570				0.467			
Neuraxial anesthesia	0.930	0.929	0.176	4.897	0.435	0.375	0.032	4.394
Sedation	0.176	0.342	0.072	1.620	0.111	0.034	0.001	2.178
Regional anesthesia	1.000			.	1.000			
Trimester (Ref: 1st Trimester)	0.353				0.772			
2nd Trimester	0.579	1.909	0.195	18.692	0.474	4.582	0.071	295.269
3rd Trimester	0.227	4.200	0.410	43.035	0.542	6.803	0.014	3228.9
Gestational age	0.132	1.074	0.979	1.177	0.729	1.045	0.815	1.339
Surgical Duration	0.571	0.996	0.982	1.010	0.542	0.916	0.692	1.214
Anesthesia Duration	0.673	0.997	0.986	1.009	0.700	1.046	0.830	1.319

Ref: Reference, Gast: Gastrointestinal

Table 3: Preterm labor risk factors univariate and multivariate logistic regression analysis

	Univariate				**Multivariate**			
	P	**OR**	**95% C.I.**		***P***	**OR**	**95% C.I.**	
Age	0.751	0.975	0.833	1.141	0.278	0.812	0.557	1.183
Parity (Ref: Nulliparae)	0.998				0.909			
Primipara	0.976	1.030	0.148	7.193	0.685	2.648	0.024	293.5
Multipara	0.946	1.062	0.187	6.052	0.958	1.172	0.003	449.2
Surgery Type (Ref: Gast. Surgery)	0.365				0.712			
Urinary Surgery	0.181	0.208	0.021	2.070	0.999			.
Others	0.979	1.023	0.189	5.526	0.410	9.503	0.045	2019.8
Anesthesia Type (Ref: General Anesthesia)	0.986				0.846			
Neuraxial anesthesia	0.706	0.700	0.109	4.477	0.367	0.089	0.000	17.112
Sedation	0.998	0.000	0.000	.	0.998	0.000	0.000	.
Regional anesthesia	1.000			.	1.000			.
Trimester (Ref: 1st Trimester)	0.681				0.808			
2nd Trimester	0.999			.	0.999			.
3rd Trimester	0.999			.	0.999			.
Gestational age	0.099	1.109	0.981	1.255	0.265	1.472	0.746	2.907
Surgical Duration	0.891	0.999	0.983	1.015	0.254	1.300	0.828	2.042
Anesthesia Duration	0.990	1.000	0.987	1.013	0.214	0.774	0.516	1.159

Ref: Reference, Gast: Gastrointestinal

not alter the rate of complication. Finally, anesthesia or surgery duration did not influence the risk of having a complicated delivery. Multivariate regression also did not reveal any potential risk factors (Table 2).

When preterm labor and lower birth weight were analyzed for the potential risk factors associated with each outcome, no relationship was found. Additionally, multivariate regression similarly did not show any relationship between these assumed risk factors and the outcome (Tables 3 and 4).

Discussion

Surgical procedures during pregnancy can present great difficulties for both the surgeon and the anesthesiologist. Maternal and fetal physiology changes affect both the pharmacodynamics and pharmacodynamics of the anesthetic drugs administered [8]. In particular, the bioavailability, distribution, and excretion of some drugs are affected by the physiological changes associated with pregnancy. The most striking change in bioavailability is liver enzyme activity. This affects the metabolism and absorption of drugs. Maternal weight gain and increased plasma volume change the distribution of

Table 4: Low birth weight risk factors univariate and multivariate logistic regression analysis

	Univariate				Multivariate			
	P	**OR**	**95% C.I.**		***P***	**OR**	**95% C.I.**	
Age	0.383	0.938	0.814	1.082	0.546	0.934	0.748	1.166
Parity (Ref: Nulliparae)	0.170				0.137			
Primipara	0.228	0.338	0.058	1.972	0.146	0.159	0.013	1.901
Multipara	0.085	0.218	0.039	1.232	0.065	0.042	0.001	1.224
Surgery Type (Ref: Gast. Surgery)	0.733				0.207			
Urinary Surgery	0.430	0.525	0.106	2.603	0.869	0.718	0.014	37.09
Others	0.746	0.764	0.149	3.916	0.162	10.359	0.391	274.6
Anesthesia Type (Ref: General Anesthesia)	0.697				0.477			
Neuraxial anesthesia	0.833	1.200	0.220	6.534	0.558	0.450	0.031	6.508
Sedation	0.314	0.442	0.090	2.166	0.123	0.026	0.000	2.668
Regional anesthesia	1.000	0.000	0.000	.	0.999	0.000	0.000	.
Trimester (Ref: 1st Trimester)	0.480				0.612			
2nd Trimester	0.721	1.522	0.151	15.296	0.333	9.312	0.102	852.9
3rd Trimester	0.334	3.182	0.304	33.259	0.336	25.965	0.034	19697
Gestational age	0.291	1.052	0.958	1.155	0.976	0.996	0.769	1.290
Surgical Duration	0.871	0.999	0.985	1.013	0.567	0.919	0.689	1.226
Anesthesia Duration	0.900	0.999	0.988	1.011	0.713	1.045	0.827	1.320

Ref: Reference, Gast: Gastrointestinal

water-soluble drugs. The increase in plasma volume leads to a decrease in the concentrations of plasma proteins, resulting in an increase in the free levels of drugs that bind to plasma proteins. Increased cardiac output during pregnancy causes an increase in renal blood flow and glomerular filtration rate and decreases the half-life of drugs by causing rapid excretion.

It is possible to categorize the risk factors of anesthesia applied during pregnancy under the maternal and fetal risk factors heading. Aspiration pneumonia is one of the leading maternal risk factors. This is due to the prolonged gastric emptying time [9]. Another maternal risk factor is difficult airway and difficult intubation due to weight gain and upper airway edema. These complications were not encountered in the patients we scanned. However, the limited number of patients may be the reason for this. The most important of the fetal risk factors is the teratogenicity of anesthetic drugs. Although nitrous oxide has been shown to be teratogenic in animal experiments, there is no evidence that anesthetic drugs are teratogenic in humans [10]. Nevertheless, despite the fact that there are guidelines for the safe use of anesthetic drugs during pregnancy, there is no definitive evidence.

In the literature, the incidence of non-obstetric surgery needed during pregnancy was reported as 0.75%–2% [1]. The incidence of non-obstetric surgery was found to be 1.13% in our study. However, it is not exactly known whether non-obstetric surgery performed during pregnancy is associated with adverse events. Vujic et al. [11] and Cho et al. [12] reported in their study that non-obstetric surgery performed during pregnancy does not increase adverse events, and the procedures can be performed safely. On the other hand, in a study carried out with data on 6.5 million patients in the UK, it was shown that non-obstetric surgery increased the risk of low birth weight and preterm labor [3]. Nonetheless, risk factors of surgery or anesthesia were not analyzed in this study.

Appendectomy and cholecystectomy are the most common non-obstetric surgeries [13]. In our study, the most common indication for non-obstetric surgery was appendectomy, followed by double-J ureteral stenting. In their study, Vujic et al. [11] stated that 63% of the patients were operated on for acute appendicitis, 11% for adnexal mass, 5% for cholelithiasis, and 21% for other reasons. Cohen et al. [5] concluded in their meta-analysis of 54 studies that the most common non-obstetric surgery is acute appendectomy. Jenkins et al. [14] determined this rate as 34% ovarian mass and 16% appendectomy, but this result may be related to case selection and the fact that the hospital where the study was carried out was a branch hospital. The double-J ureteral stenting stood out in our study because it was not defined as non-obstetric surgery and was not included in many studies in the literature. However, since we applied sedation or general anesthesia and looked at the study from an anesthesia perspective, we included these patients. Another surgery frequently performed during pregnancy is cervical circulation, which is classified as obstetric. Yu et al. [15] stated in their study that the most common surgery performed during pregnancy was cervical circulation, with 33.12%. However, since cervical circulation was in the obstetric surgery group in our study and in the literature, it was not included in our studies. Nevertheless, the high incidence is again noteworthy.

When the studies in the literature were examined, Balinskaite et al. [3] stated that 55% of the patients who had non-obstetric surgery were multipara. However, no study in the literature, including this study, has evaluated parity as a risk factor. Although parity is not a statistical risk factor for complications in our study, it is significant that the rate is low in multiparous patients.

Cho et al. [12] and Jenkins et al. [14] also found that prolonged surgery was associated with increased adverse events. This was associated with longer exposure to anesthetic drugs and surgical stress. However, Vujic et al. reported that the mean duration of surgery was 50 minutes and did not increase the incidence of adverse events. In our study, the mean surgery duration was 70.4 minutes, which did not increase the risk of adverse events.

We observed that none of the anesthesia methods applied in our study independently increased the risk of complications. It was also observed that the most common anesthesia method was sedation. Patients who were sedated in the studies were either not included at all or included in the general anesthesia group. This situation may be associated with the low dose and anesthetic medication duration in sedation. Due to the retrospective and descriptive nature of the study, we found it correct to include the data of patients who underwent sedation in the study. Choosing the anesthesia method is very difficult for all clinicians. There is a perception that general anesthesia will increase these risks. Nevertheless, the data on this subject in the literature are extremely contradictory. Jenkins et al. [14] and

Devroe et al. [16] concluded in their study that general anesthesia increased adverse events. On the other hand, there are also studies that reached similar adverse event rates in the anesthesia methods [11,12,15].

Another difficulty in non-obstetric surgery is the timing of surgery. The American College of Obstetricians and Gynecologists Committee recommends postponing elective surgeries until after pregnancy; however, if the surgery cannot be postponed, it should be applied in the 2nd trimester [17]. In our study, the majority of surgeries were performed in the second trimester. It was observed that surgeries performed in all trimesters had similar adverse event rates. In the literature, it was observed that two studies examined the trimesters in which surgery was performed, and similar adverse event rates were obtained in all trimesters in those studies [14,16].

Limitations

Our study had limitations. The first of these is that we were only able to scan the data for the years 2015–2020. The reason for this is that the program regarding the database in our hospital has changed with the COVID-19 pandemic, and this program has not been integrated for analysis. Another limitation is that we could not access the data of patients who had non-obstetric surgery in our hospital yet had subsequent pregnancy follow-ups in another health center. This led to a decrease in the number of patients analyzed. Prospective observational studies planned in this field will make greater contributions to the literature.

Conclusion

Our study analyzed the surgical and anesthesia factors of non-obstetric surgery. It was concluded that neither surgical nor anesthetic factors independently increased the risk of preterm labor or low birth weight. However, these results alone cannot be sufficient due to the small size of the study group and the retrospective nature of the study. All of the studies in the literature were designed retrospectively. This is due to concerns about ethics and the sensitivity of the included patient group. Evaluating these studies in general, postponing elective surgery during pregnancy, performing the surgeries that cannot be postponed in the second trimester, keeping surgery and anesthesia duration short, and planning and applying the whole process by a multidisciplinary team are the prominent recommendations.

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J Surg Med. 2023;7(10):665-668.
DOI: 10.28982/josam.7991

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

The role of CYP2C9 gene polymorphism in rheumatoid arthritis

Hatice Yıldırım Yaroğlu [1], Ali Biçer [2]

[1] Department of Stem Cell and Regenerative Medicine, Institute of Health Science, Mersin University, Mersin, Turkey
[2] Department of Physical Therapy and Rehabilitation, Mersin University Faculty of Medicine, Mersin, Turkey

ORCID ID of the author(s)

HYY: 0000-0003-4866-313X
AB : 0000-0001-9783-0825

Corresponding Author
Hatice Yıldırım Yaroğlu
Mersin University Hospital Çiftlikköy Campus, Department of Stem Cell and Regenerative Medicine. Yenisehir, Mersin, Turkey
E-mail: haticeyildirim@mersin.edu.tr

Ethics Committee Approval
The study was approved by the Mersin University Clinical Research Ethics Committee (date: November 21, 2008 and no: 2008/111). 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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 10

Abstract

Background/Aim: The inflammatory disorder rheumatoid arthritis (RA) affects quality of life and worsens with symptoms in the extra-articular tissues and systemic joints. The most significant member of the Cytochrome P450 enzyme family, Cytochrome P450 2C9 (CYP2C9), plays an essential role in the alkylation, demethylation, and hydroxylation of a variety of substances. Insufficient studies as to whether the susceptibility to rheumatoid arthritis is genetic exists. Therefore, our study presents new information on whether CYPC9 is a genetic risk factor. In this study, we sought to determine whether rheumatoid arthritis and the CYP2C9 gene polymorphism are related.

Methods: This study was conducted as a prospective case-control study. Fifty patients with RA and 50 healthy individuals were included in our study group. Blood from the controls and patients was drawn into ethylenediaminetetraacetic acid (EDTA)-containing tubes, and using a DNA isolation kit, DNA was isolated from leukocytes. Real-time polymerase chain reaction (RT-PCR) was used to assess the genotypes of CYPC9*2 and CYP2C9*3 with the LightCycler-CYP2C9 mutation detection kit.

Results: The heterozygous CYP2C9*2 genotype was found to carry a 2.85-fold risk when compared with the controls (odds ratio [OR]=2.85, 95% confidence interval [CI]: 0.52–15.50; P=0.22); however, this risk was not statistically significant. It was found that people with the CYP2C9*3 heterozygous genotype had a statistically significant 2.79-fold higher risk compared to the controls (OR=2.79, 95% CI: 1.13–7.00 P=0.04).

Conclusion: The heterozygous genotype of CYP2C9*3 may contribute to the onset of RA.

Keywords: CYP2C9, polymorphism, rheumatoid arthritis

How to cite: Yıldırım Yaroğlu H, Biçer A. The role of CYP2C9 gene polymorphism in rheumatoid arthritis. J Surg Med. 2023;7(10):665-668.

Introduction

The prevalent systemic inflammatory autoimmune disease known as rheumatoid arthritis (RA) causes painful joint inflammation that produces a significant impact on the quality of a patient's life. RA patients are at greater risk for cancer, respiratory and cardiovascular diseases, osteoporosis, early mortality, and serious infections than found in the general population. RA is also defined as a disease that is affected by both genetic and environmental factors [1,2]. In recent years, close interactions between newly identified genes in RA, genetic factors, and epigenetic mechanisms have attracted attention. In addition, the effect of environmental factors on the progression of this disease and new mechanisms of the innate and adaptive immune system, which are thought to be effective in different phases of the disease, are also being investigated [1–3]. Based on epidemiological studies, it has been suggested that some hormonal events in addition to hereditary and environmental factors may contribute to RA onset. It is thought that concentrations of sex-specific steroid hormones and circulating immune complexes may contribute to the promotion of inflammatory responses in synovial fluid and cartilage. While only a small proportion of rheumatoid arthritis patients experience spontaneous remission, it is known that approximately 20% of the disease progresses chronically despite treatment [4,5].

The heme protein superfamily, known as cytochrome P450, catalyzes numerous and various processes, primarily hydroxylation. These cytochromes play an essential role in the oxidative metabolism of substances produced in the body naturally, such as steroids and fatty acids. They also take part in the oxidative metabolism of many other structural molecules, including exogenous substances, such as medicines, carcinogens, and environmental factors [6]. In distinct gene families and subfamilies, CYP genes are categorized based on commonalities in their sequences. The CYP2C gene subfamily consists of four genes and is arranged on chromosome 10q24 in a specific order: CYP2C8–CYP2C9–CYP2C19–CYP2C18, and around 82% of the amino acids in these follow the same pattern. The CYP2C9 gene, which has nine exons in total and a length of about 55 kb, encodes a protein of 490 amino acid residues. CYP2C9 has been found to have two widely distributed variant alleles, the CYP2C9*2 allele (R144C) and CYP2C9*3 allele (I359L), which cause a 30% and 80% decrease in enzymatic activities, respectively [7–9]. Other possible genes that may predispose a person to RA have not yet been identified even though the Human Leukocyte Antigen (HLA) system, in particular the HLA-DRB1 molecule, is crucial for the diagnosis of RA [10]. A central feature of RA is inflammation, and DNA and lipids are components of the inflammatory response. Inflammation produces reactive oxygen species (ROS) via oxidation, a process that leads to various cytotoxic products, including lipids, alkenes, and DNA hydroperoxides [11]. Evidence implicating ROS and its products has been identified in RA pathology. During hypoxia–reperfusion, phagocytes in the pannus and synovial fluid in addition to synovial endothelial cells produce ROS [11,12].

Individual differences are also important in the detoxification process of the products resulting from ROS activity. It is thought that polymorphism in enzymes, especially CYP2C9, that detoxify ROS and its products may also play a role in joint damage and functional deterioration [11–13]. Therefore, the purpose of this investigation was to ascertain how CYP2C9 polymorphism contributed to RA etiology.

Materials and methods

Study subjects

This study was conducted as a prospective case-control study. The research group consisted of 50 (18 men, 32 women) unrelated healthy individuals and 50 (18 men, 32 women) RA patients from Mersin University Hospital, Department of Physical Therapy and Rehabilitation. The control group consisted of individuals with no rheumatic illness or known comorbidities. Patients with infectious diseases, hematological, kidney, and/or liver diseases, and/or malignancies were excluded from the study.

G*Power 3.0.10 for Windows was used for power analysis. To detect a difference in the CYP2C9 polymorphism between the patient and control groups, at least 60 patients in each group are required with a Type I error of 0.05 and 80% power. Five subjects who did not meet the inclusion criteria and five subjects with no DNA sample available for analysis in both groups were excluded from the study. The Mersin University Clinical Research Ethics Committee granted approval for the current study in compliance with the requirements of the Declaration of Helsinki (Approval number: 2008/111, Date: November 21, 2008). After being made aware of the study's goals, all participants signed a consent form.

DNA isolation and genotyping

Peripheral blood was obtained and added to tubes with ethylenediaminetetraacetic acid (EDTA) for use in genetic analyses. DNA extraction was performed from circulating leukocytes by utilizing a highly pure polymerase chain reaction (PCR) template preparation kit (Roche Diagnostics, GmbH, Mannheim, Germany, catalog no: 1 796 828). Using a CYP2C9 mutation detection kit and real-time PCR (qPCR), the CYPC29*2 and CYP2C9*3 alleles were identified. (Roche Diagnostics GmbH, Mannheim, Germany; catalog number: 3113914).

A CYP2C9 reaction mixture containing a dNTP mix, DNA polymerase reaction buffer, enzyme solution (Taq polymerase), control template, hybridization probes 3 and 4, sterile H_2O, and CYP2C9 reaction mixture was used for PCR.

Statistical analysis

The distribution of CYP2C9 genotypes between the RA and control groups was assessed using a chi-squared test. By generating odds ratios (OR) and 95% confidence intervals (CI) from logistic regression models, the connection between CYP2C9 genotypes and RA patients was assessed. SPSS software demo version 20 was used to do all statistical calculations (IBM SPSS Inc. Free Download, Chicago, Illinois, USA). Every test was run with a significance threshold of 0.05.

Results

The study included 50 RA patients (32 females and 18 men) and 50 controls (32 females and 18 males). The mean (SD) age was 52.86 (8.00) in patients and 50.48 (8.92) in controls. Between the patients and the controls, no statistically significant age difference was found (P=0.21). In the patient, the frequency of the wild and heterozygous CYP2C9*2 genotypes was found to be 84% and 10%, respectively, while it was 96% and 4% in the controls. The prevalence of the CYP2C9*2 mutant genotype was 6%; however, the mutant genotype in the controls could not be identified, making it impossible to calculate the odds ratio (OR). The risk of RA was 2.85 times higher in people with the CYP2C9*2 heterozygous genotype (OR=2.85, 95% CI: 0.52–15.50 P=0.22) compared to the control; however, this higher risk was not statistically significant (Table 1). Wild and heterozygous CYP2C9*3 genotype frequencies in patients were 62% and 38%, respectively, whereas they were 82% and 18% in controls, respectively. The risk of RA was shown to be significantly higher in individuals with the CYP2C9*3 heterozygous genotype when compared with controls (OR=2.79, 95% CI: 1.13–7.00, P=0.04) as shown in Table 1. The patient and the CYP2C9*2 genotype did not show a significant correlation.

Table 1: CYP2C9 genotypes and risk of RA

Variable	Genotype	Patient n=50 n (%)	Control n=50 n (%)	OR (95% CI)*	*P*-value
CYP2C9*2	wild	42 (84)	48 (96)	1 (reference)	0.22
	heterozygote	5 (10)	2 (4.0)	2.85 (0.52–15.50)	
	mutant ‡	3 (6.0)	-	-	
CYP2C9*3	wild	31 (62)	41 (82)	1 (reference)	0.044
	heterozygote	19 (38)	9 (18)	2.79 (1.11–7.00)	

CYP2C9: Cytochrome P_{450} subtype, RA: rheumatoid arthritis, *OR: odds ratio, CI: confidence interval from logistic regression, ‡ Odds ratio cannot be calculated, wild alleles were used as references.

Discussion

It would be clinically beneficial to accurately target more appropriate therapy based on early and reliable identification of at-risk RA patients for poor long-term outcomes. Finding genetic indicators of clinical outcomes is therefore of tremendous interest [3,10]. According to studies, xenobiotic metabolizing enzymes including CYP, glutathione S-transferase (GST), and N-acetyltransferase 2 (NAT2) genes may affect the prevalence and course of RA [13]. An essential cytochrome P450 enzyme, known as cytochrome P450 2C9, is crucial for the oxidation of both xenobiotic and endogenous substances [14]. Due to an imbalance between the pro and antioxidant systems brought on by inherited deficits of this enzyme activity, excessive ROS might be produced. ROS are crucial mediators of inflammatory and immunological responses because they produce oxidative cellular damage *in vivo* [15]. RA pathophysiology includes the involvement of reactive oxygen species [16]. Patients with RA experience oxidative damage to joint lipids, DNA, and other cellular components [16–18]. Synovial phagocytes and synovial superoxide can be made by chondrocytes and endothelial cells [14–19]. In several studies, RA and xenobiotic metabolizing enzymes have been linked to deletion polymorphism of glutathione S- transferase mu 1 (GSTM1), which is thought to increase vulnerability to RA, according to Morinobu and colleagues [20]. CYP1A1 4887A appears to help inhibit the emergence of RA according to a study by Yen et al. [21]. Pawlik et al. [22] suggest that polymorphism of NAT2 may be a hereditary risk factor for joint injury. They discovered that the probability of getting RA was 4.39 times higher in slowvNAT2 acetylators than in rapid acetylators. However, no research on the relationship between CYP2C9 gene polymorphisms and RA is available. The candidate gene development study shows that the existence of single nucleotide polymorphism (SNPs) or haplotypes for estrogen receptors 1 and 2 (ESR1 and ESR2, respectively), CYP1B1, CYP2C9, low-affinity immunoglobulin gamma Fc region IIIA (FcR3A), and sex-hormone binding globulin (SHBG) affects the probability of developing bone erosion in RA. This research also proves that genotyping of hormone-related SNPs can help accurately predict the course of disease in seropositive patients and that the influence of most SNPs or haplotypes is dependent on the rheumatoid factor (RF) status [5]. A case-control study was conducted to determine whether 47 possibly functional SNPs in 16 genes related to steroid hormones are connected to the prevalence of RA and the responsiveness to anti-tumor necrosis factor (TNF) medication. That study demonstrated how the CYP2C9 SNP 1799853 affects the body's reaction to anti-TNF medications and drugs that block the effects of estrogen. Exonic variant CYP2C9 rs1799853 modifies the amino acid sequence, lowers the enzyme's activity, and subsequently seems to slow down the metabolism of some medicines. The response to anti-TNF medications is therefore believed to be related to the CYP2C9 gene. It is currently unclear whether the gene's impact on drug response is directly caused by flaws in the metabolism of anti-TNF medications or, alternatively, whether it is caused by variations in the metabolism of steroid hormones [23]. Our findings imply that genes implicated in protection from oxidative stress may have an impact on the RA disease process. In our analysis, the CYP2C9*2 genotype was not linked to a higher risk of contracting RA. However, heterozygous CYP2C9*3 individuals with the genotype were shown to have a 2.79 times higher risk of developing RA. Therefore, it is hypothesized that CYP2C9*3 will act as a catalyst for the onset of RA.

Limitations

The main limitation of our study is the small number of participants, which should be supplemented by larger investigations. Despite these limitations, this study is still an important preliminary study and forms the basis for future studies.

Conclusion

In conclusion, it is possible that genetic polymorphisms in xenobiotic metabolizing enzymes have a role in the progression of the disease by influencing food and environmental factors. An evaluation of the literature indicates that this study is the first to describe the connection between CYP2C9 polymorphism and RA. The incidence of CYP2C9 polymorphisms in RA patients and whether they represent an essential risk factor for the onset of RA require further research in larger populations.

Acknowledgements

We would like to thank Prof. Dr. Lülüfer Tamer and Prof. Dr. Lokman Ayaz for contributions to the study.

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J Surg Med. 2023;7(10):669-672.
DOI: 10.28982/josam.7983

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

High-risk human papillomavirus infection prevalence in non-malignant tonsillar tissue: A single-center cross-sectional study

Gul Bayram [1], Tugce Simsek [2], Selin Hazir [1], Fatma Zeynep Ozen [3], Mehmet Mustafa Erdogan [4], Sinan Seyhan [4], Hasan Kazaz [5], Erkan Tezcan [6]

[1] Mersin University, Vocational School of Health Services, Mersin, Turkey
[2] Department of Otorhinolaryngology and Head and Neck Surgery, Private Clinic, İstanbul, Turkey
[3] Department of Medical Pathology, Amasya University Sabuncuoglu Serefeddin Training and Research Hospital, Amasya, Turkey
[4] Department of Otorhinolaryngology and Head and Neck Surgery, Amasya University Sabuncuoglu Serefeddin Training and Research Hospital, Amasya, Turkey
[5] Department of Otorhinolaryngology and Head and Neck Surgery, Trabzon Kanuni Training and Research Hospital, Trabzon, Turkey
[6] Department of Otorhinolaryngology and Head and Neck Surgery, Çanakkale Onsekiz Mart University Medical Faculty Hospital, Çanakkale, Turkey

ORCID ID of the author(s)

GB: 0000-0002-4154-8596
TS: 0000-0002-1425-8833
SH: 0000-0002-0714-5929
FZO: 0000-0003-2468-8375
MME: 0000-0001-9955-0704
SS: 0000-0002-8993-8008
HK: 0000-0002-7889-2315
ET: 0000-0003-1413-1266

Corresponding Author
Gul Bayram
Mersin University, Vocational School of Health Services, Mersin, Turkey
E-mail: gulbayram78@gmail.com

Ethics Committee Approval
The study was approved by the Amasya University Clinical Research Ethics Committee at April 4, 2019 numbered 19.
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.

Financial Disclosure
This research was funded by Amasya University reseaarch foundation; number FMB_BAP_19_0401.

Published
2023 October 11

Abstract

Background/Aim: The prevalence of human papillomavirus (HPV) in non-malignant tonsils can vary according to geographical location, age group, and risk factors. Some studies have found a relatively low prevalence of HPV, while other studies have found higher rates in non-malignant tonsils. The presence of HPV in non-malignant tonsils may be associated with precursor lesions that have the potential to develop into cancer. The aim of the current study was to detect the prevalence of HPV and p16 (one of the HPV types) in non-malignant tonsils and determine the existence of HPV in tonsil tissue using molecular and histological techniques.
Methods: One hundred-three samples from non-malignant tonsils and one sample from squamous cell carcinoma of the tonsils were analyzed for the prevalence of HPV using molecular and histological methods. Real-time polymerase chain reaction (qPCR) was performed to detect HPV in the tissue samples.
Results: HPV was not found in any tissue specimens based on histopathological and p16 immunohistochemical evaluations. HPV was not detected in all tissue samples using reverse transcriptase quantitative polymerase chain reaction (RT-qPCR).
Conclusions: In our study of one hundred and four patients, HPV and p16 were not genetically detected in the tonsils that underwent surgery for reasons other than cancer. Hence, more comprehensive studies can contribute to evaluating the relationship between benign tonsil tissue and HPV infection, potentially leading to improved diagnostic and preventative measures.

Keywords: papillomavirus, HPV type 16, non-malignant tonsil, real-time PCR, high-risk human papillomavirus

How to cite: Bayram G, Simsek T, Hazır S, Ozen FZ, Erdogan MM, Seyhan S, Kazaz H, Tezcan H. High-risk human papillomavirus infection prevalence in non-malignant tonsillar tissue: A single-center cross-sectional study. J Surg Med. 2023;7(10):669-672.

Introduction

The incidence of head and neck squamous cell carcinoma (HNSCC) is a significant global health concern. HNSCC is reported to affect nearly 600,000 people each year [1]. While tobacco and alcohol use have been reported as major risk factors for HNSCC, a significant shift in the epidemiology of these cancers has occurred, especially tonsil SCC, in developed countries. In many developed nations, a substantial proportion of tonsil SCC cases have been found to now be associated with high-risk human papillomavirus (HPV) infection, particularly the HPV type 16 [2,3]. Despite significant research on HPV-associated oropharyngeal squamous cell carcinoma (OPSCC), relatively little information is available about the natural history and timeline of oropharyngeal HPV infections. Understanding the progression of HPV infection in the oropharynx is a complex and challenging area of study [4]. Detection of HPV-related oropharyngeal precancerous lesions is crucial for early detection and intervention, but this situation presents challenges that require the development of effective assessment procedures [4, 5]. The low prevalence of HPV in non-malignant (benign) tonsils means that the presence of HPV in tonsils without cancer is relatively uncommon. In patients who test positive for HPV, especially high-risk types, such as HPV-16, higher incidences of malignant (cancerous) tonsils have been found. This finding suggests that HPV-positive individuals present a greater risk of developing tonsil cancer. It is essential to find precursors or early signs of HPV-related tonsillar cancer. This step is crucial because detection of these precursors can lead to early intervention and improved outcomes in addition to the HPV vaccination, which can lead to a reduction in the risk of HPV-related cancers, including tonsillar cancer [6]. Until now, high-risk HPV is a well-known cause of cervical cancer, and efforts have been made to raise awareness about this relationship. However, current studies highlight the increasing incidence of oropharyngeal cancer [7].

The current study aimed to detect the prevalence of high-risk HPV and p16 in non-malignant tonsils and to analyze the presence of HPV in tonsillar tissue using molecular and histological techniques.

Materials and methods

Clinical specimen collection

The current study was designed as a retrospective case series. It was a single-center, retrospective cross-sectional study. Tonsil samples from 104 patients who underwent tonsillectomy between 2005 and 2020 at Amasya University Medical Faculty Hospital were included in the study. Of the 104 patients included in the study, 30 (28.8%) were women and 74 (71.2%) were men. The mean age of patients was 22.5 years. Tissue samples of the patients were stored in paraffin blocks. One hundred-three non-malignant tonsil samples and one tonsillar squamous cell carcinoma sample were examined for HPV prevalence using molecular and histological methods.

DNA isolation

A QIAamp DNA FFPE Tissue Kit (Germany) was used to extract genomic CapitalBio NanoQ drop (China). All isolated DNA samples were stored at −20 °C.

Real-time PCR

Real-time polymerase chain reaction (qPCR) was performed for the detection of HPV in tissue samples. The PCR reaction was prepared using the Gp5 + / 6 + primer pair and 1 × SYBR Green PCR master mix (QIAGEN) with a final concentration of 25 µl [8,9]. RT-PCR reaction was performed with positive and negative controls.

The beta-globin gene primers/probe were previously described by de Araujo et al. [8]. Isolated DNA samples were evaluated by amplification of the -globin gene as an internal control for DNA adequacy.

Histological evaluation of tonsillar tissues

One-half tonsil from each patient was fixed, embedded in paraffin, and examined using hematoxylin and eosin (H&E) staining to confirm benign non-neoplastic tonsillar histology.

p16 Immunohistochemistry

Four micrometer-thick serial tissue sections from formalin-fixed paraffin-embedded blocks were cut and mounted on poly-L-lysine coated glass slides. After deparaffinization and rehydration, heat-induced antigen retrieval was performed using citrate buffer (pH 6 at 100 °C for 20 min). Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide for 10 min, and the sections were blocked for 10 min with 1.5% normal goat serum (NGS) (Invitrogen, 50062Z) diluted in phosphate-buffered saline (PBS, pH 7.4) before incubation with primary antibody. Tissue sections were incubated in a humidified chamber with primary monoclonal anti-p16 antibody (BD Pharmingen, Clone G175-405), which was diluted 1:20 with 1.5% NGS and 0.1 % Triton-X in PBS overnight at 4 °C. After the incubation period and three washes with PBS, sections were incubated with biotinylated secondary antibody and streptavidin peroxidase reagent (Abcam, USA) for 10 min. To visualize immunostaining, the sections were incubated with 3,3'-diaminobenzidine tetrahydrochloride chromogen solution (DAB). Sections were counterstained with Mayer's hematoxylin and mounted on a mounting medium. Negative control slides were incubated with PBS instead of primary antibody. p16-positive tonsil cancer was used for positive control. All tissue sections were evaluated under a light microscope (Olympus BX51), and results based on immunohistochemistry were evaluated after the examination of tissue sections by two investigators.

Statistical analysis

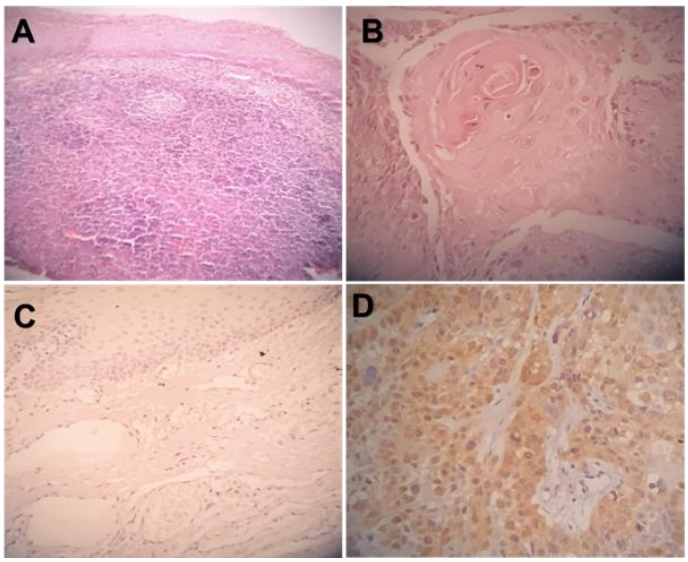
HPV prevalence is defined as percentages and 95% confidence intervals (95% CI), which were calculated according to the binomial distribution. Age and sex-adjusted ratios (PR) and 95% CI prevalence were calculated based on selected patients' characteristics using binomial regression models with a log link.

Results

HPV was not detected in all tissue samples based on qPCR. Also, HPV was not detected on histopathological slides. Histopathological and p16 immunohistochemical evaluation, archival non-malignant tonsillar tissues were analyzed for histopathological evaluation using H&E staining (Figure 1). p16 is a tumor suppressor protein that is a surrogate marker for HPV infection. Diffuse strong nuclear and cytoplasmic

immunostaining were not observed in the 105 non-malignant tonsillar tissues (Figure 1).

Fig.1. Hematoxylin- eosin staining of non-malignant tonsil (A), malignant tonsil (B) tissues. Imumunohistochemical expression of p16 protein was not seen in non-malignant tonsil (C), positive control (D).



Discussion

The existence of HPV in non-malignant tonsils is often referred to as asymptomatic and is not included in the etiology of tonsillar hypertrophy or chronic tonsillitis. Hence, HPV prevalence in tonsillectomy patients is thought to reflect that of the general population. The prevalence of high-risk HPV infection in the tonsil is ≤ 1%; thus, oropharyngeal HPV-related cancer will develop in a small proportion of infected patients [6].

It has been reported that HPV infections (oral and oropharyngeal) are transmitted sexually and non-sexually [10]. Several studies have demonstrated that individuals with a history of numerous sexual partners causes a higher risk of acquiring HPV infection in the oropharynx. HPV-16 has been found to be a major causative factor for oropharyngeal SCC and it is often transmitted through sexual activity, including oral sex [1,11]. However, the relationship between sexual behavior and the existence of benign HPV in the tonsils is unclear. One study reported that most patients with HPV infection (4 out of 5 people) were young adults who had recent sexually transmitted infections. Yet, tonsil HPV infections have been reported in children in previous studies [12]. In contrast to high-risk cervical HPV infections, researchers deduced that a high proportion of tonsillar high-risk HPV infections could lead to cancer [13]. Tonsillar HPV prevalence rates were reported to be between 0% and 12% in previous studies involving only children or adults [14,15]. Researchers reported high-risk HPV based on PCR in two (1%) of 195 malignant tonsils. Furthermore, fluorescence *in situ* hybridization (FISH) analysis could not detect oncogenic HPV 16 and 18 in PCR-positive samples [16]. The absence or low number of HPV-positive cases in benign tonsillar diseases has also been shown in previous studies [17–19]. Another study detected HPV rates of 12.5% (high-risk HPV) and 15% (low-risk HPV) in benign tonsillar tissue from adults and children in Belgium [20]. Besides this precancerous HPV-16 type was not detected in any of the 104 patients, and the presence of HPV in tonsil tissue samples was not detected using both molecular analysis techniques (reverse transcriptase quantitative polymerase chain reaction [RT-qPCR] and nested PCR) in our study.

Another study showed that the HPV DNA rate decreased from childhood (11.5%) to middle age and old age (2.4%) [12]. Cervical HPV infection incidence increases just after the sexually active period at 20-24 years of age and then declines [21]. However, oral HPV infection incidence is almost equally distributed in all age groups [22]. The way in which rare HPV infections behave tonsil tissue is also shown by the fact that none of the 511 frozen homogenized tonsil samples taken during the mad cow disease epidemic in the UK in the 1990s to investigate prion diseases were HPV-positive [13]. Fakhry et al. [23] reported the prevalence of HPV-16 as 4.7% in 401 HIV-positive tonsil brushing samples. Consistent with previously published SPLIT findings, no association was found between HPV16 and evidence of cytological dysplasia among HIV-positive persons [23]. The largest population-based study of mouthwashes to date reported the prevalence of HPV 6.9% for any HPV type and 1.0% for HPV-16 [4].

The reticular squamous epithelium of the tonsils is more susceptible to HPV infection than other anatomical regions of the upper respiratory tract, possibly due to its porous structure and lack of structural integrity. In an HPV-positive tonsil tumor, patients typically have cervical lymph node metastases at presentation, although the primary tumor is usually small [24]. The low rate of HPV infection in benign tonsils and difficulties in detecting premalignant lesions resembling cervical intraepithelial neoplasia can be explained by the fact that HPV infection is confined to a very small area deep within the tonsils. Dysplastic tonsillar epithelium with high-risk HPV could be a leading lesion in tonsillar carcinogenesis. Researchers reported high-risk HPV in only five of 477 patients who underwent tonsillectomy for chronic tonsillitis or tonsillar hypertrophy [6]. In a study at Helsinki University, oncogenic HPV-16 was detected in 6.3% (13 out of 206) of benign tonsil samples scanned by PCR. Also, of these 13 HPV-positive cases, 11 were detected in patients who were < 26 years of age [12].

Numerous studies have shown that individuals with HPV-associated oropharyngeal squamous cell carcinomas (SCCs) tend to have a more favorable prognosis. They often experience better treatment responses and longer survival rates compared to those with non-HPV-associated oropharyngeal SCCs. While the prognostic significance of HPV in oropharyngeal cancers is well-established, its role in cancers of the sino-nasal tract (the nasal cavity and paranasal sinuses) and nasopharynx is an area of active research. It's important to enlighten whether HPV has a similar prognostic significance in cancers of the sino-nasal tract and nasopharynx. Researchers have found evidence to support the idea that individuals with virus-related diseases have better overall and disease-specific survival rates compared to other groups. However, to fully understand the implications and significance of these findings, more context and details about specific studies are needed [25,26]. In addition to this evidence, it was found that HPV-positive patients had higher survival rates, although the differences in overall survival between patients with HPV-positive and HPV-negative sino-nasal SCC were not statistically

significant [27]. However, due to the limited number of patients and the heterogeneity of tumor type and treatment modalities, no definite conclusions can be drawn about the prognostic value of HPV in sino-nasal tract carcinomas [28].

Conclusion

It is important to note that the detection of HPV in non-malignant tonsils does not necessarily indicate the presence of cancer. However, this finding underscores the importance of understanding the role of HPV in oropharyngeal health and the potential risk factors for oropharyngeal cancer. In our study consisting of one hundred and four patients, genetically HPV and p16, one of the HPV types, were not detected in the tonsils operated for reasons other than cancer. Regular medical monitoring and HPV vaccination can be important preventive measures. As a result, it is suggested that more comprehensive studies will contribute to the relationship between benign tonsil tissue and HPV.

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J Surg Med. 2023;7(10):673-677.
DOI: 10.28982/josam.7953

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Evaluation of carotid artery Doppler measurements in late-onset fetal growth restriction: a cross-sectional study

Gökçe Naz Küçükbaş [1], Yasemin Doğan [2]

[1] Department of Obstetrics and Gynecology, Maternal-Fetal Unit, Kocaeli City Hospital, Kocaeli, Turkey
[2] Department of Obstetrics and Gynecology, Maternal-Fetal Unit, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

ORCID ID of the author(s)

GNK: 0000-0002-2755-3700
YD: 0000-0002-2614-4411

Corresponding Author
Gökçe Naz Küçükbaş
Department of Obstetrics and Gynecology, Kocaeli City Hospital, Tavşantepe Neighborhood, Akif Street No: 63, 41060, Kocaeli, Turkey
E-mail: nazkuc@gmail.com

Ethics Committee Approval
The study was approved by the Kocaeli Derince Education and Research Ethics Committee (Date: May 26, 2022, Decision No: 2022-046). 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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 12

Abstract

Background/Aim: It has been reported that both the internal carotid artery (ICA) and the common carotid artery (CCA) are associated with hypoxia, also observed in late-onset fetal growth restriction (FGR). However, it has not yet been investigated whether these Doppler measurements differ in cases of late-onset FGR. This study evaluated the ICA and the CCA Doppler parameters in late-onset FGR fetuses and compared these measurements with those of healthy fetuses.

Methods: This cross-sectional observational study comprised 75 singleton pregnancies diagnosed with late-onset FGR between the 32nd and 37th weeks of gestation, alongside 75 healthy fetuses paired 1:1 based on obstetric history and gestational age between June 2022 and May 2023. The Delphi consensus of 2016 was used for the definition of late-onset FGR. The exclusion criteria were congenital anomalies, presence of any additional disease, maternal body mass index over 35 kg/m^2, abdominal scars hindering ultrasound visualization, use of medications such as antenatal steroids, sympathomimetics, and indomethacin that affect vascular function, drug use, smoking during pregnancy, concurrent preeclampsia, and multiple pregnancies. Upon the patients' admission to the hospital, their demographic characteristics were documented, and ultrasonographic examinations and Doppler measurements were subsequently performed. The Doppler velocimetry of the umbilical artery (UA) encompassed measurements of the systolic to diastolic ratio (S/D), pulsatility index (PI), and peak systolic velocity (PSV). The carotid artery Doppler velocimetry of the middle cerebral artery (MCA), ICA, and CCA encompassed measurements of the PI, resistance index (RI), and PSV. We assessed the diagnostic performance of Doppler measurements for late-onset FGR through receiver operating characteristic (ROC) analysis.

Results: In the late-onset FGR group, the mean UA-SD was higher (2.7 [0.6] *vs.* 2.5 [0.5], *P*=0.006), and the mean UA-PI (0.8 [0.2] *vs.* 0.9 [0.2], *P*=0.011) and mean PSV (35.6 [8.2] *vs.* 41.1 [7.1], *P*<0.001) were lower compared to the control group. In the late-onset FGR group, carotid Doppler measurements were more pronounced than UA Doppler measurements. Moreover, ICA Doppler measurements exhibited superior diagnostic performance in predicting late-onset FGR compared to other Doppler measurements (Area under the curve [AUC]=0.777, *P*<0.001 for ICA-PI; AUC=0.751, *P*<0.001 for ICA-RI; AUC=0.749, *P*<0.001 for ICA-PSV).

Conclusion: In fetuses with late-onset FGR, UA Doppler measurements showed minimal differences compared to healthy fetuses, but differences in carotid Doppler measurements, especially in the ICA, were more pronounced. Therefore, in the management of fetuses suspected of having late-onset FGR, a more detailed Doppler examination might be required.

Keywords: carotid artery, Doppler measurements, fetal growth restriction, umbilical artery

How to cite: Küçükbaş GN, Doğan Y. Evaluation of carotid artery Doppler measurements in late-onset fetal growth restriction: a cross-sectional study. J Surg Med. 2023;7(10):673-677.

Introduction

Fetal growth restriction (FGR), also referred to as intrauterine growth restriction, is a pathological state in which the fetus is unable to attain its innate genetic growth potential [1]. This condition affects up to 10% of pregnancies and is the second most common cause of infant morbidity and mortality after premature birth [2]. The pathogenesis of FGR can be attributed to maternal, fetal, placental, and genetic factors. However, a predominant underlying mechanism is compromised uteroplacental perfusion, leading to suboptimal fetal nutrition and subsequent FGR [3,4].

FGR is commonly classified into early-onset FGR, occurring before the 32nd week of pregnancy, and late-onset FGR, taking place after. In cases of early-onset FGR, umbilical artery (UA) blood flow serves as the clinical benchmark for detection and management [5,6]. However, this metric often presents as normal in late-onset FGR cases [7], emphasizing the necessity for a more accurate predictor of late-onset FGR. A study assessing structurally smaller fetuses with normal UA values identified decreased impedance levels in the middle cerebral artery (MCA) [8]. On the contrary, the vasodilation brought about by hypoxia leads to an increase in placental vascular resistance and a decrease in cerebral resistance, ultimately resulting in a reduction of the cerebroplacental ratio (CPR). This ratio is calculated by dividing the MCA-pulsatility index (PI) by the UA-PI [9]. Moreover, both MCA and CPR have been associated with adverse perinatal outcomes and poor neurodevelopment [10-12].

The MCA, which facilitates blood flow to the cerebrum, is the larger terminal branch of the internal carotid artery (ICA), which originates from the common carotid artery (CCA) and perfuses intracranial structures such as the brain and eyes [13]. Additionally, it has been reported that both the ICA and the CCA are associated with hypoxia [14,15], also observed in late-onset FGR [7]. Given the aforementioned rationales, we postulated that Doppler measurements of both the CCA and ICA could differ in late-onset FGR cases. This study aims to assess the Doppler parameters of the CCA and ICA in fetuses with late-onset FGR and compare these measurements with those of fetuses without growth restriction.

Materials and methods

This cross-sectional observational study was conducted on pregnancies having follow-ups at the Kocaeli Derince Education and Research Hospital Perinatology Clinic between June 2022 and May 2023. The study received approval from the Ethical Committee of Kocaeli Derince Education and Research Hospital (Approval Date/Number: May 26, 2022/046). The present study adhered to the ethical regulations and principles stipulated in the Declaration of Helsinki. Prior to their involvement in the study, informed consent was obtained from all participants. In a previous study, the FGR group was found to have a lower mean UA-PI than the control groups (1.27 [0.64] *vs.* 1.02 [0.29], *P*<0.001, respectively) [16]. Considering the differences in means mentioned in this study, a minimum sample size of 69 for each group was determined using G*Power v3.1 software, with a 5% alpha error probability and 90% power [17]. The sample size formula was as follows: $N = 2 \times [(Z_{1-\alpha/2} + Z_{1-\beta}) / ES]^2$, where the standard normal deviation for $\alpha = Z_\alpha = 1.96$, and the standard normal deviation for $\beta = Z_\beta = 1.28$. ES is the effect size, defined as $ES = |\mu_1-\mu_2|/\sigma$, where $|\mu 1 - \mu 2|$ is the absolute value of the difference in means between the two groups and σ is the standard deviation of the outcome of interest [18].

Study population

A total of 132 pregnant women complicated by late-onset FGR between the 32nd and 37th weeks of gestation were evaluated based on eligibility criteria. The inclusion criteria were patients diagnosed with late-onset FGR between the 32nd and 37th weeks of gestation according to the 2016 Delphi consensus [6]. The exclusion criteria were congenital anomalies, presence of any additional disease, maternal body mass index over 35 kg/m^2, abdominal scars hindering ultrasound visualization, use of medications such as antenatal steroids, sympathomimetics, and indomethacin that affect vascular function, drug use, smoking during pregnancy, concurrent preeclampsia, and multiple pregnancies. After this exclusion process, 75 singleton pregnancies complicated with late-onset FGR between the 32nd and 37th weeks of gestation were included in the study. The control group comprised pregnant women who delivered at term without any additional diseases and were matched 1:1 in terms of gestational age and obstetric histories such as gravida, parity, living, and abortion with late-onset FGR.

Study protocol

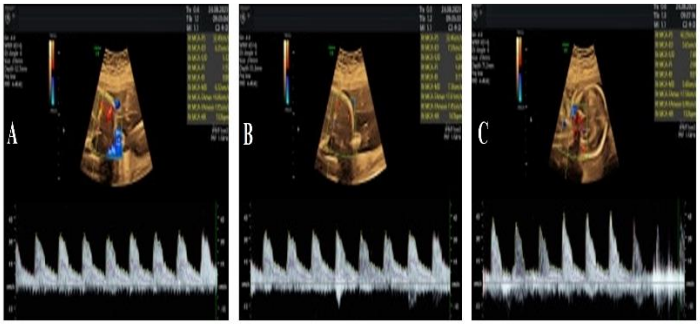
Upon the patients' admission to the hospital, their demographic characteristics such as gravida, parity, living, and abortion were documented, and subsequently, ultrasonographic examinations such as biparietal diameter, head circumference, abdominal circumference (AC), femur length, estimated fetal weight (EFW), and mean amniotic fluid index (mAFI), and Doppler measurements were performed. The Delphi consensus of 2016 was used for the definition of late-onset FGR [6]. The diagnosis of late-onset FGR was established when the AC or EFW was below the 3rd percentile at or beyond 32 weeks of gestation. In cases where the EFW or AC ranges between the 3rd and 10th percentiles, at least one abnormal Doppler finding (UA-PI > 95th percentile, CPR < 5th percentile) or AC/EFW crossing centiles by more than two quartiles on growth charts was regarded as late-onset FGR [6].

Ultrasonographic evaluation

Two experienced maternal-fetal medicine experts carried out the ultrasound evaluation. A 2–9 MHz convex transducer from the Voluson E6 (General Electric, USA) was used for the procedure. The Hadlock I formula was employed to calculate the EFW. Fetuses in the control group had an EFW between the 10th and 90th percentiles, while those in the late-onset FGR group had an EFW below the 10th percentile. The amniotic fluid index was noted. A vertical measurement of the deepest amniotic fluid pockets of four quadrants using midline and umbilicus was obtained in millimeters. The amniotic index of each pregnancy was obtained by summing the vertical measurement of amniotic pockets of the four quadrants [19]. Throughout the ultrasound examination, the thermal and mechanical indices were maintained at levels below 1.0 mW/cm^2. Gestational age was confirmed using first-trimester crown-rump length in all cases.

The Doppler velocimetry of the UA encompassed measurements of the systolic to diastolic ratio (S/D), PI, and PSV [20]. The Doppler velocimetry of the MCA (Figure 1A), ICA (Figure 1B), and CCA (Figure 1C) encompassed measurements of the PI, resistance index (RI), and PSV. These measurements were automatically determined by the sonographic device based on the following formulas: S/D ratio = systolic/diastolic ratio, RI = (systolic velocity - diastolic velocity) / systolic velocity, PI = (systolic velocity - diastolic velocity) / mean velocity, MCA-CPR = MCA-PI / UA-PI, ICA-CPR = ICA-PI / UA-PI, and CCA-CPR = CCA-PI / UA-PI. The highest systolic velocity of the waveform was defined as PSV in cm/s^2. The insonation angle was kept below 30 degrees during pulsed wave Doppler to ensure accurate measurements [21].

Figure 1: Middle cerebral artery (A), internal (B), and common (C) carotid artery flow by pulsed-wave Doppler ultrasonography examination.



Doppler positioning was at the proximal one-third of the MCA, in line with the circle of Willis, on an axial section of the fetal cranium. The ICA waveform was captured at the point where it bifurcates into the middle and anterior cerebral arteries on the axial plane [22]. The waveform for the CCA was captured at the neck region at the parasagittal plane, specifically recording from the left CCA. For each measurement, the sample gate was set to 2 mm, and no interference from nearby vessels was recorded [23]. Doppler velocimetry of the UA was conducted on the free loops of the umbilical cord, examining the spectral pattern for flow pattern. Reference ranges for UA Doppler were sourced from https://www.perinatology.com/calculators/umbilicalartery.htm Instances of absent or reverse end-diastolic flow were noted. Doppler waveform recordings were not taken during fetal breathing or movements. Waveforms were visualized on the screen, and if they appeared uniform, three consecutive waves were used for calculations [22]. For each Doppler measurement, intraobserver and interobserver variability had an intraclass correlation coefficient ranging from 0.83 to 0.95 [24].

Statistical analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean and standard deviation (SD) values, while non-normally distributed variables are presented as median (25th–75th quartile) values. For comparisons between groups, the Student T-test and Mann-Whitney U test were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance. Threshold values were determined by the Youden index method. A comparison of the area under the curves (AUC) was performed with a nonparametric approach using the theory of generalized U-statistics to generate an estimated covariance matrix previously reported by DeLong et al. [25]. Significance was accepted at *P*-value <0.05 (*) for all statistical analyses.

Results

The distribution of gravida, parity, and gestational week was comparable between the late-onset FGR group and the control group (*P*=0.954, *P*=0.950, *P*=0.911, respectively). The late-onset FGR group displayed lower mean values for biometric measurements, including biparietal diameter (34.7 [1.1] vs. 33.6 [1.6], *P*<0.001), head circumference, AC, and EFW in comparison to the control group, as presented in Table 1.

Table 1: Demographic and clinical characteristics of the groups.

Variables	Control n=75	Late-onset FGR n=75	*P*-value
Gravida	1 (1–2)	1 (1–2)	0.954
Parity	0 (0–1)	0 (0–1)	0.950
Abortion	0	0	0.999
Living	0 (0-1)	0 (0-1)	0.852
Gestational week	34.7 (1.1)	34.8 (1.5)	0.911
Biparietal diameter, weeks	35.1 (1.1)	33.6 (1.6)	<0.001
Head circumference, weeks	35.3 (1.6)	34.0 (1.9)	<0.001
Abdominal circumference, weeks	35.0 (1.3)	32.0 (1.3)	<0.001
Femur length, weeks	34.9 (1.0)	32.9 (1.8)	<0.001
Estimated fetal weight, g	2451.4 (275.1)	2054.7 (286.8)	<0.001
mAFI, mm	63.5 (13.1)	61.1 (12.7)	0.257

Data are shown as mean (SD) or median (25th-75th quartile) or number and percentage (%). mAFI: mean amniotic fluid index, FGR: fetal growth restriction

In the group with late-onset FGR, the mean UA-SD was found to be higher (2.7 [0.6] *vs*. 2.5 [0.5], *P*=0.006), while the mean UA-PI (0.8 [0.2] *vs*. 0.9 [0.2], *P*=0.011) and the mean UA-PSV (35.6 [8.2] *vs*. 41.1 [7.1], *P*<0.001) were lower when compared to the control group. The Doppler measurements of MCA, ICA, and CCA showed lower PI and PSV levels in the late-onset FGR group (*P*<0.001, *P*<0.001, respectively), while the RI levels were higher (*P*<0.001). However, the differences were more pronounced in ICA Doppler measurements, as shown in Table 2.

Table 2: Comparison of Doppler measurements between the control group and late-onset fetal growth restriction groups.

Variables	Control n=75	Late-onset FGR n=75	*P*-value
Umbilical artery			
Systolic to diastolic ratio	2.5 (0.5)	2.7 (0.6)	0.006
Pulsatility index	0.9 (0.2)	0.8 (0.2)	0.011
Peak systolic velocity	41.1 (7.1)	35.6 (8.2)	<0.001
Middle cerebral artery			
Pulsatility index	4.6 (1.4)	4.2 (0.7)	0.021
Resistance index	1.3 (0.2)	1.5 (0.3)	<0.001
Peak systolic velocity	57.2 (17.5)	47.4 (10.9)	<0.001
Internal carotid artery			
Pulsatility index	5.5 (1.6)	4.0 (1.7)	<0.001
Resistance index	1.4 (0.5)	1.9 (0.5)	<0.001
Peak systolic velocity	53.4 (18.8)	38.7 (10.8)	<0.001
Common carotid artery			
Pulsatility index	4.1 (1.5)	3.6 (1.4)	0.028
Resistance index	1.2 (0.3)	1.4 (0.6)	0.037
Peak systolic velocity	41.4 (14.0)	36.6 (10.2)	0.018
Cerebroplacental ratio			
Middle cerebral artery	4.6 (4.2–6.3)	3.8 (3.4–5.4)	0.025
Internal carotid artery	6.0 (4.3–7.2)	4.1 (2.7–6.0)	0.002
Common carotid artery	4.5 (3.1–6.3)	3.3 (2.8–5.7)	0.044

Data are shown as mean (SD) or median (25th–75th quartile) or number and percentage (%). FGR: fetal growth restriction

The median MCA-CPR (3.8 *vs*. 4.6, *P*=0.025), ICA-CPR (4.1 *vs*. 6.0, *P*=0.002), and CCA-CPR (3.3 *vs*. 4.5, *P*=0.044) levels were higher in the late-onset FGR group compared to the control group (Table 2). The comprehensive analysis of the diagnostic efficacy of Doppler indices in predicting late-onset

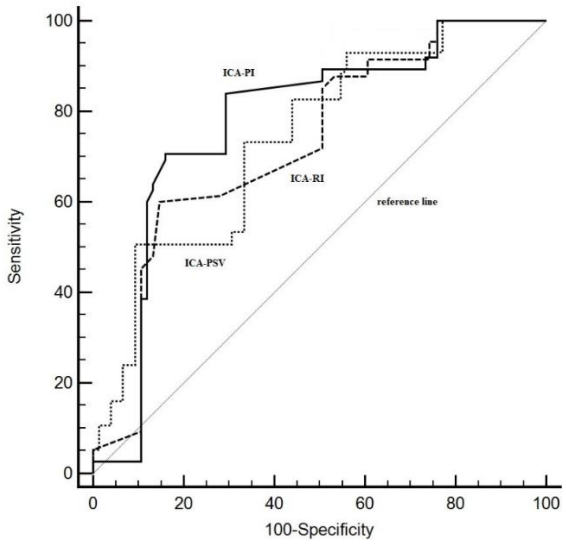
FGR is elaborated in Table 3. Accordingly, ICA Doppler measurements had superior diagnostic performance compared to other Doppler indices (AUC=0.777, *P*<0.001 for ICA-PI; AUC=0.751, *P*<0.001 for ICA-RI; AUC=0.749, *P*<0.001 for ICA-PSV). On the other hand, ICA-PI displayed a superior diagnostic performance compared to ICA-RI (difference between AUC=0.026, *P*=0.047) and ICA-PSV (difference between AUC=0.028, *P*=0.045) (Figure 2).

Table 3: Diagnostic performance of Doppler indices in predicting late-onset fetal growth restriction.

Variables	AUC (SE)	Sensitivity (%)	Specificity (%)	Cut-off value	*P*-value
Umbilical artery					
Systolic to diastolic ratio	0.615 (0.05)	77.3	34.7	>2.2	0.010
Pulsatility index	0.609 (0.05)	28.0	96.0	<1.0	0.015
Peak systolic velocity	0.692 (0.05)	58.7	93.3	≤36.0 cm/s	<0.001
Middle cerebral artery					
Pulsatility index	0.596 (0.05)	90.6	12.0	<5.0	0.025
Resistance index	0.693 (0.05)	86.7	62.7	>1.4	<0.001
Peak systolic velocity	0.650 (0.05)	80.0	64.0	≤55.0 cm/s	0.002
Internal carotid artery					
Pulsatility index	0.777 (0.04)	84.0	70.7	<3.9	<0.001
Resistance index	0.751 (0.04)	87.5	47.2	>1.5	<0.001
Peak systolic velocity	0.749 (0.04)	82.4	57.2	≤37.2 cm/s	<0.001
Common carotid artery					
Pulsatility index	0.622 (0.05)	50.7	77.3	<3.7	0.034
Resistance index	0.595 (0.05)	46.7	77.3	>1.3	0.044
Peak systolic velocity	0.608 (0.05)	69.3	62.7	≤39.5 cm/s	0.034
Cerebroplacental ratio					
Middle cerebral artery	0.605 (0.05)	38.7	85.3	≤3.9	0.036
Internal carotid artery	0.681 (0.05)	69.3	64.0	<4.7	0.001
Common carotid artery	0.586 (0.05)	77.3	49.3	<3.5	0.049

AUC: area under the curve, SE: standard error

Figure 2: Diagnostic performance of internal carotid artery Doppler indices in predicting late-onset fetal growth restriction.



ICA: internal carotid artery, PI: pulsatility index, RI: resistance index, PSV: peak systolic velocity

Discussion

To the best of our knowledge, this is the first study in the present literature that assesses the association between Doppler indices derived from four distinct arteries and late-onset FGR. The Doppler acquired from each artery revealed a significant difference in the late-onset FGR group compared to the control group. However, the ICA Doppler indices demonstrated a better diagnostic performance in predicting late-onset FGR than the Doppler indices from other arteries.

Ultrasound-based assessment of fetal weight is the most fundamental morphometric test used for FGR detection and diagnosis [26]. A reduced umbilical venous blood flow results in decreased blood flow to the liver. This leads to a reduction in AC and an increase in resistance in the UA. As the pathological condition progresses, a loss of end-diastolic flow or reverse flow is observed in the UA [27]. However, in cases of late-onset FGR, the UA Doppler might appear normal, indicating a less severe placental dysfunction [7]. The UA is straightforward to examine, while various physiological elements can alter UA Doppler indices. As the fetal heart rate decelerates, the prolonged cardiac cycle makes the diastolic flow rate approach the zero line more closely. This can lead to an increase in the S/D ratio. Besides, fetal breathing can induce similar alterations by extending the cardiac cycle and rendering the spectral curve irregular [28]. In this study, all Doppler measurements were carried out exclusively during times without any fetal heart rate abnormalities, breathing, or movement to negate the impacts of these factors.

Fetuses affected by late-onset FGR have been observed to exhibit elevated values of UA-SD and reduced UA-PSV compared to the control group. However, the diagnostic performance of these parameters in predicting FGR was lower. In a retrospective cohort study that investigated pregnancies impacted by late-onset FGR, an abnormal UA-SD ratio was reported in 23% of the infants [29]. These findings indicate that fetuses with late-onset FGR often exhibit normal UA Doppler measurements. Despite normal UA Doppler findings, MCA has been shown to be independently associated with late-onset FGR [30]. However, an advanced brain vasodilation indicative of chronic hypoxia, as indicated by an MCA-PI < 5th percentile, can be observed in 25% of late-onset FGR [31]. A previous study, which encompassed FGR, SGA, and AGA infants, indicated that the indices of UA-PI and MCA-PI were similar among the groups, while the UA-PSV levels were lower in infants diagnosed with late-onset FGR [8]. Contrary to these findings, there are studies reporting that both UA and MCA indices are associated with late-onset FGR [32,33]. Discrepancies between studies highlight the need to assess different Doppler measurements or their combinations in predicting late-onset FGR.

The MCA-CPR can significantly enhance the sensitivity of both UA and MCA alone, as heightened placental impedance in the UA typically coincides with decreased cerebral resistance in the MCA [34]. In uncomplicated pregnancies, the diastolic phase of the pulse waveform in cerebral arteries is consistently lower than that in umbilical arteries, irrespective of the gestational age. This ensures that the resistance in cerebral vessels is greater than that in the placental vessels, making the MCA-CPR exceed 1. However, in pathological pregnancies, when the blood flow distribution favors the brain, the MCA-CPR drops below 1 [35]. In the current study, the values of MCA-CPR were observed to be lower in the group with late-onset FGR than in the control group. Additionally, 7.8% of late-onset FGR fetuses had an MCA-CPR below 1. However, some studies have reported that the MCA-CPR has a low or insignificant diagnostic performance in distinguishing late-onset FGR fetuses from the SGA or the control group [8,36]. On the other hand, the link between late-onset FGR and hypoxia might cause discrepancies in Doppler readings from systemic arteries that supply the MCA [37,38]. However, we could not find any research that comprehensively evaluates both ICA and CCA Doppler indices in cases of late-onset FGR. In our study, PI and PSV levels in

both ICA and CCA Doppler measurements were observed to be lower in the late-onset FGR group, while RI levels were higher. Additionally, the levels of ICA-CPR were also lower in the late-onset FGR group. Moreover, while ICA Doppler indices had comparable diagnostic performance in differentiating late-onset FGR, they exhibited superior diagnostic performance compared to Doppler indices from other vessels. These findings suggest that changes in the ICA might offer an early indication of late-onset FGR before changes in the MCA become clinically apparent.

Limitations

This study has several significant limitations. Firstly, the Doppler indices' sequential alterations throughout the course of pregnancy, from diagnosis to delivery, were not evaluated. Secondly, distinguishing between SGA and late-onset FGR fetuses is clinically challenging, and groups with SGA were not included in this study. Therefore, this study does not depict the variances in Doppler measurements between late-onset FGR and SGA. Lastly, as this cross-sectional study evaluated pregnancies between 32 and 37 weeks of gestation, it is imperative to assess the clinical implications of these observations in terms of prognosis and management. There is a need for future large-scale prospective studies that include control groups when analyzing SGA, late-onset FGR, differences in carotid Doppler measurements, and their relationship with maternal and fetal outcomes.

Conclusion

This preliminary study highlights significant alterations in the hemodynamics of the carotid arteries in fetuses affected by late-onset FGR. Notably, Doppler indices of ICA and CCA such as PI, PSV, and CPR, exhibit a decrease, while RI displays an increase within this particular group, indicating the presence of cerebral vasodilation. Furthermore, the ICA demonstrates better diagnostic efficacy when compared to the CCA. This suggests that changes in the ICA may be more reflective of cerebral blood flow alterations, making it a more reliable measurement in fetuses with late-onset FGR. Nevertheless, larger-scale research is needed to validate these findings and to determine how to implement these results in routine clinical practice. By better understanding the cerebral hemodynamic changes associated with late-onset FGR, healthcare professionals can intervene earlier and potentially improve outcomes for the fetus.

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J Surg Med. 2023;7(10):678-681.
DOI: 10.28982/josam.7965

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Two-dimensional vs. three-dimensional vision during the laparoscopic radical prostatectomy: A matched comparison of operative and long-term functional outcomes

Yavuz Bastug [1], Serdar Aykan [2]

[1] Department of Urology, University of Health Sciences, Haydarpasa Numune Training & Research Hospital, Istanbul, Turkey
[2] Department of Urology, Memorial Bahcelievler Hospital, Istanbul, Turkey

ORCID ID of the author(s)

YB: 0000-0002-9256-940X
SA: 0000-0001-8963-6811

Corresponding Author
Yavuz Bastug
Department of Urology, University of Health Sciences, Haydarpasa Numune Training & Research Hospital, Tıbbiye Cad, No:23, 34668, Uskudar/Istanbul, Turkey
E-mail: yavuzbastug@gmail.com

Ethics Committee Approval
The study was approved by the institutional review board of Bagcilar Training and Research Hospital (Approval date and ID: May 6, 2010 and 2010-23).
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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 13

Abstract

Background/Aim: The three-dimensional (3D) display system can solve essential problems in conventional laparoscopic radical prostatectomy (LRP), like depth perception and spatial orientation. Several studies reported initial comparisons of LRP with 2D and 3D vision systems in terms of operative outcomes, with 3D systems coming out on top. However, there are few published comparison studies on the long-term outcomes of LRP with 2D and 3D vision systems. In this regard, we aimed to compare operative and long-term functional results of 3D-High definition (HD) LRP with conventional two-dimensional (2D)-HD display systems.

Methods: A total of 115 cases that underwent LRP between October 2010 and December 2016 were prospectively evaluated, and a prospective cohort study was conducted. Inclusion criteria at baseline were as follows: age at surgery <75 yr, prostate-specific antigen (PSA) concentration <20 ng/ml, clinical tumor stage <T4, no diagnosis of metastatic disease, and informed consent to participate in the study. Patients who underwent salvage treatments after LRP and patients with incomplete follow-up were excluded. The patients were divided into groups, Group 1 (n=72) and Group 2 (n=43), according to the display systems used, 2D-HD vs. 3D-HD during LRP. Demographic data, operative and postoperative, and long-term follow-up outcomes were recorded. Additionally, urinary continence rate determined with a patient questionnaire and erectile functions determined with the International Index of Erectile Function (IIEF) questionnaire were recorded. All obtained parameters were compared between the groups using the independent t-test and the chi-square test. Differences were considered significant at two-sided $P<0.05$ and 95% confidence interval.

Results: All patients completed a 24-month follow-up procedure. The groups were similar in age, serum PSA level, prostate volume, preoperative Gleason score, and cancer-positive core number. There were significantly better results in group 2 than in group 1 for operative parameters, catheterization time, and hospital stay ($P<0.001$, for all parameters). At long-term follow-up, the urinary continence rate was significantly higher in group 2 than in group 1 ($P=0.023$). Similarly, significantly higher IIEF scores were determined in the group 2 ($P<0.001$).

Conclusion: Our results suggest that using a 3D-HD display system during LRP provides much better long-term functional and operative outcomes and may provide a cheap and equal alternative to the RARP procedure.

Keywords: outcome assessment, prostatectomy, laparoscopy, three-dimensional image

How to cite: Bastug Y, Aykan S. Two-dimensional vs. three-dimensional vision during the laparoscopic radical prostatectomy: A matched comparison of operative and long-term functional outcomes. J Surg Med. 2023;7(10):678-681.

Introduction

Prostate cancer (PCa) is the most common malignancy and the fifth leading cause of cancer-related death in men worldwide [1]. The surgical treatment of choice for patients with early-stage PCa is radical prostatectomy (RP), which has been shown to reduce mortality [2]. Throughout the modern history of RP, three significant techniques—open retropubic RP (RRP), laparoscopic RP (LRP), and robot-assisted RP (RARP)—have been used as standard operative approaches [3]. Today, laparoscopic and robotic approaches have primarily taken over open radical prostatectomy. However, laparoscopy has many limitations, and a steep learning curve is required for the surgeon. These shortcomings have led to the concept that robots may improve the precision and accuracy of anatomical dissection by offering enhanced freedom and easy maneuverability, thereby improving overall outcomes [4]. However, the high cost of RARP is a severe barrier. As a result, RARP was not extensively adopted right away, and a less expensive version is still needed [5]. Specific enhancements to conventional LRP were made to provide high-definition (HD) vision in order to acquire a less expensive alternative to RARP, such as three-dimensional (3D) vision systems with articulating laparoscopic hand devices [6]. The 3D display system can solve essential problems in conventional LRP, like depth perception and spatial orientation [7]. Several authors and we previously published initial comparisons of LRP with 2D and 3D vision systems regarding operative outcomes, with 3D systems coming out on top [8,9]. However, to our knowledge, there are few published comparison studies on the long-term and long-term functional outcomes of LRP with 2D and 3D vision systems. In the present study, we aimed to investigate the long-term functional outcomes of LRP with a 3D vision system (HD Viking Systems, La Jolla, CA) by comparing it with a conventional 2D-HD (Karl Storz, Tuttlingen, Germany) display system.

Materials and methods

Patient selection and data collection

A prospective cohort study was performed to investigate the outcomes of patients who underwent LRP between October 2010 and December 2016. The study was conducted according to STROBE guidelines following the Helsinki Declaration principles, Ethical committee approval, and informed consent by those participating.

Inclusion criteria at baseline were as follows: age at surgery <75 yr, prostate-specific antigen (PSA) concentration <20 ng/ml, clinical tumor stage <T4, no diagnosis of metastatic disease, and informed consent to participate in the study. Patients who underwent salvage treatments after LRP and patients with incomplete follow-up were excluded. All LRP procedures were performed by a single experienced surgeon (S.A.). The patients were divided into groups, Group 1 (n=72) and Group 2 (n=43), according to the LRP procedure using 2D-HD and 3D-HD vision systems, respectively. The study groups were created by a non-random method. However, they matched the comparison method where participants in each group are assigned so that they are similar in patient demographics and characteristics such as age, body mass index (BMI), serum PSA level, prostate volume, pathological Gleason score on biopsy, and cancer positive biopsy core numbers. Clinical data were collected preoperatively and at regular follow-up visits postoperatively. Patient-reported outcomes, including functional outcomes, were collected using validated questionnaires. Operative and postoperative parameters, including operative time, vesicourethral anastomosis time, estimated blood loss, length of hospital stay, and urethral catheterization, were noted. Pathological data included prostate specimen weight, tumor stage according to the 2002 tumor-node-metastasis classifications, pathologic Gleason score, and presence of positive surgical margins were also determined and noted.

Functional outcome and follow-up

After LRP, patients were followed up at 1-month intervals for the first three months following surgery, then at 3-month intervals for five years. Follow-up examinations included measurement of PSA levels and a DRE, computed tomography scan, magnetic resonance imaging, or bone scintigraphy in the event of suspected disease recurrence. The continence and erectile functions were the essential parts of functional outcomes. Incontinence was measured using the question, “How often do you change a pad, diaper, or sanitary aid during a typical day (24 h)?” Continence was defined as "completely dry" or using only one safety pad in a day, and using more than one protective pad was classified as incontinence. Erectile functions were determined using International Index of Erectile Function (IIEF) questionnaires before and after the surgery. If the score was lower than 11, the patient was defined as having erectile dysfunction.

Statistical analysis

We determined the minimum number of participants required using G*power version 3.1.9.2 data analysis software (Department of Cognitive and Industrial Psychology, Heinrich Heine Universität, Düsseldorf, Germany). The alpha level (the probability of detecting a significant difference) and power were considered 0.05 and 0.75, respectively, in determining the sample size. According to the initial power analysis, we determined the minimum sample size in each group as 40. The IBM Statistical Package for the Social Sciences (SPSS) for MAC 21.0 (IBM, Armonk, New York, NY) was used for statistical analysis. Data distributions and normality tests were evaluated with the Shapiro–Wilk test. Descriptive statistic methods were used to evaluate data, including mean (SD) and median (interquartile range). We compared the normally distributed data between the groups using the independent t-test. The chi-square test was also used to compare the nonparametric categorical variables. Differences were considered significant at two-sided P <0.05 and 95% confidence interval.

Results

Patients, follow-up and preoperative and operative data

A total of 115 patients were included in the study. The mean age, BMI, serum PSA level, prostate volume, preoperative Gleason score, and cancer-positive core number at biopsy results were 63.65 (8.41) years, 30.33 (5.32) kg/m^2, 8.76 (6.15) ng/mL, 55.34 (23.30) mL, 6.13 (1.0) and 3.83 (2.10), respectively. All patients completed a 24-month follow-up procedure, finally.

Patient demographics and clinical data between the groups are provided in Table 1. The groups were similar in age, serum PSA level, prostate volume, preoperative Gleason score, and cancer-positive core number.

Table 1: Preoperative data of the groups.

Parameters	Group 1 (n=72) Mean (SD)	Group 2 (n=43) Mean (SD)	*P*-value
Age, year	64.4 (5.59	62.4 (5.6)	0.07*
BMI, kg/m^2	30.3 (3.2)	30.4 (2.3)	0.09*
PSA, ng/Ml	9.1 (5.9)	8.2 (5.8)	0.28*
Biopsy Gleason Score	6.1 (0.6)	6.2 (0.5)	0.27*
Positive biopsy specimen, n,	3.8 (2.6)	3.9 (2.0)	0.75*
Prostate volume, mL	55.2 (24.7)	55.6 (17.6)	0.93*

BMI: Body mass index, PSA: Prostate specific antigen, SD: Standard deviation, *: Independent t test.

The mean operative time, vesicourethral anastomosis procedure time, estimated blood loss, hospital stay, and duration of urethral catheter time were 166.46 (28.15) min., 65.07 (14.12) min., 117.26 (31.56) mL, 5.43 (0.92) days and 17.70 (1.90) days. Statistically significant better results were noted for Group 2 than Group 1 in terms of operative time, estimated blood loss, catheterization time, hospital stay, and vesicourethral anastomosis procedure time (P<0.001 for all) (Table 2).

Table 2: Comparison of operative data of groups.

Parameters	Group 1 (n=72) Mean (SD)	Group 2 (n=43) Mean (SD)	*P*-value
Operative time, min	189 (29.81)	128.72 (15.7)	<0.001*
Vesicourethral anastomosis time, min	87.43 (16.8)	27.65 (6.68)	<0.001*
Estimated blood loss, mL	138.54 (31.88)	81.63 (33.47)	<0.001*
Hospital stay, day	6 (1)	4.49 (0.869)	<0.001*
Duration of catheter, day	20.53 (1.97)	12.98 (2.43)	<0.001*

SD: Standard deviation, *: Independent t test.

Most patients had pathological T2 and T3 disease (87 and 24 patients, respectively). Pathologically, T1 and T4 diseases were reported only for three patients and one patient, respectively. Positive surgical margin was reported in 15 patients (13.04%) after LRP. The distribution of pathological tumor stage, pathological Gleason score, and positive surgical margin status rate were comparable in both groups (Table 3).

Table 3: Pathological data of the groups.

Parameters		Group 1 (n=72) Mean (SD)	Group 2 (n=43) Mean (SD)	*P*-value
Pathological prostatic tissue volume, mL		59.62 (26.16)	53.83 (19.36)	0.13*
Pathological carcinomatous tissue volume, mL		16.64 (12.11)	13 (9.21)	0.09*
Pathological Gleason score		6.81 (0.69)	6.81 (0.85)	0.95*
Pathological stage		**n (%)**	**n (%)**	***P*-value**
	T1c	-	3 (6.9%)	0.06#
	T2a	2 (2.7%)	6 (13.9%)	
	T2b	9 (12.5%)	4 (9.3%)	
	T2c	43 (59.7%)	23 (53.4%)	
	T3a	11 (15.2%)	6 (13.9%)	
	T3b	5 (6.9%)	1 (2.3%)	
	T3c	1 (1.3%)	-	
	T4	1 (1.3%)	-	
Positive surgical margin		11 (15.2%)	4 (9.3%)	0.35#

SD: Standard deviation, *: Independent t test, #: Chi-square test.

Functional outcomes

Postoperative urinary continence status and erectile function parameters of the patients are provided in Tables 4 and 5 for each follow-up visit. The numbers of patients who reported early continence was higher in Group 2 (53.5%) than in Group 1 (26.4%) at postoperative three months (P=0.003). At the final follow-up on postoperative 24th months, the rate of the continent patients was significantly higher in Group 1 (93.1%) compared to Group 2 (76.4%) (P=0.02). There were comparable IIEF scores for both groups in the preoperative period. Patients in Group 2 had significantly higher IIEF scores than those in Group 1 during the entire follow-up period after LRP (P<0.001, for all). Among the 43 patients, 20 (46.5%) had successful sexual intercourse at the end of 1st year after LRP in group 1. On the other hand, the successful sexual intercourse rate was only 7 (9.7%) patients in group 2 (P<0.001). The complication rates were comparable for groups.

Table 4: Urinary continence status of the patients between the groups during the follow up.

Follow up periods	Group 1 (n=72)	Group 2 (n=43)	*P*-value
3 month			
Continent patients, n (%)	19 (26.4%)	23 (53.5%)	0.003*
Incontinent patients, n (%)	53 (73.6%)	20 (46.5%)	
6 month			
Continent patients, n (%)	40 (55.6%)	34 (79.1%)	0.01*
Incontinent patients, n (%)	32 (44.4%)	9 (20.9%)	
9 month			
Continent patients, n (%)	45 (62.5%)	37 (86.1%)	0.007*
Incontinent patients, n (%)	27 (37.5%)	6 (13.9%)	
12 month			
Continent patients, n (%)	53 (73.7%)	39 (90.7%)	0.02*
Incontinent patients, n (%)	19 (26.3%)	4 (9.3%)	
24 month			
Continent patients, n (%)	55 (76.4%)	40 (93.1%)	0.02*
Incontinent patients, n (%)	17 (23.6%)	3 (6.9%)	

*Chi-square test.

Table 5: IIEF scores of the patients between the groups during the follow-up.

Parameters	Group 1 (n=72)	Group 2 (n=43)	*P*-value
Preoperative IIEF score, Mean (SD)	13.4 (5.8)	15.14 (6.9)	0.15
IIEF score at 3th month, Mean (SD)	5.68 (1.9)	8.07 (4.1)	<0.001*
IIEF score at 6th month, Mean (SD)	6.22 (2.7)	9.86 (5.5)	<0.001*
IIEF score at 12th month, Mean (SD)	6.22 (2.99	10.7 (6.5)	<0.001*
IIEF score at 24th month, Mean (SD)	6 (2.8)	8.94 (6)	<0.001*

IIEF: International Index of Erectile Function, SD: Standard deviation, *: Independent t test.

Discussion

It is essential to achieve cancer control with minimal complications and a short convalescence period with preservation of continence and potency after RP [10]. This way, minimally invasive surgical procedures such as RARP and LRP could successfully provide these [11]. However, while LRP has the benefits of minimally invasive surgery, the loss of depth awareness caused by 2D vision systems is a drawback in traditional laparoscopic surgery [12]. The next-generation 3D display systems bridged the gap between traditional 2D and robotic technologies. Several publications revealed the extraordinary progress made in using 3D vision systems during LRP in recent years [13-16]. However, most of them described their short-term findings and outcomes [8]. The present study is the first to provide long-term outcomes of a 3D display LRP procedure with more than a year of follow-up. Our results showed that long-term functional outcomes were much better for LRP with 3D display systems than for LRP with 2D display systems. In addition, LRP, with a 3D display system, improved operative data. However, oncologic outcomes were similar in both groups.

On the other hand, better oncologic outcomes may be provided with a 3D visualization system in LRP in the future with longer-term follow-up. These superior functional data may be related to the unsurpassed display characteristics of 3D vision. Previously, Becker et al. [17] reported the favorable effects of 3D display systems on depth perception and spatial orientation. Enhanced spherical optics can improve the surgeon's spatial perception and hand-eye coordination during surgery [18]. Thus, better dissection, grasping skills, and suturing can enhance optimal surgical performance. In our view, improved operative and perioperative circumstances influence the functional outcomes of LRP, and improved functional outcomes directly influence early recovery after the operation [19]. Further studies

on this issue are needed to present the superior effects of 3D-HD display systems on LRP.

Several previous series showed better early results with 3D LRP than 2D LRP [6]. To compare long-term outcomes, Bove et al. [20] investigated their cases' 3D LRP and 2D LRP results. They published superior overall pentafecta rates of 62.7% and 67% in 2D and 3D LRP at 12 months after surgery. Our recent findings were similar to those of previous reports. However, in the present study, we showed the beneficial effects of LRP with 3D display at 24 months follow-up. We showed that in addition to better surgical outcomes, 3D vision positively affects functional outcomes that build up over time.

Limitations and/or strengths

The study has some limitations. First, the number of patients in the groups is small and unequal. This was due to uncompleted follow-up visits for some patients. The second limitation is that the results include 24-month follow-up data. More extended follow-up data with high numbers of patients might have provided more accurate results of LRP with a 3D display system. However, this is the first study prospectively conducted and introduced long-term better functional results of LRP with 3D system in selected patients. The critical strength of the present study was the matched comparison method, where participants in each group are assigned as similar in patient demographics and characteristics to reduce potential sources of bias.

Conclusions

The present study demonstrated the positive effects of a 3D vision system on long-term functional outcomes of LRP, besides better surgical outcomes. Our results suggest that using more advanced technology on vision systems could provide much better outcomes after LRP in the future, and it may provide a cheap and equal alternative to the RARP procedure. In the future, using more advanced technology on vision systems could provide much better results for the LRP procedure. LRP with a 3D display system and advanced instruments may also be a less expensive alternative to RARP in selected patients.

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J Surg Med. 2023;7(10):682-689.
DOI: 10.28982/josam.7967

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Exploring praxia deficits in bipolar disorder: A cross-sectional analysis of functionality and quality of life

İpek Özönder Ünal

Department of Psychiatry, Tuzla State Hospital, Tuzla, İstanbul, Turkey

ORCID ID of the author(s)

İÖÜ: 0000-0003-3509-0061

Corresponding Author
İpek Özönder Ünal
Department of Psychiatry, Istanbul Tuzla State Hospital, Içmeler Mahallesi, Piri Reis Caddesi, No: 74 Tuzla / İstanbul, Turkey
E-mail: ipekozonder@gmail.com

Ethics Committee Approval
The study was approved by the Ethics Committee of Istanbul Bilgi University, Turkey (protocol code 2023-40162-033 and date of approval February 21, 2023).
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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 13

Abstract

Background/Aim: Patients with bipolar disorder often experience praxia deficits, which might impede their functionality and quality of life. This study sought to delve into praxis defects in these patients, contrasting their praxia performance with healthy controls and illuminating the interrelation between praxia performance, functionality, and quality of life.

Methods: In this cross-sectional study conducted from February to July 2023, we enrolled 203 patients diagnosed with bipolar disorder 1. Participants were recruited from the Ibni Sina and Sifa Community Mental Health Centers, both of which are affiliated with the Istanbul Tuzla State Hospital. Additionally, 201 healthy controls (HC) were recruited, primarily from the friends and relatives of the hospital staff. Patients diagnosed with bipolar disorder 1, between 18 and 65 years of age, were included based on their diagnosis as determined by the Structured Clinical Interview for DSM-5 Clinical Version (SCID-5-CV). Their right-handedness was ascertained via the Edinburgh Handedness Inventory. To minimize the confounding effects of acute mood episodes on praxia deficits, patients were required to score below 5 on the Young Mania Rating Scale (YMRS) and 7 or lower on the 17-item Hamilton Depression Rating Scale (HDRS). This criterion ensured the exclusion of individuals experiencing an active mood episode. Additionally, participants needed to have been in remission for at least six months. Healthy controls, aged 18-65 and confirmed as right-handed, were included, provided they had no personal or familial history of psychiatric conditions. A detailed interview using SCID-5-CV confirmed that the healthy controls had no history or suspicion of bipolar disorder (BD) or any other psychiatric disorder and no relatives with a psychiatric disorder. All participants (203 bipolar disorder patients and 201 healthy controls) underwent evaluations using the Test for Upper Limb Apraxia (TULIA), while the bipolar cohort received the Global Functioning Assessment-Functioning (GAF-F) and the World Health Organization Quality of Life-Brief Version (WHOQOL-BREF). Statistical analyses were conducted using SPSS 22.0.

Results: We identified a critical TULIA score threshold of 217, which differentiates bipolar patients from healthy individuals with a sensitivity of 79.3% and a specificity of 77.1% (area under the curve (AUC) 0.799, $P<0.001$). TULIA scores in bipolar patients were significantly positively correlated with functionality (GAF-F; r=0.502, $P<0.001$) and quality of life-general health (WHOQOL; r=0.389, $P<0.001$). TULIA pantomime subscores (OR=0.92, 95% CI 0.86-0.99, $P=0.022$) and CPZ use of more than 250mg per day (OR=2.24, 95% CI 1.19-4.21, $P=0.012$) were independent predictors of impairment in functioning in bipolar patients.

Conclusion: Praxia deficits in bipolar disorder patients may be intricately tied to specific clinical features that influence both their functionality and life quality. Comprehensive praxia deficit assessments can pave the way for devising tailored interventions, enhancing praxia and, by extension, the quality of life of bipolar patients.

Keywords: apraxia, bipolar disorder, functioning, occupational therapy, quality of life

How to cite: Özönder Ünal İ. Exploring praxia deficits in bipolar disorder: A cross-sectional analysis of functionality and quality of life. J Surg Med. 2023;7(10):682-689.

Introduction

Bipolar disorder (BD) is a chronic condition characterized by cycles of mania, hypomania, and depression, profoundly impacting patients' quality of life, cognition, and socio-occupational functioning [1]. Despite interventions, following the first manic episode, only about one-third of BD patients regain functionality within a year. A significant proportion (30-60%) find it challenging to return to their former socio-occupational status, underscoring the early onset of functional impairment in BD [2]. Effective management of depressive episodes is pivotal in maintaining functionality and preventing the worsening of manic episodes [3-6]. Contemporary therapeutic approaches emphasize not only symptom alleviation but also the restoration of normal functionality to help BD patients lead a meaningful life [4]. Enhanced well-being is linked with a decreased risk of relapse, pushing researchers and clinicians to value functional recovery alongside clinical remission [5].

Praxia refers to the ability to execute or carry out learned purposeful movements. Despite having the desire and physical ability to perform the movements, this is not always possible for BD patients. It is a neurological condition, distinct from muscle weakness, paralysis, or motor coordination issues. In the realm of psychiatry, the study of praxia and its associated deficits has garnered significant interest, especially given its emerging relevance in disorders like schizophrenia. Nearly half of schizophrenia patients display praxia deficits, affecting upper limb movement patterns such as timing, sequence, and spatial configuration [7-9]. Praxia deficits in these patients have been linked to decreased functionality [10]. While motor deficits in schizophrenia are often attributed to treatments, untreated schizophrenia patients also display signs of parkinsonism and minor neurological symptoms. Notably, reduced motor skills have been detected in those at high risk for psychosis or with a family history of schizophrenia [11].

As we delve deeper into the realms of praxia performance, it is vital to dissect the intricate functionalities governed by praxis into more precise categories: namely, imitation and pantomime performances, each further subdivided into non-symbolic, intransitive, and transitive actions. Imitation involves the replication of observed actions, a skill that is indispensable in learning and executing routine tasks efficiently. Pantomime, on the other hand, entails the symbolic representation of actions without the involvement of objects, a facet pivotal in non-verbal communication and the smooth navigation of social contexts. Breaking it down further, non-symbolic actions are characterized by gestures devoid of a direct reference. Intransitive actions involve movements not directed toward an object but they bear a specific meaning, while transitive actions involve interactions with objects to convey meaning. These distinct yet intertwined realms of praxis performance embed themselves in everyday functionalities, governing a range of actions from basic self-care routines to complex occupational tasks. A deficit in any of these subcategories could potentially disrupt the fluidity of daily activities, rendering seemingly straightforward tasks cumbersome and impeding effective communication. Therefore, a nuanced understanding of praxia performance is not merely academic; it bears substantial implications for daily functioning and thereby the quality of life for individuals with bipolar disorder, delineating avenues for targeted therapeutic interventions that can foster enhanced daily living and well-being [7-9].

Given the shared spectrum of BD and schizophrenia in the DSM-5, coupled with their significant overlaps, it becomes imperative to explore praxia deficits noted in schizophrenia within the BD demographic. Although in-depth studies specifically focusing on praxia performance in BD are limited [12], there is a growing body of research that suggests areas of proximate concern. Notably, potential disturbances in frontal-executive functions have been observed during hypomanic phases, and there are indications of slight cognitive impairments during euthymic periods in BD patients. While these findings do not directly imply praxia deficits, they inhabit a closely related research domain, hinting at overlapping neuropsychological facets. It is also worth noting that medications, particularly antipsychotics and mood stabilizers, might influence these observations, given that some are known to induce motor side effects [13].

Consequently, this study embarks on a cross-sectional investigation of praxia deficits in BD patients, contrasting their outcomes with healthy controls. Furthermore, it delves into the relationship between praxia deficits, functionality, and quality of life. We hypothesize a discernible decline in praxis performance in BD patients relative to controls and posit that this deterioration correlates with diminished functionality and life quality in the BD cohort.

Materials and methods

Study design and participants

In this cross-sectional study, we enrolled 203 patients diagnosed with bipolar disorder 1 from the Ibni Sina and Sifa Community Mental Health Centers, affiliated with the Istanbul Tuzla State Hospital. Additionally, 201 healthy controls (HC) were recruited, primarily from friends and relatives of the hospital staff.

Patients diagnosed with bipolar disorder 1, aged between 18-65, were included based on their diagnosis as determined by the Structured Clinical Interview for DSM-5 Clinical Version (SCID-5-CV). Their right-handedness was ascertained via the Edinburgh Handedness Inventory. To minimize the confounding effects of acute mood episodes on praxia deficits, patients were required to score below 5 on the Young Mania Rating Scale (YMRS) and 7 or lower on the 17-item Hamilton Depression Rating Scale (HDRS). This criterion ensured the exclusion of individuals experiencing an active mood episode. Additionally, participants needed to have been in remission for at least six months. Healthy controls, aged 18-65 and confirmed as right-handed, were included, provided they had no personal or familial history of psychiatric conditions. A detailed interview using SCID-5-CV confirmed that the healthy controls had no history or suspicion of BD or any other psychiatric disorder and no relatives with a psychiatric disorder.

The exclusion criteria for all participants included illiteracy, pregnancy, lactation, substance abuse, specific

neurological conditions, recent head trauma, motor abnormalities, recent electroconvulsive treatments, certain organic mental disorders, and the inability to provide informed consent. Additionally, any patient with coexisting psychiatric disorders was excluded from the study.

Data collection

Over the span from February to July 2023, every patient who sought care at the Community Mental Health Centers was evaluated as a potential participant for the study, ensuring an unbiased, consecutive sampling approach to mitigate selection bias. Patients were initially approached based on their diagnoses of bipolar disorder 1, as ascertained by the SCID-5-CV. The application of strict inclusion and exclusion criteria, which were meticulously established to minimize confounding variables, were utilized to refine our participant pool. This strategy also aimed to maintain the integrity of our findings by limiting inclusion. Furthermore, our healthy controls, largely recruited from acquaintances of the hospital staff, underwent a detailed interview utilizing the SCID-5-CV to ensure no history or familial linkage to psychiatric disorders, thereby establishing a robust comparative baseline. To shield against measurement bias, evaluators, blinded to participant group assignments, underwent standardized training to ensure uniformity in data collection procedures.

During the recruitment of patients with bipolar disorder, 37 individuals were precluded due to various reasons such as illiteracy, pregnancy, lactation, and substance abuse. Subsequently, 31 individuals faced exclusion due to the existence of specific neurological conditions, recent incidents of head trauma, or discernible motor abnormalities. A further scrutiny led to the exclusion of six individuals due to their recent history of undergoing electroconvulsive treatments or having certain identifiable organic mental disorders. In the final tier of exclusion, 23 individuals were eliminated due to their inability to provide informed consent or due to the presence of coexisting psychiatric disorders. Furthermore, 29 patients were unable to complete the procedure and were thus omitted from the study. Consequently, the final analytical phase was conducted with a robust sample of 203 patients, substantiating the strength and precision of the results derived from our exploration.

In recruiting HCs, our rigorous screening and selection strategy was sequentially implemented to uphold the validity of our findings. Twenty-two individuals were immediately excluded due to various factors including illiteracy, pregnancy, lactation, and a history of substance abuse. Subsequently, an additional 14 candidates were excluded, attributed to the identification of distinct neurological conditions, recent head trauma incidents, or apparent motor abnormalities. In the third and final stage of our exclusion strategy, eight participants were disqualified due to not providing informed consent or a diagnosis of coexisting psychiatric disorders. Additionally, 17 participants were unable to successfully conclude the procedure and were thus also excluded. Consequently, the final analysis was rigorously conducted with a substantiated and reliable sample of 201 HCs, ensuring that the subsequent findings were rooted in a meticulously curated dataset.

After data collection, retrospective power analyses were performed to validate the robustness and reliability of our findings. With an observed standard effect size varying between 0.71 and 0.95 across different outcomes, a sample size of 200 participants per group facilitated a robust study power, anchoring at an approximate 99% with an allowable 5% margin of error. This post-hoc validation serves to confirm that our study was adequately powered to detect significant effects and differences, bolstering the reliability and validity of the results obtained, despite the post-hoc nature of the power analysis.

Measures

Sociodemographic and Clinical Information: A structured questionnaire was designed to gather participants' sociodemographic data, clinical information, and medication history. Information, such as age, gender, education level, occupation, duration of illness, and medication type and dose were recorded.

Edinburgh Handedness Inventory: This was used to assess hand preference in daily activities to determine dominant hand usage [8].

Test for Upper Limb Apraxia (TULIA): Proven sensitive to detect upper extremity movement disorders in schizophrenia, TULIA offers a comprehensive motion performance evaluation in imitation and pantomime areas, each with three subcategories focusing on intransitive (actions without objects), transitive (actions involving objects), and meaningless movements. The imitation and pantomime tests aim to assess patients' ability to reproduce observed actions and express particular actions without the aid of verbal instruction, respectively. Performance in these areas can be critical markers of an individual’s daily functioning capacity, reflecting their ability to understand and carry out essential tasks that influence their quality of life. The tests evaluate individuals on a scale ranging from 0 to 5 based on content and temporospatial errors, where higher scores signify superior performance and, by extension, fewer praxia deficits. TULIA scores vary between 0 to 240. Its Turkish standardization, validity, and reliability were completed in 2019 [14].

YMRS is an 11-item scale quantifying manic state severity and validated for Turkish audiences by Karadağ et al. [15]. HDRS is a 17-item scale gauging depression severity, validated for Turkish use by Akdemir et al. [16]. GAF-F evaluates general functionality on a 0-100 scale, with higher scores indicating better functionality [17]. WHOQOL-BREF is a condensed WHOQOL-100 version gauging quality of life, validated in Turkey by Eser et al [18].

Ethical considerations

The Ethics Committee of Istanbul Bilgi University (protocol code 2023-40162-033; approval date February 21, 2023) approved this study. It is performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences for Windows (SPSS) version 22.0. The normal distribution of the variables was determined through the Kolmogorov-Smirnov test and Skewness-Kurtosis values. Descriptive statistics provided insights into demographic data. Depending on data distribution, the Student’s T-test or Mann-Whitney U-test was implemented for comparing independent

groups. Pearson and Spearman correlation tests ascertained correlations of normally and non-normally distributed data, respectively. To identify independent factors forecasting functionality in BD patients, univariate and multivariate logistic regression analyses were utilized. The receiver operating characteristic (ROC) analysis showcased the application of TULIA subscores in distinguishing BD patients from healthy controls. Statistical significance was deemed at *P*-level <0.05. Only patients with complete datasets were incorporated in the analysis, ensuring no missing data.

Results

Table 1 presents the demographic and clinical characteristics of the study participants, including patients diagnosed with bipolar disorder and healthy controls.

Table 1: Sociodemographic and clinical features

	Patients with Bipolar Disorder (n=203)	Healthy Controls (n=201)	*P*-value
Age, mean (SD)	39.1 (9.4)	40.3 (8.9)	0.14
Gender, n (%)			
Female	103 (51.7)	97 (48.3)	0.72
Male	98 (48.3)	104 (51.7)	
Marital status, n (%)			
Single / divorced/widowed	108(53.2)	105 (52.2)	0.35
Married	95(46.8)	96 (47.8)	
Smoking, n (%)			
Yes	120 (59.1)	103 (51.2)	0.11
No	83 (40.9)	98 (48.8)	
Education year, mean (SD)	9.2 (3.0)	8.7 (2.2)	0.06
Family History of Psychiatric Illness, n (%)			
Yes	63 (31)		
No/Unknown	140 (69)		
Duration of illness (years), mean (SD)	6.3 (3.3)		
	Med (min-max)		
Number of Hospitalizations	1.98 (0-5)		
Total Number of Episodes	4 (1-35)		
Number of Depressive Episodes	1 (0-15)		
Number of Manic Episodes	2 (1-20)		
Number of Episodes with mixed Features	0 (0-5)		

SD: Standard Deviation, Med (min-max): median (minimum-maximum)

Healthy controls had significantly higher TULIA scores, TULIA imitation and TULIA pandomime subscores compared to patients with bipolar disorder (*P*<0.001) (Table 2).

Table 2: Comparison of TULIA scores between patients with bipolar disorder and healthy controls

	Patients with Bipolar Disorder (n=203)	Healthy Controls (n=201)	*P*-value
TULIA	213.1 (10.8)	221.5 (6.7)	<0.001
TULIA Imitation	107.9 (4.9)	111.2 (4.4)	<0.001
TULIA Pandomime	105.2 (6.7)	110.3 (3.5)	<0.001

TULIA: Test for Upper Limb Apraxia, Values are given mean (SD)

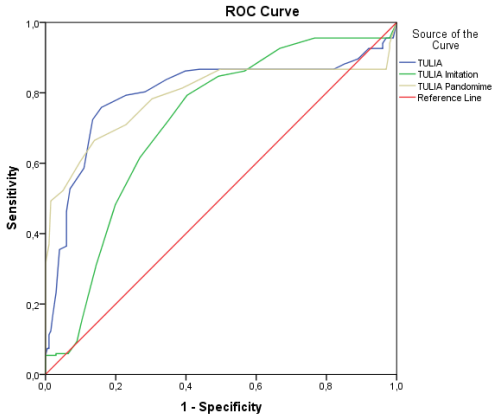
The ROC analysis revealed that using a TULIA score lower than 217 as a cut-off, differentiating patients with bipolar disorder from healthy controls resultedin a sensitivity of 79.3% and a specificity of 77.1% (area under the curve (AUC) 0.799, *P*<0.001). Using 109 as a cut-off value for the TULIA imitation subscore differentiated patients with bipolar disorder from healthy controls with a sensitivity of 71.9% and a specificity of 65.2% (area under the curve (AUC) 0.715, *P*<0.001). When 108 was the cut-off value for the TULIA pandomime subscore differentiating patients with bipolar disorder from healthy controls, a sensitivity of 70.9% and a specificity of 77.1% (area under the curve (AUC) 0.791, *P*<0.001) was revealed. (Table 3, Figure 1).

Table 3: Receiver operating characteristic (ROC) analysis of inflammation biomarkers for predicting patients with bipolar disorder vs. healthy control group distinction

	AUC	*P*-value	Lower Bound	Upper Bound	Cut-off point	Sens (%)	Spec (%)
TULIA	0.799	<0.001	0.752	0.847	217	79.3	77.1
TULIA Imitation	0.715	<0.001	0.664	0.766	109	71.9	65.2
TULIA Pandomime	0.791	<0.001	0.743	0.839	108	70.9	77.1

AUCArea under curve, Sens: sensitivity, Spec: Specificity, TULIA: Test for Upper Limb Apraxia

Figure 1: ROC curve analysis of TULIA, TULIA Imitation and TULIA Pandomime differentiating patients with bipolar disorder from healthy controls (cut-off scores were found 217, 109 and 108, and Area-Under-Curves 0.799, 0.715 and 0.791 respectively)



Following our initial comparison between sociodemographic data and TULIA scores of bipolar disorder patients and healthy controls, we delved deeper into the BD patient cohort. Our primary objective was to understand the interplay between disease-specific characteristics and praxia deficits. This more granular investigation aimed to shed light on how intrinsic factors of the disorder might influence praxia performance. With this focus in mind, we present our findings as follows:

In our study, we evaluated TULIA, GAF-F and WHOQOL-BREF Scale scores of patients with bipolar disorder. The mean TULIA score was found to be 213.12 (0.84), with the subscores of TULIA imitation being 107.90 (4.95) and TULIA pandomime being 105.22 (6.70). The mean GAF-F score was determined as 80.20 (8.25). The WHOQOL-BREF general health subscore was found to be 69.89 (14.16), and the median WHOQOL physical health subscore was 67.86 (ranging from 0 to 100). The median WHOQOL psychological subscore was 50.00 (ranging from 0 to 95.8); the median WHOQOL social relationships subscore was 50.00 (ranging from 0 to 100); and the median WHOQOL environment subscore was 59.38 (ranging from 0 to 100).

A correlation analysis was conducted to investigate the relationships between TULIA, GAF-F, and WHOQOL-BREF scores, as well as the severity of symptoms measured by YMRS and HDRS. These results are shown in Table 4.

Table 4: Correlation Analysis between TULIA, TULIA Imitation, TULIA Pandomime, GAF-F, YMDS, HDRS, WHOQOL-BREF scores and subscores

	TULIA	TULIA Imitation	TULIA Pandomime	GAF
GAF-F[a]	0.502**	0.459**	0.473**	1.000
WHOQOL General Health[a]	0.389**	0.387**	0.344**	0.216**
WHOQOL Physical Health[b]	0.303**	0.239**	0.281**	0.090
WHOQOL Psychological[b]	0.320**	0.298**	0.283**	0.203**
WHOQOL Social Relationships[b]	0.172*	0.146*	0.239**	0.153*
WHOQOL Environment[b]	0.048	0.44	0.093	0.169*
YMRS[b]	-0.107	-0.137	-0.064	-0.010
HDRS[b]	-0.164*	-0.138*	-0.185**	-0.156*

[a]Pearson, [b]Spearman's Correlation Analysis. *P<0,05, **P<0,01; GAF-F: Global Functioning Assessment-Functioning, HDRS: Hamilton Depression Rating Scale, TULIA: Test for Upper Limb Apraxia, WHOQOL-BREF: World Health Organization Quality of Life-Brief Version, YMRS: Young Mania Rating Scale

To ensure standardized comparisons among various antipsychotic dosages, we utilized the chlorpromazine equivalent method. This method equates the potency of different antipsychotics to that of chlorpromazine, a commonly used benchmark in psychopharmacology. Through this approach, we achieved a uniform reference point, facilitating a more coherent analysis of the potential impacts of different antipsychotic

dosages on praxia performance. A weak negative correlation was found between mean five-year chlorpromazine (CPZ) dosage and TULIA imitation, TULIA pandomime and TULIA scores (r=-0.175, *P*=0.012; r=-0.140, *P*=0.046; r=-0.172, *P*=0.014, respectively).

We aimed to investigate the potential impact of mood stabilizers, specifically lithium and valproate, on TULIA, TULIA imitation, and TULIA pandomime scores among bipolar disorder patients. We found no statistically significant difference in TULIA, TULIA imitation and TULIA pandomime scores among patients with bipolar disorder who were treated with valproate (n=81), lithium (n=78), a combination of valproate and lithium (n=21), or none of these (n=23) (*P*=0.099, *P*=0.394 and *P*=0.376, respectively.)

For the purposes of this study, patients were categorized based on their usage of specific long-acting antipsychotics (LAIAs). The LAIAs considered in the study were aripiprazole, risperidone and paliperidone. Dosages for these antipsychotics varied. Our findings revealed that patients not on LAIAs (n=109) exhibited statistically significant lower TULIA (211.2 vs. 215.3), TULIA imitation (107.2 vs. 108.7), and TULIA pantomime (104.0 vs. 106.6) scores in comparison to those on LAIAs (n=94). The p-values associated with these differences were *P*=0.006, *P*=0.029, and *P*=0.005, respectively.

Among patients with bipolar disorder, TULIA scores were negatively correlated with the number of depressive episodes, number of total episodes, and number of hospitalizations (r=-0.245, *P*<0,001; r=-0.185, *P*=0.008; r=–0.292, *P*<0.001, respectively.), whereas TULIA imitation subscores were negatively correlated with number of depressive episodes, number of total episodes. and number of hospitalizations (r=-0.197, *P*=0.005; r=-0.146, *P*=0.037; r=-0.255, *P*<0.001, respectively), and TULIA pandomime subscores were negatively correlated with the number of depressive episodes, number of total episodes, and number of hospitalizations (r=-0.233, *P*=0.001 ;r=-0.167, *P*=0.017 ;r=-0.259, *P*<0.001, respectively). Regarding functionality, GAF-F scores were negatively correlated with number of depressive episodes and number of hospitalizations (r=-0.159, *P*=0.024; r=-0.207, *P*=0.003, respectively). TULIA score, TULIA imitation and TULIA pandomime subscores were negatively correlated with the duration of the illness (r=-0.180, *P*=0.010; r=-0.203, *P*=0.004 and r=-0.141, *P*=0.045, respectively).

Multiple logistic regression analysis was performed to evaluate the factors predicting impairment in functioning in bipolar patients. The dependent variable was impairment in functioning (GAF-F scores < 81), and the independent variables included age, WHOQOL total score, CPZ use, TULIA imitation, and TULIA pantomime subscores. It is important to note that while TULIA (total) was significant in the univariate analysis, only the TULIA pantomime and imitation subscores were considered for the multivariate analysis. This decision was made because TULIA (total) is a composite of both the pantomime and imitation subscores, and as such, it would not be expected to act independently when both of its constituent subscores were already included in the model. The analysis revealed that TULIA pantomime subscores (OR=0.92, 95% CI 0.86-0.99, *P*=0.022) and CPZ use of more than 250 mg per day (OR=2.24, 95% CI 1.19-4.21, *P*=0.012) were independent predictors of impairment in functioning in bipolar patients, after controlling for the effects of other variables. These results suggest that lower TULIA pantomime subscores and CPZ use more than 250 mg per day may increase the risk of impairment in functioning in bipolar patients (Table 5).

Table 5: Univariate and Multivariate Regression Analysis evaluating the factors predicting impairment in functioning (GAF-F score <81) in bipolar patients.

	OR	Lower	Upper	*P*-value
Univariate Regression Analysis				
Age	1.037	1.006	1.069	0.021
Education year	0.932	0.848	1.025	0.146
Duration of illness	1.044	0.960	1.136	0.316
Female vs. Male	0.899	0.518	1.561	0.705
Single vs. married	1.089	0.627	1.892	0.762
Smoking (yes vs no)	1.108	0.632	1.941	0.721
TULIA	0.911	0.875	0.949	<0.001
TULIA Imitation	0.831	0.761	0.908	<0.001
TULIA Pandomime	0.885	0.840	0.934	<0.001
WHOQOL-BREF Total	0.951	0.924	0.980	0.001
CPZ>250mg/day vs.<250mg/day	2.22	1.252	3.928	0.006
Number of depressive episodes <2 vs ≥2	0.973	0.561	1.689	0.923
Multivariate Regression Analysis				
Age	1.030	0.995	1.066	0.094
TULIA Imitation	0.898	0.804	1.004	0.058
TULIA Pandomime	0.922	0.860	0.988	0.022
WHOQOL-BREF Total	0.988	0.953	1.025	0.531
CPZ>250mg/day vs.<250mg/day	2.241	1.193	4.209	0.012

CPZ: Chlorpromazine equivalent dose, GAF-F: Global Functioning Assessment-Functioning, OR: Odds Ratio, TULIA: Test for Upper Limb Apraxia, YMRS: WHOQOL-BREF: World Health Organization Quality of Life Brief Version

Discussion

The current study investigated praxia performance in patients with bipolar disorder and healthy controls, as well as its relationship with clinical variables, functioning, and quality of life among patients with bipolar disorder. Furthermore, a TULIA score higher than 217 showed good sensitivity and specificity in distinguishing healthy controls from patients with bipolar disorder. Our results also showed a negative correlation between TULIA scores and mean five-year chlorpromazine (CPZ) equivalent dosage, as well as a significant effect of the number of depressive episodes on praxia performance in bipolar patients. Importantly, we found that praxia deficits were negatively associated with functionality and quality of life of bipolar patients. Overall, our findings suggest that investigating praxia deficits may provide valuable insights into its relationship with clinical variables and functioning.

Elucidating the complex relationships within bipolar disorder, this investigation navigates through the intersections of depressive symptoms, praxia deficits, and functional outcomes. The convergence between our findings and established research becomes evident, reinforcing the substantial influence depressive symptoms exert on functional trajectories within this disorder [19-20]. A nuanced understanding is observed in the interplay between praxia performance and the multifaceted domains of quality of life as evaluated through WHOQOL-BREF scores. The interdependence of praxia performance and overall well-being, while intuitively corroborated, incubates possibilities of bidirectional influences, warranting deeper exploration into their causal relationships. Moreover, the non-significant associations of manic symptoms instigate further inquiry into the potential differential impacts of various symptom typologies on functional and praxia outcomes within bipolar disorder. Overall, our findings provide important insights into the relationships between praxia deficits, functioning outcomes, and symptom severity in BD, highlighting the potential impact of depressive

symptoms and praxia deficits on functional and quality-of-life outcomes in this population.

This study illuminates a noteworthy interface between praxia deficits and various clinical attributes, including episode count and hospitalizations, in individuals navigating through the complexities of BP. The elicited connections with TULIA scores convey deeper implications concerning the trajectory and management of the disorder, particularly regarding the deteriorative nature of praxia skills amid its progression.

An intriguing perspective arises when considering the symbiotic relationship between praxia performance and overall functionality, as reflected by GAF-F scores, which kindles a dialogue about the comprehensive impact of mood episodes on patient functionality. The pivotal role of depressive episodes in this context, in particular, accentuates the necessity to strategically address its frequency and severity in treatment plans. Thus, these insights pave the way for future research trajectories, focused not merely on understanding these relationships but also on developing targeted interventions that conscientiously address both the motor and emotional aspects inherent in bipolar disorder management.

The nuanced relationship between motor performance, especially as quantified via TULIA pandomime scores, and functional impairment in bipolar patients, introduces a compelling facet to our understanding of disorder management. Notably, medication-related factors, particularly pertaining to CPZ dosage, warrant a distinct exploration concerning their implicit role in patient functioning. An in-depth exploration into gestural praxis's contributions toward functioning provides a framework for developing targeted interventions and facilitates a deeper exploration into how motor performance intricately intertwines with overall patient functionality and well-being.

The effects of mood stabilizers on subtle neurological symptoms, including praxia, have not been extensively investigated. Based on the current study, we found no statistically significant difference in TULIA scores among patients with bipolar disorder who were treated with valproate, lithium, a combination of valproate and lithium, or none of these. Although there is no study showing the effect of lithium on praxia performance, it has been reported that temporary apraxia has occurred in a few cases of lithium toxicity [21]. On the other hand, no studies in the literature report that valproate may cause praxia defects. The occurrence of dose-dependent tremors in approximately 25% of patients using valproate is well-known, but parkinsonism may develop with cognitive retardation in only a very few cases, and the manifestation improves when the drug is discontinued. A meta-analysis emphasized that treatment with mood stabilizers did not significantly impair verbal and visual memory, attention, executive function, processing speed, or psychomotor performance [22-23]. Overall, our findings suggest that treatment with mood stabilizers, including lithium and valproate, does not appear to have a significant impact on praxia deficits in patients with bipolar disorder. However, further research is needed to confirm these findings and explore potential differences in praxia performance among patients treated with different mood stabilizers.

Understanding the intersection between praxia performance and antipsychotic medications, especially those quantified through CPZ equivalent dosages, enriches the discussion regarding optimized pharmacological intervention in bipolar disorder. This relationship delineates a critical exploration into the dual-faceted impact of antipsychotics, wherein the modulation of motor symptoms, either as a potential therapeutic or side-effect profile, becomes paramount. The observed patterns within CPZ dosages and praxia performance align with some prior investigations [24], yet offer a contrast to others, revealing an intricate landscape where antipsychotic dosages and motor capabilities entwine [25]. This discrepancy underscores the imperative to delve deeper into understanding the subtleties surrounding medication management and its reverberations on motor function.

Similarly, the role of long-acting antipsychotics (LAIA) in shaping praxia performance in bipolar disorder patients provides an intriguing perspective, given their established efficacy in relapse prevention during maintenance treatment [26]. The potential dual benefits concerning relapse mitigation and potentially favorable impacts on motor side effects warrant a further, more granular exploration into delineating the optimal therapeutic strategies employing LAIA, as echoed by several studies [27,28]. Navigating through the multilayered impacts of various antipsychotic treatments on praxia performance underscores a vital aspect of tailored therapeutic strategies and propels the discourse toward a clearer understanding of pharmacological impacts in bipolar disorder management.

Given the discernible effect of praxia deficits on the daily functioning and overall life quality in bipolar disorder patients, the role of occupational therapy might emerge as a pivotal component in the holistic management approach. Occupational therapists, with their expertise in enhancing individuals' abilities to perform daily activities, may potentially ameliorate the disruptions caused by praxia deficits in BD patients. Tailored interventions can be devised to foster improvements in the imitation and pantomime domains of praxis, focusing on transitive, intransitive, and non-symbolic actions, respectively, to enhance daily functioning. For instance, guided exercises can be designed to facilitate smoother transitive actions involving objects, aiding patients in regaining competence in essential daily tasks, such as grooming, dressing, and cooking. Moreover, therapy sessions might focus on refining intransitive actions, thereby potentially enhancing non-verbal communication and easing social interactions. The nurturing of non-symbolic actions could further impart a sense of freedom and creativity, cultivating a ground for therapeutic expressions through art or dance. As patients witness improvement in their daily functioning, this could resonate positively with their self-esteem and life satisfaction, forging a pathway toward a more fulfilled life. However, it is essential to approach this with a nuanced understanding, incorporating individualized therapy plans that resonate with the unique needs and preferences of each individual, to truly harness the potential of occupational therapy in nurturing a richer quality of life in bipolar disorder patients [29-30].

Our study underscores the significance of praxia deficits as a pivotal marker of functional capabilities in individuals with bipolar disorder. This entails a compelling call for clinicians to incorporate assessments of praxia performance into their

diagnostic routines. It not only illuminates potential challenges faced by bipolar disorder patients in daily activities but also accentuates the influence of praxia deficits on their overall quality of life. Importantly, our data hint at a distinctive threshold: a TULIA score exceeding 217 might serve as a differentiator between healthy individuals and those with bipolar disorder. Such a differentiation metric could be instrumental in clinical settings, providing a more nuanced understanding of the patient's condition and guiding more tailored interventions. Introducing the TULIA as a routine screening instrument in clinical practices could efficiently pinpoint bipolar disorder patients facing praxia challenges, facilitating early interventions and tailored therapeutic strategies.

Limitations

This study was the one of the first to present real-life data, investigating the relationship among upper limb apraxia, quality of life, and functionality in patients with bipolar disorder. However, there are some limitations. The cross-sectional study design does not allow for comparison before medical treatment. The complex use of various medications and combinations may confound the possible effect of medication on praxia deficits. The use of self-reported measures may be subject to reporting bias and social desirability bias. Additionally, the study had a small sample size and the cross-sectional design limits the ability to draw causal conclusions. Longitudinal studies with larger clinical samples could provide more comprehensive findings.

Conclusions

This research elucidates a tangible intersection between praxia performance and bipolar disorder, unveiling a noteworthy disparity in comparison to healthy controls. A discernible TULIA score threshold surfaces as a potential demarcation line, offering a novel, albeit preliminary, tool for differentiating healthy individuals from those navigating the complexities of bipolar disorder. Inextricably intertwined with quality of life, praxia performance emerges not merely as a metric but a mirror reflecting various facets of the daily functioning and overall well-being of affected individuals. Upon deeper examination, the frequency of depressive episodes unfurls as a potential influencing factor on praxia performance, accentuating a need for further scrutiny in unraveling the multifaceted relationship between mood fluctuations and motor function. Notably, certain parameters, such as TULIA pandomime subscores and specific CPZ equivalent dosage thresholds, forge ahead as possible harbingers of functional impairment, thereby meriting consideration in future predictive models and clinical evaluations.The practical repercussions of these findings permeate various spheres of clinical management in bipolar disorder. The link between praxia, daily functionality, and quality of life underscores the necessity of embedding praxia assessment within the broader evaluative and interventional framework. However, the pathway from research to clinical application is nuanced and demands meticulous validation through further research, particularly in translating TULIA scores into applicable clinical thresholds and understanding the underlying mechanisms connecting depressive episodes to praxia performance.

As we contemplate these findings, numerous avenues for future research unfurl, brimming with potential to deepen and diversify our understanding of bipolar disorder and praxia performance. Investigations exploring the longitudinal impacts of varied antipsychotic medications, deciphering the underlying neurobiological correlates of praxia performance, and constructing refined predictive models encapsulating diverse clinical and demographic variables emerge as pivotal pursuits. Similarly, the horizon looks promising for delving deeper into targeted interventions, such as cognitive remediation therapy and occupational therapy, gauging their efficacy in enhancing praxia performance and, by extension, the functional well-being of bipolar disorder patients. Further explorations could chart the intersections between praxia performance and other facets of bipolar disorder, notably cognitive disruptions and the intricacies of emotional regulation. These holistic inquiries not only promise to validate and refine the preliminary understandings etched out by the present study but also forge pathways toward more holistic, personalized, and efficacious management paradigms. Thus, they harbor the potential to navigate toward more comprehensive, personalized, and efficacious management paradigms for individuals grappling with bipolar disorder, while spotlighting potential risk factors or predictive markers for the onset or exacerbation of the illness.

Acknowledgments

I want to thank to Tomris Duymaz for her invaluable guidance and support throughout the research process and all the individuals that participated in this study

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J Surg Med. 2023;7(10):690-693.
DOI: 10.28982/josam.7994

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Rates of upgrade to malignancy in surgical excision of intraductal papillomas of the breast: A retrospective cohort study

Zehra Ünal Özdemir

Haydarpaşa Numune Training and Research Hospital, Department of General Surgery, Istanbul, Turkey

ORCID ID of the author(s)

ZÜÖ: 0000-0002-4063-9402

Corresponding Author
Zehra Ünal Özdemir
Haydarpaşa Numune Training and Research Hospital, Department of General Surgery, Istanbul, Turkey
E-mail: drzehraunal@gmail.com

Ethics Committee Approval
Ethical approval was obtained from the Haydarpaşa Numune Training and Research Hospital Education Planning Board (Approval number: August 25, 2023-223051729). 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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 19

Abstract

Background/Aim: Intraductal papillomas (IDP) of the breast, though benign, share an association with the duct epithelium, similar to some breast malignancies. Percutaneous biopsies often fail to fully characterize these lesions. The decision to perform surgical excision for IDP of the breast is frequently based on the presence of atypia observed during percutaneous biopsy. However, consensus remains lacking regarding the management of IDP of the breast without atypia. This study was undertaken to share findings on IDP, contributing to a better understanding of their nature and guiding treatment approaches.

Methods: We conducted a retrospective evaluation of data from 42 female patients diagnosed with intraductal papilloma through percutaneous biopsy, who subsequently underwent surgical excision between January 1, 2015, and August 25, 2023. Patients not diagnosed with intraductal papilloma, those with prior breast malignancy diagnoses, and those identified incidentally during other surgical procedures were excluded from the study. Data recorded included patient ages, the largest lesion diameters measured by ultrasonography, the percutaneous biopsy method (Fine needle aspiration biopsy [FNAB] or Core needle biopsy [CNB]), atypia status observed during percutaneous biopsy, histopathological features observed during surgical excision, and lesion diameter in cases where malignancy was upgraded. If ductal carcinoma in situ (DCIS) or invasive cancer was identified in the surgical excision specimen, it was classified as an upgrade.

Results: The median age of the patients was 48.5 years (range: 12.9 years). FNAB was performed in ten cases (23.8%), while CNB was used in 32 cases (76.2%). There was no significant difference in the detection of atypia when comparing FNAB and CNB (P=0.57). Eight patients (19%) were diagnosed with atypical intraductal papilloma. Among them, three patients with atypia and two patients without atypia exhibited an upgrade to malignancy. The study revealed a malignancy upgrade rate of 37.5% for IDP with atypia and 5.9% for those without atypia. Furthermore, the average age of patients with malignancy upgrades was higher than that of patients with benign lesions (P=0.02).

Conclusion: In light of the malignancies detected in cases of breast IDP, even in the absence of atypia, opting for surgical excision, particularly in older patients, can help prevent the oversight of these cancers.

Keywords: breast cancer, intraductal papilloma, upgrade, excision, atypia

How to cite: Ünal Özdemir Z. Rates of upgrade to malignancy in surgical excision of intraductal papillomas of the breast: A retrospective cohort study. J Surg Med. 2023;7(10):690-693.

Introduction

Breast cancer stands as the most frequently diagnosed cancer among women worldwide [1,2]. Within the realm of breast pathology, papillary lesions can manifest as either benign, atypical, or malignant. Intraductal papillomas (IDP), specifically, represent benign lesions characterized by finger-like fibrovascular cores enveloped by layers of epithelial and myoepithelial cells [3]. Discrepancies between the findings from needle biopsies and surgical excisions for papillary breast lesions have led to diverse treatment strategies for intraductal papillomas (IDP). The consensus in the management of IDP, diagnosed through needle biopsy, revolves around surgical excision when atypia is present [4,5]. For those IDP lacking atypia, close monitoring is typically recommended, although surgical removal may also be considered due to the observed rates of upgrades detected in surgical excision specimens [6]. The literature reports upgrade rates to malignancy ranging from 0% to 33% for IDP cases without atypia in needle biopsy results [7,8]. Some experts contend that the limited tissue fragments obtained in imaging-guided needle biopsies may not always provide a comprehensive sampling of the entire lesion, potentially leading to missed cancer diagnoses [9].

No established parameters exist for predicting the progression to malignancy. Consequently, the significance of data derived from lesions diagnosed as intraductal papilloma in contributing to the literature cannot be overstated.

This study presents the rates of upgrades to malignancy detected through surgical excision in 42 patients diagnosed with IDP via percutaneous needle biopsy. Additionally, a retrospective analysis of data believed to be associated with these upgrades is provided.

Materials and methods

The retrospective study protocol received approval from the Haydarpaşa Numune Training and Research Hospital Education Planning Board (EPB) on August 25, 2023, with reference number 223051729. This study retrospectively assessed the data of 42 patients who were diagnosed with intraductal papilloma through percutaneous biopsy between January 1, 2015, and August 25, 2023, and whose surgical procedures were conducted by a single surgeon. Data for this analysis were sourced from the hospital database and physician records. Inclusion criteria encompassed patients diagnosed with intraductal papilloma through percutaneous needle biopsy guided by ultrasonography, who subsequently underwent surgical excision. The surgical excisions for all patients were performed by the same surgeon following ultrasound-guided wire marking.

Exclusion criteria for this study were defined as individuals with a prior malignancy diagnosis and incidental IDP discovered during procedures unrelated to percutaneous biopsy. Parameters examined in the study included patient ages, ultrasonographically measured maximum lesion diameters, the central or peripheral location of lesions relative to the nipple areola in ultrasonographic imaging, Breast Imaging Reporting and Data Systems (BIRADS) categories as indicated in radiological reports, the percutaneous biopsy method (Fine needle aspiration biopsy [FNAB] or Core needle biopsy [CNB]), atypia status in percutaneous biopsies, surgical excision pathology results, histopathological features, and the diameter of the detected lesion if an upgrade was identified.

In ultrasonographic imaging, IDPs were categorized as central or peripheral based on their location. Lesions described as retroareolar, periareolar, and situated less than 2 cm from the nipple were classified as centrally located, while lesions positioned 2 cm or more distant from the nipple were categorized as peripherally located. Additional pathological findings, such as microcalcifications, radial scars, and complex sclerosing lesions, were also recorded in the surgical excision specimen. Notably, instances of detecting ductal carcinoma in situ (DCIS) or invasive cancer in the surgical excision specimen were documented as upgrades.

Statistical analysis

Statistical analysis for the cases included in the study was conducted using IBM SPSS (version 22.0; IBM, Armonk, NY, USA). Categorical data were assessed using Chi-square and Fischer's exact test. In cases where numerical data adhered to a normal distribution, the student t-test was applied. Conversely, when numerical data did not follow a normal distribution, the Mann-Whitney U test was employed. A significance level of *P*-value <0.05 was deemed statistically significant.

Results

The median age of the 42 female patients included in the study was 48.5 (12.9) years, with an age range of 18-81 years. All patients underwent diagnosis through percutaneous needle biopsy guided by ultrasonography. It was determined that ten (23.8%) of the biopsies were performed using FNAB, while 32 (76.2%) were conducted using CNB. Eight (19%) of the patients were found to have atypical intraductal papilloma. Among these eight patients, three were subsequently upgraded to malignancy. Specifically, one patient was detected with FNAB, and the other two were identified through CNB.

Interestingly, the two cases that were upgraded to malignancy through surgical excision did not exhibit any atypia in their initial biopsies, both of which were performed using CNB. Notably, there was no statistically significant difference found when comparing the ability of FNAB and CNB to detect atypia (P=0.57).

The average lesion size determined through ultrasonography was 10.6 (5.1) mm, with a range of 6-22 mm. Specifically, the ultrasonographic diameter measured 9.9 (4.3) mm for benign lesions and 14.8 (6.9) mm for malignant lesions. Notably, the ultrasonographic diameter was found to be larger in patients whose lesions were upgraded to malignancy when compared to those with benign lesions, although this difference did not reach statistical significance (P=0.155).

Following surgical excision, malignancy was identified in five out of 42 patients diagnosed with IDP, representing an incidence of 11.9%. Among these five patients with malignancy, three presented with IDP accompanied by atypia, while two had IDP without atypia. The specific malignancy types observed in these cases included three with DCIS, one with tubular carcinoma, and one with encapsulated papillary carcinoma in conjunction with DCIS.

Interestingly, it was determined that IDP were most frequently upgraded to DCIS, accounting for 9.52% of cases. The

average tumor diameter among those with malignancy upon surgical excision measured 13 mm, with a range spanning from 5 to 25 mm. Moreover, the mean age of the five patients who experienced an upgrade to malignancy was 64.6 (9.5) years, whereas the mean age of the 37 benign patients without malignancy was 46.3 (11.9) years. This difference in mean ages between the two groups was statistically significant (P=0.02).

Out of the IDPs, 22 (52.4%) were identified as centrally located, while the remaining 20 (47.6%) were situated peripherally. Among the cases that upgraded to malignancy, two (9.1%) were centrally located, and three (15.0%) were found in peripheral locations. It is worth noting that there was no statistically significant difference observed between central and peripheral locations in terms of cases upgrading to malignancy (P=0.65).

Of the two IDPs without atypia that progressed to malignancy, one was centrally located, while the other was peripherally situated.

All patients in the study were classified as BIRADS 4. When examining the subgroup distribution within this category, it was found that 25 patients were classified as BIRADS-4a (59.5%), three as BIRADS-4b (7.1%), and four as BIRADS-4c (9.5%). Notably, ten patients (23.8%) did not fall into any specific subgroup within BIRADS-4.

Among the patients diagnosed with malignancy, three were categorized as BIRADS-4 with no specified subgroup, one was classified as BIRADS-4a, and one was designated as BIRADS-4c.

During surgical excision, the diagnoses of 20 out of the 37 patients with IDP remained unchanged, whereas 17 patients were found to have additional pathologies that were not initially detected. Importantly, all five patients who underwent an upgrade to malignancy also had additional pathologies identified during surgical excision. This observation yielded a statistically significant result (P=0.041). The additional pathological findings are detailed in Table 1.

Table 1: Distribution of additional pathologies in benign and malignant cases.

Additional pathology	Benign (n/%)	Malignant (n/%)	Total (n/%)
None	20 / 54.1	0 / 0.0	20 / 47.6
Microcalcification	11 / 29.7	2 / 40.0	13 / 31.0
Radial scar	1 / 2.7	2 / 40.0	3 / 7.1
Complex sclerosing lesion	1 / 2.7	0 / 0.0	1 / 2.4
Fibroadenoma	2 / 5.4	1 / 20.0	3 / 7.1
Microcalcification + Complex sclerosing lesion	1 / 2.7	0 / 0.0	1 / 2.4
Microcalcification + Fibroadenoma	1 / 2.7	0 / 0.0	1 / 2.4
Total	37 / 100.0	5 / 100.0	42 / 100.0

P=0.041

The upgrade to malignancy was observed in three (37.5%) out of eight patients diagnosed with IDP that included atypia. In contrast, among the 34 patients diagnosed with IDP without atypia, 2 (5.9%) experienced an upgrade to malignancy. When considering the entire cohort of 42 patients diagnosed with IDP, whether with or without atypia, a total of five cases (11.9%) were upgraded to malignancy, as summarized in Table 2.

Table 2: Atypia conditions and upgrade rates of cases.

Atypia	No upgrade (n/%)	Upgrade to malignancy (n/%)	Total (n/%)
No	32 / 94.1	2 / 5.9	34 / 100
Yes	5 / 62.5	3 / 37.5	8 / 100
Total	37 / 88.1	5 / 11.9	42 / 100

P=0.040

Discussion

In this study, we assessed the rates of malignancy progression during surgical resection in patients diagnosed with IDP through imaging-guided needle biopsy. Our findings revealed that patients who underwent an upgrade to malignancy were generally older. This observation aligns with previous research suggesting a correlation between advanced age and progression. For instance, Ahmadiyeh et al. [10] noted a significantly higher average age among individuals with atypical papillomas compared to those without atypia. Multiple studies have also reported advanced age as a risk factor for pathological advancement in papillary lesions [7,11,12]. Our study supports the existing literature by confirming a significant association between advanced age and the likelihood of an upgrade.

This study concluded that there was no significant difference in the diagnostic accuracy between FNAB and CNB when used for percutaneous biopsy in diagnosing IDP, as compared to the histopathological examination results of surgical excision material. In a related study, Şimşir et al. [13] asserted that breast papillary lesions could be effectively classified as either benign or atypical through the use of FNAB.

In another study assessing biopsies of papillary breast lesions, it was reported that both FNAB and CNB yielded comparable outcomes [14]. This study observed no significant difference between the performance of FNAB and CNB in distinguishing between the benign and atypical characteristics of breast papillary lesions.

The ultrasonographic diameter was measured at 9.9 (4) mm for benign papillomas and 14.8 (6.9) mm for lesions that progressed to malignancy. This study revealed a trend where the diameters of IDPs that advanced to malignancy tended to be larger than those that did not progress to malignancy. In a separate investigation involving 520 cases, a lesion size of 1.5 cm on imaging was identified as an independent predictor of malignancy [15]. Another study indicated an increased likelihood of atypia when the lesion size exceeded 1.2 cm [16]. Jaffer et al. [17] reported no instances of upgrade in 46 patients diagnosed with IDP lesions smaller than 2 mm. In a study involving 102 cases, lesions that eventually progressed to malignancy were typically 1.7 cm in size [9].

Chen et al. [18] discovered that peripheral localization of IDPs in lesions without atypia was linked to higher upgrade rates in postmenopausal women. However, in our study, no significant relationship was identified between central and peripheral localization and the progression to malignancy.

Moseley et al. [9] reported that DCIS accounted for 69% of intraductal papilloma upgrades. In our study, among the malignancies identified, DCIS was the most prevalent upgrade, accounting for 80% of cases.

Surgical excision specimens of breast IDPs often reveal the presence of other accompanying lesions. Microcalcifications are commonly associated with IDPs and were found to be the most frequently occurring accompaniment in this study. Additional accompanying lesions included radial scar, complex sclerosing lesion, and fibroadenomas. Notably, microcalcifications and radial scar were more frequently observed in cases where IDPs progressed to malignancy. The literature supports the notion that

microcalcification is the most common accompanying lesion in the progression of IDPs to malignancy [19].

A meta-analysis has indicated that the risk of malignancy in IDPs escalates in BIRADS-4b and BIRADS-4c cases [20]. However, it is important to note that this study did not conduct a BIRADS subgroup analysis for all patients, preventing a comprehensive evaluation in this regard.

There is a consensus regarding surgical excision when atypia is identified through percutaneous biopsy in cases of IDP [4,5]. However, differing opinions emerge when atypia is not detected in percutaneous biopsy results.

In cases of atypical IDP, the literature reports upgrade rates to malignancy ranging from 45.4% to 22.5% [7,10]. Conversely, for IDP without atypia, a series of 407 cases in the literature suggests a relatively lower upgrade rate of 5.8% following surgical excision of benign papillary breast lesions [21]. In their study involving 102 cases, Moseley et al. [9] reported a malignancy upgrade rate of 2.9% and a high-risk benign lesion upgrade rate of 7.8% after surgical excision in cases without atypia on biopsy. Our study's upgrade findings align with the current literature [6,9,10,21]. It is also imperative to emphasize the importance of close monitoring and informed communication with patients in cases where atypia is not detected in percutaneous biopsy and surgical intervention is not pursued.

Limitations

Our study has a limitation in that it is retrospective. Furthermore, due to the lack of specified BIRADS subgroups in all cases, an assessment pertaining to the subgroups was not feasible. To gain a more comprehensive understanding of the clinical progression of the disease, there is a need for randomized prospective studies on this subject. Another limitation of our study is its relatively small sample size in terms of the number of cases.

Conclusion

IDP cases represent benign lesions identified through radiological or pathological examinations. While surgical excision is a well-established treatment option for cases containing atypia, a clear treatment approach is not evident for cases lacking atypia. This study revealed that surgical excision, particularly in older age groups, promptly aided in diagnosing malignancy in cases of IDP without atypia.

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J Surg Med. 2023;7(10):694-699.
DOİ: 10.28982/josam.7978

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Self-reported occupational exposure and its association with sperm DNA fragmentation in infertile men

Zeynep Caliskan [1], Canan Kucukgergin [2], Gulsan Aktan [3], Nurgul Bulut [4], Gul Ozdemirler [1]

[1] Department of Medical Biochemistry, Istanbul Yeni Yuzyil University, Istanbul, Turkey
[2] Department of Medical Biochemistry, Istanbul University, Istanbul, Turkey
[3] Department of Andrology, Istanbul University, Istanbul, Turkey
[4] Department of Biostatistics and Medical Informatics, Istanbul Medeniyet University, Istanbul, Turkey

ORCID ID of the author(s)

ZC: 0000-0001-8165-2024
CK: 0000-0002-1797-5889
GA: 0000-0003-2382-7927
NB: 0000-0002-7247-6302
GO: 0000-0001-8891-6387

Corresponding Author
Zeynep Caliskan
Istanbul Yeni Yuzyil University, Maltepe Mahallesi, Yılanlı Ayazma Cd., No: 26, 34010 Zeytinburnu, İstanbul, Turkey
E-mail: z.sezginn@gmail.com

Ethics Committee Approval
Ethical approval was obtained from the Istanbul Yeni Yuzyil University Ethics Committee (Date: October 3, 2022, No: 2022/0710-922).
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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 24

Abstract

Background/Aim: Sperm quality has experienced a decline in recent years, with this issue being particularly pronounced in industrialized nations, suggesting a potential link to occupational exposures. Evaluating sperm DNA fragmentation can yield valuable insights into male fertility, although its association with occupational exposures remains less well-established. Our study aimed to investigate the relationship between self-reported occupational exposures and sperm DNA fragmentation in infertile men.
Methods: This retrospective cohort study involved 391 infertile men who sought fertility treatment at a university clinic between 2017 and 2020. A brief questionnaire was administered to collect data on patients' demographic characteristics, medical history, occupation, and exposure types. In this comparative study, patients were categorized into two groups based on their occupational exposures (the unexposed and exposed groups). The exposed group was further sub-grouped according to their specific exposure types, which included cement, solvents, metals, pesticides, mechanical vibration, and heat. The primary outcome in this study was assessed using the terminal deoxynucleotidyl transferase-mediated nick end-labeling test (TUNEL), with results expressed as the sperm DNA fragmentation index (DFI).
Results: Patients in the exposed group exhibited a significantly higher sperm DFI compared to those in the unexposed group (14 [17] vs. 8 [9], $P<0.001$). After accounting for potential confounding factors, our results demonstrated that several occupational exposure factors significantly increased the risk of elevated sperm DFI (>15%) levels, including solvents (odds ratio (OR) 8.2, 95% confidence interval (CI) 3.6–18.5, $P<0.001$), metals (OR: 2.2, 95% CI: 1.0–4.7, $P=0.048$), pesticides (OR: 14.6, 95% CI: 1.6–130.7, $P=0.016$), mechanical vibration (OR: 2.6, 95% CI: 1.5–4.6, $P<0.001$), and heat (OR: 6.4, 95% CI: 1.7–23.5, $P=0.005$).
Conclusion: The findings of our study corroborate earlier research suggesting that occupational exposures may have adverse effects on sperm DNA fragmentation in men. The identification and management of such exposures as part of routine clinical practice could offer a complementary approach to enhancing infertility treatment outcomes.

Keywords: male infertility, occupational exposure, sperm DNA fragmentation

How to cite: Caliskan Z, Kucukgergin C, Aktan G, Bulut N, Ozdemirler G. Self-reported occupational exposure and its association with sperm DNA fragmentation in infertile men. J Surg Med. 2023;7(10):694-699.

Introduction

Infertility affects approximately 15% of couples, with the male factor being responsible, either partially or solely, in one out of every two cases. Male infertility has been attributed to various etiologies, with particular attention given to sperm DNA damage, which has been extensively studied for its impact on the structural and functional characteristics of sperm. Numerous studies have reported elevated levels of sperm DNA fragmentation in infertile men [1]. Sperm DNA fragmentation refers to the integrity of the genetic material contained within sperm and serves as an indicator of the quality of sperm DNA. The integrity of sperm DNA plays a critical role in transmitting genetic information that influences fertilization, embryo development, implantation, and pregnancy. Sperm DNA damage can arise from defective spermatogenesis, abnormalities in chromatin remodeling, incomplete apoptosis, and heightened testicular and post-testicular oxidative stress [2]. Moreover, various external factors can compromise chromatin integrity, leading to gradual DNA damage over time.

Studies on occupational exposure have suggested that work-related activities involving chemical and physical exposures can potentially impact male reproductive function, potentially leading to infertility [3]. Occupational tasks often expose individuals to a multitude of physical and chemical hazards. Among the physical hazards are excessive heat, mechanical vibrations, ionizing radiation, and, more recently, electromagnetic fields, which have been linked to disruptions in spermatogenesis and alterations in sperm characteristics [4]. In addition to physical hazards, chemical hazards like pesticides, solvents, and heavy metals have been associated with compromised semen quality and elevated abortion rates, as indicated by numerous studies [5,6]. However, the complexity of occupational exposure scenarios, compounded by various confounding factors such as smoking, alcohol consumption, body mass index, dietary habits, and socioeconomic status, has made it challenging to unequivocally attribute the significance of a single workplace hazard to date [3,7].

Numerous studies have established a connection between occupational exposure to specific harmful substances and an increased incidence of sperm DNA damage, resulting in reduced fertility. Sperm DNA fragmentation has emerged as a sensitive biological marker for detecting exposure to occupational toxicants [8]. While most epidemiological investigations into occupational exposure have traditionally focused on conventional semen parameters, such as sperm concentration, motility, and morphology, there remains a limited understanding of the link between occupational exposure and sperm DNA fragmentation. Gathering general occupational exposure data through self-reported questionnaires can be a valuable means of identifying occupational risk factors associated with elevated levels of sperm DNA fragmentation in clinical settings. Despite its limitations, this approach offers accuracy and reliability comparable to other widely used exposure assessment techniques, such as quantitative exposure measurement [9]. The present study was undertaken to explore the relationship between exposure to occupational risk factors (as reported in the questionnaire) and the extent of sperm DNA fragmentation in infertile men, with the aim of comprehending the extent to which occupational exposure influences sperm quality.

Materials and methods

Study population

We conducted a retrospective cohort study involving 391 infertile men who had sought fertility treatment at Istanbul University Andrology Clinic between 2017 and 2020. Data for this study were obtained from a questionnaire regarding their occupations. Prior to accessing patient information and initiating the research, we obtained permission from the Istanbul Yeni Yuzyil University Ethics Committee on October 3, 2022 (No: 2022/0710-922). The study was carried out in compliance with the Helsinki Declaration.

Inclusion criteria for the study encompassed male patients diagnosed with infertility, with ages ranging from 20 to 53 years. Comprehensive medical histories were collected for all participating patients. Exclusion criteria comprised individuals with infertility due to female factors, men with anatomical anomalies, varicocele, genetic or endocrine factors, genitourinary inflammation, or infection.

The database contained various patient details, including names, ages, medical histories regarding prior conditions that could impact sperm DNA fragmentation, smoking status (yes/no), alcohol consumption (yes/no), occupation (job title), and the type of exposure encountered in their work. Occupational exposure data were utilized to classify patients into two distinct groups: the unexposed group, comprising men who did not report any exposure and whose professions did not involve contact with any of the agents mentioned above, and the exposed group.

The unexposed group consisted of individuals such as policemen, businessmen, traders, civil servants, teachers, and students. In contrast, the exposed group encompassed cement industry workers, hairdressers, painters, printers, carpenters, cleaners, chemical and textile workers, metal workers, goldsmiths, electricians, welders, farmers, machine operators, mechanical engineers, mechanics, forklift drivers, cooks, bakers, taxi drivers, couriers, and software developers.

Additionally, the exposed group was further subdivided into six categories based on their specific type of exposure, namely: cement, solvents, metals, pesticides, heat (prolonged sitting or excessive heat), and mechanical vibrations (Table 1).

Table 1: Classifications of occupational exposure groups based on a questionnaire

Groups		Occupation
Unexposed group		Policemen, businessmen, traders, civil servants, teachers, and students
Exposed group	Cement	cement industry workers
	Solvents	hairdressers, painters, printers, carpenters, cleaners, chemical and textile workers
	Metals	metal workers, goldsmiths, electricians, welders
	Pesticides	farmers
	Mechanical vibrations	machine operators, mechanical engineers, mechanics, forklift driver
	Heat (prolonged sitting or excess heat)	cooks, bakers, taxi drivers, couriers, software developers

Sperm DNA Fragmentation Index

Semen samples were collected via masturbation and placed into sterile containers, following a period of 3-4 days of abstinence. Spermatozoa were then subjected to direct swim-up preparation, and sperm DNA fragmentation was evaluated using the TUNEL method, as outlined in our prior study [10]. The

primary objective of this study was to measure sperm DNA Fragmentation Index (DFI).

Sample size

The sample size was determined by considering the number of eligible patients without missing data for the period spanning from 2017 to 2020. For a retrospective comparative study, the sample size was computed using the standard method. With a test power of 95% and a type I error rate of 0.05, the minimum required sample size in each group was calculated to be 71, assuming an effect size of 0.6.

Statistical analysis

Descriptive statistics were used to summarize the data, including median values, minimum and maximum ranges, as well as counts and percentages (% frequencies). To assess the normality of the data distribution, the Kolmogorov-Smirnov test was employed. Given that the numerical characteristics exhibited non-normal distributions, comparisons between the unexposed and exposed groups were conducted using the Mann-Whitney U test. Comparisons involving more than two groups were assessed using the Kruskal-Wallis test, with Bonferroni adjustment applied for multiple comparisons.

For categorical characteristics, group data were analyzed using the Pearson Chi-square test. After dividing participants into two groups based on their sperm DNA Fragmentation Index (DFI) levels, specifically above and below 15 (as per our previous study), odds ratios (OR) and their respective 95% confidence intervals for the risk factors were computed through multiple logistic regression analysis. This analysis was adjusted for the participants' exposure status, accounting for smoking, age, and alcohol variables.

All calculations were performed using the SPSS 22.0 program, with a selected statistical significance level of *P*-value <0.05.

Results

The study recruited 391 infertile men aged between 20 and 53 years. The mean age of the participants was 32. The largest age group, comprising 55.75% of the population, fell between 30 and 39 years old, while the smallest age group, consisting of 12.28%, was over 40 years old. Most participants exhibited high sperm DNA Fragmentation Index (DFI) levels (<15%) (66.5%). The median sperm DFI among the participants was 10 (14).

Based on the information gathered from the questionnaire, infertile men were divided into two groups according to their exposure status: the unexposed group (n=199) and the exposed group (n=192). Solvent exposure was the most prevalent risk factor among the exposed population (42.2%), followed by exposure to metals (19.3%), heat (17.7%), and cement (12.0%). Only 5.7% and 3.1% of men were exposed to mechanical vibrations and pesticides in their occupational settings, respectively. The differences in mean age, smoking, and alcohol consumption between the unexposed and exposed groups were found to be statistically insignificant (*P*=0.112, *P*=0.550, *P*=0.506, respectively). However, there was a significant difference in the median distribution of sperm DFI between the exposed and unexposed groups (14 [17] vs. 8 [9], *P*<0.001).

Upon conducting multiple comparisons, it was observed that the median sperm DFI value in the group exposed to solvents was significantly higher than that in the non-exposed group (*P*<0.001). Additionally, the sperm DFI median value showed a significant increase in men who were exposed to pesticides (*P*=0.008), vibration (*P*=0.037), and heat (*P*=0.035) (Table 2).

Logistic regression was employed to assess the correlation between occupational exposure type and sperm DFI. Table 3 presents the adjusted ORs, with the unexposed group serving as the reference group with an OR of 1. Notably, individuals exposed to solvents had an 8.2-fold higher likelihood of having a sperm DFI >15% (OR: 8.197 [3.628–18.520], *P*<0.001). Exposure to metals was associated with a 2.2-fold higher risk of having a sperm DFI value above 15 (OR: 2.169 [1.008–4.670], *P*=0.048), while those exposed to pesticides had a substantially higher risk, with a 14.6-fold increase (OR: 14.642 [1.640-130.747], *P*=0.016). Exposure to mechanical vibration was estimated to elevate the risk by 2.6 times (OR: 2.573 [1.452–4.559], *P*<0.001). Men exposed to heat exhibited a 6.4-fold higher sperm DFI value compared to those in the unexposed group (OR: 6.411 [1.747–23.521], *P*=0.005). However, there was no statistically significant association between sperm DFI value and exposure to cement (*P*=0.059).

Table 3: Logistic regression analysis of association between sperm DFI and occupational exposures

	Sperm DFI >15	
	OR (%95 CI)	***P*-value**
Unexposed	1.00	0.001
Cement	2.509 (0.965-6.521)	0.059
Solvents	8.197 (3.628-18.520)	0.001
Metals	2,169 (1.008-4.670)	0.048
Pesticides	14.642 (1.640-130.747)	0.016
Mechanical vibration	2.573 (1.452-4.559)	0.001
Heat	6.411 (1.747-23.521)	0.005

OR: Odds ratio

Discussion

Male infertility is a substantial health concern characterized by numerous contributing factors. Among these factors, industrialization and economic growth have emerged as significant contributors due to heightened exposure to hazardous substances, leading to a detrimental impact on sperm quality. Consequently, it is imperative to gain a comprehensive understanding of how occupational factors can influence sperm quality. This study aimed to investigate the correlation between sperm DNA fragmentation (SDF) and self-reported occupational exposures using a questionnaire specifically designed for routine consultations.

Table 2: Demographic characteristics and sperm DFI levels of exposure groups

					Exposed group					
		Unexposed group (n=199)	**Exposed group (n=192)**	***P*-value**	**Cement (n=23)**	**Solvents (n=81)**	**Metals (n=37)**	**Pesticides (n=6)**	**Mechanical vibration (n=11)**	**Heat (n=34)**
Age (years), mean (SD)		32 (8)	33 (8)	0.112*	30 (7)	31.5 (7)	33 (10)	36 (7)	33 (8)	34 (4)
Sperm DFI, median (IQR)		8 (9)	14 (17)[a]	0.001*	11 (12)	20.5 (14.8)[a]	10 (12)	35 (25)[a]	13 (14)[a]	16 (30)[a]
Smoking n (%)	**No**	119 (59.8)	101 (52.6)	0.550**	10 (41.7)	21 (61.8)	18 (48.6)	3 (50.0)	43 (52.4)	6 (54.5)
	Yes	80 (40.2)	91 (47.4)		14 (58.3)	13 (38.2)	19 (51.4)	3 (50.0)	39 (47.6)	5 (45.5)
Alcohol consumption n (%)	**No**	163 (81.9)	166 (86.5)	0.056**	16 (66.7)	32 (94.1)	31 (83.8)	6 (100.0)	74 (90.2)	9 (81.8)
	Yes	36 (18.1)	26 (13.5)		8 (33.3)	2 (5.9)	6 (16.2)	0 (0.0)	8 (9.8)	2 (18.2)

SD: standard deviation, IQR: inter quartile range, *Kruskal-Wallis, **Pearson Chi-Square, [a] *P*<0.001 compared with the unexposed group.

The findings revealed a notable association between self-reported occupational exposure to solvents, metals, pesticides, mechanical vibration, and heat and an elevated risk of experiencing high levels of SDF. These associations remained significant even after adjusting for confounding variables such as smoking and alcohol consumption.

Exposure to solvents emerged as the most prevalent occupational factor within our study population, affecting 42.2% of participants. Previous research has extensively documented the potential impact of solvent exposure on male infertility and semen quality [9,11,12]. For instance, De Fleurian et al. [11] investigated the influence of self-reported physical or chemical occupational exposures on semen quality and found a significant association between solvent exposure and semen impairment (adjusted OR: 2.5; 95% CI: 1.4–4.4). However, studies specifically addressing sperm DNA damage have primarily focused on distinct solvent exposures, yielding inconsistent results.

Occupational exposure to benzene, for example, has been linked to DNA damage in immature germ cells in men, resulting in compromised sperm DNA integrity [13]. A recent study even highlighted the heightened risk of DNA fragmentation in fertile men exposed to paint thinners containing toluene, polyurethane, butyl carbitol, and numerous other components [14]. Moreover, workplace styrene exposure was associated with increased sperm DNA damage, as assessed through the Comet assay [15]. Furthermore, a study on coke oven workers exposed to polyaromatic hydrocarbons revealed significantly elevated levels of bulky DNA adducts and 8-oxo-7,8-dihydro-2’-deoxyguanosine compared to the control group, indicating potential sperm DNA damage and subsequent loss of integrity [16].

In contrast, Jurewicz et al. [17] reported no discernible correlation between occupational solvent exposure and SDF Index (DFI). However, our study findings indicate that the percentage of DNA fragmentation observed in the spermatozoa of the unexposed group was notably lower than that of workers exposed to solvents. Moreover, individuals with occupational solvent exposure faced an eight-fold higher risk of experiencing elevated levels of sperm DFI (>15%). It is plausible to hypothesize that this increased sperm DFI may be linked to the heightened production of reactive oxygen species (ROS) triggered by exposure to various solvents in occupational settings.

Current research regarding the impact of metal exposure on sperm DNA integrity in humans presents a challenge due to inconsistent findings. Non-essential heavy metals, encompassing but not limited to lead, cadmium, arsenic, mercury, and barium, have the potential to adversely affect male fertility and sperm quality. The detrimental effect of heavy metals on male fertility is attributed to their capacity to stimulate the production of ROS, leading to lipid peroxidation and damage to sperm DNA [18]. A comprehensive study conducted on infertile men in China aimed to explore the relationship between urinary metal concentration and sperm DNA damage. Their findings suggest that exposure to mercury (Hg), nickel (Ni), and manganese (Mn) may potentially result in increased sperm DNA damage [19].

In vitro research has revealed that lead can compete with or replace zinc in human protamine P2 (HP2), a zinc-containing protein crucial for binding to sperm DNA during spermatogenesis. Exposure to lead led to a dose-dependent reduction in HP2-DNA binding, potentially affecting sperm DNA and contributing to sperm DNA damage [20]. Conversely, a study involving coke oven workers exposed to metal mixtures did not observe a significant correlation between SDF and either metal mixtures or individual metals [21].

In our study, while we did not find a significant difference in SDF Index (DFI) between the group with metal exposure and the unexposed group, we did identify an increased risk of high DFI associated with metal exposure.

Various pesticides, encompassing pyrethroids, organophosphates, phenoxyacetic acids, carbamates, organochlorines, and combinations thereof, have undergone examination concerning their impact on male fertility [22]. Notably, exposure to organophosphates has been associated with abnormal semen characteristics, including reduced sperm counts, motility, viability, density, abnormal morphology, and increased DNA damage [23]. Individuals exposed to insecticides in their occupational settings, particularly fenvalerate or carbaryl, have displayed a notable induction of DNA damage in spermatozoa [24,25]. In fact, Xia et al. [25] suggested that carbaryl may function as a genotoxic agent due to its ability to cause DNA fragmentation and numerical chromosomal abnormalities during spermatogenesis.

In our study, we observed a significant association between pesticide exposure and high SDF Index (DFI). It is worth noting, however, that this association may be influenced by the relatively small proportion of participants (3.1% of our study population) who reported such occupational exposures.

Physical factors, such as mild heat stress, have the potential to disrupt sperm DNA integrity. It’s crucial to recognize that the optimal temperature for spermatogenesis is slightly lower than the body’s core temperature, typically differing by approximately 1–2°C. Consequently, germ cells become susceptible to localized heating of the testes. A prior study conducted in Poland reported that sedentary work associated with heat stress (where individuals spent ≥ 50% of their work time in a sedentary position) can double the risk of sperm DNA damage while not altering conventional semen parameters. This phenomenon may be attributed to the sedentary work style leading to an increase in testicular temperature, thereby resulting in failure in sperm chromatin remodeling during spermiogenesis [26]. Furthermore, heat stress amplifies the generation of ROS, leading to additional damage to mature sperm DNA [27]. Occupations involving prolonged sitting or daily commutes, such as driving, are more likely to raise scrotal temperatures, which have been linked to increased sperm DNA damage [28] and reduced sperm motility [11].

Additionally, previous studies have indicated that infertile males with varicocele tend to exhibit higher scrotal temperatures than expected, and this elevated testicular temperature has been shown to impact sperm DNA integrity. Our findings align with these observations, as we discovered that individuals working in roles such as software developers, drivers, or cooks were at an increased risk of experiencing elevated SDF due to extended periods of sitting and exposure to excessive heat. However, it is crucial to acknowledge that the limited number of subjects in the heat-exposed group underscores the need for longitudinal studies to validate our findings.

Research into the potential hazards of mechanical vibrations on the male reproductive system primarily relies on empirical, clinical, and epidemiological analyses involving both laboratory animals and male individuals working in the industrial and transportation sectors. These investigations also explore the repercussions of such vibrations on libido. Notably, it has been observed that mechanical vibrations are associated with conditions like oligospermia and teratozoospermia, whereas exposure to elevated temperatures and extended periods of sitting has been linked to reduced sperm motility [11].

In a prospective cohort study conducted by Eisenberg et al. [29], 23% of participants were exposed to whole-body vibrations, and 27% encountered noise in their occupational environments. Parallel to our research, they reported that the mean ejaculate concentration, total sperm count, and DNA fragmentation index (DFI) were relatively lower in the control group. However, their results did not reach statistical significance. Our current study's findings also align with those of Jurewicz et al. [17], who identified a significant negative correlation between occupational exposure to vibrations, decreased sperm motility, and increased DNA fragmentation.

Daoud et al. [30] identified a statistically significant association between exposure to cement and an increased risk of oligozoospermia (adjusted OR: 1.1; 95% confidence interval [CI], 0.9–1.4) in their study. In contrast to the findings of De Fleurian et al. [11], who reported a nearly significant correlation between decreased semen quality and cement exposure, with an OR of 2.5 (95% CI, 0.95–6.5), we observed no statistically significant association between occupational cement exposure and SDF Index (DFI). Furthermore, no prior research has investigated the impact of occupational cement exposure on sperm DFI.

Even in individuals not exposed to occupational risk factors, there is a minimal occurrence of DNA fragmentation in spermatozoa. Several factors may contribute to this phenomenon, including but not limited to age, lifestyle choices, sedentary work habits, infections, and exposure to external factors such as air pollution, environmental contaminants, ionizing radiation, and ambient temperatures. The origin of DNA fragmentation in spermatozoa is nearly inevitable in our everyday lives. Hence, it is worth noting that DNA fragmentation in spermatozoa is a phenomenon that can manifest in males, albeit with varying degrees of prevalence.

Our research offers several notable advantages. Firstly, we conducted a comprehensive assessment of occupational exposure through a questionnaire. This knowledge regarding occupational risk factors can prove to be a valuable tool in clinical settings, aiding medical professionals in the diagnosis and treatment of infertile couples by contributing to a better understanding of the suboptimal SDF Index (DFI). Additionally, our results were adjusted for potential confounding factors that could have an association with sperm DFI. To minimize potential bias, the interviews were conducted in a way that ensured the interviewer had no prior knowledge of the sperm DFI results.

Furthermore, we recruited participants from the same center, collected semen samples consistently, and analyzed sperm DFI using a standardized protocol. The TUNEL method for assessing sperm DFI, based on our experience and the literature, is presented as a valuable tool and a superior fertility indicator compared to standard semen analysis. Lastly, our study holds significance due to the conflicting data in this area and the relatively large sample size.

Limitations

However, our research exhibits several limitations. Firstly, our study population consisted exclusively of infertile men, making it unfeasible to analyze a representative sample of the general male population. Given that these men represent only a subset of the population, it is crucial to exercise caution when interpreting the findings of such research. Additionally, the retrospective nature of the study, relying on data from a single institute's database, introduces the potential for selection bias and limits the generalizability of the results.

The second limitation stems from the use of a self-reported questionnaire as a qualitative measure of exposure and exposure type. Obtaining exposure data through participant interviews can be a challenging task, as their responses may not be reliable due to susceptibility to recall bias and exposure misclassification. As a result, this method is considered less precise compared to biological evaluations of exposure, which offer greater accuracy. However, we assumed that participants had adequate knowledge of their respective work environments.

Third, some of our sub-groups had relatively small sample sizes, leading to wide confidence intervals that could introduce observation bias.

Fourth, our research did not assess the duration or intensity of occupational exposure, which are crucial factors for evaluating their impact on reproductive function.

Finally, due to practical constraints, we were unable to comprehensively analyze the influence of other potential confounding variables, such as body mass index (BMI), education and income levels, physical activity, cell phone use, drug use, and coffee consumption, on sperm DNA damage.

Additional research is necessary to validate the observed associations in this study and implement relevant interventions based on these findings. To thoroughly investigate the link between occupational exposures and DNA fragmentation, comprehensive epidemiological studies should be undertaken. These studies should encompass measurements of bodily excretions, atmospheric specimens, and volatile organic compounds in the environment.

Conclusion

In summary, our research has successfully highlighted that occupational exposure to solvents, metals, pesticides, mechanical vibration, and heat may be considered risk factors associated with increased SDF. Consequently, occupational risk factors should be recognized as potential threats to sperm fertility and reproductive health. This study also reaffirms the utility of utilizing a questionnaire to assess occupational exposure, advocating for its integration into routine consultations to aid in the detection and management of occupational hazards among infertile men. Moreover, it can serve as a valuable tool for patient communication regarding potential workplace risks.

This study stands as the first in Turkey to establish a link between self-reported occupational exposures and SDF Index (DFI). Consequently, our findings can inform health policymakers about the impact of occupational exposure on the reproductive health of the labor force in Turkey. Additionally, men grappling

with infertility should carefully scrutinize their work history, considering that exposure to specific agents may contribute to, if not trigger, infertility.

Finally, our research provides clinicians with valuable insights into occupational hazards, enabling the development of more effective infertility treatment strategies tailored to address specific risk factors. Future research and public health interventions are imperative to gain a more comprehensive understanding of occupational exposures and their implications.

Acknowledgments

The authors extend their heartfelt gratitude to Prof. Ates Kadioglu, from the Department of Surgical Sciences, Division of Urology at Istanbul University, for providing invaluable assistance with clinical data.

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J Surg Med. 2023;7(10):700-704.
DOI: 10.28982/josam.7726

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Revision rhinoplasty with free diced cartilage grafts: Outcome evaluations with the Nasal Obstruction Symptom Evaluation (NOSE) scale

Hüseyin Kandulu

Huseyin Kandulu Clinic for Plastic Surgery, Istanbul, Turkey

ORCID ID of the author(s)

HK: 0000-0002-8011-8839

Abstract

Background/Aim: The Nasal Obstruction Symptom Evaluation (NOSE) scale is a validated, reliable, and feasible instrument used to evaluate nasal obstruction severity. We aimed to assess patient satisfaction using the NOSE score after revision rhinoplasty with free diced cartilage (fDC) grafts.

Methods: In this cross-sectional study, 36 patients who underwent a revision rhinoplasty procedure completed the Turkish version of the NOSE questionnaire before and six months after rhinoplasty. Pre- and postoperative NOSE scores were compared using the Mann Whitney U test.

Results: The pre- and postoperative total mean NOSE scores were 68.06 and 8.47, respectively. The NOSE score significantly decreased six months after rhinoplasty surgery (P<0.001). Adapting to exercise was the parameter with the highest improvement rate.

Conclusion: The outcome of the NOSE questionnaires in patients with nasal deformities shows that a revision rhinoplasty surgery with the placement of fDC grafts contributes to the improvement of nasal functions. The Turkish version of the NOSE scale is a useful tool to assess patient satisfaction among the Turkish population.

Keywords: revision rhinoplasty, diced cartilage grafts, NOSE scale

Corresponding Author
Hüseyin Kandulu
Teşvikiye, Terrace Fulya Teşvikiye Mah. Hakkı Yeten Cad.No.13 Center 1 Kat 11 D.59, Istanbul, Turkey
E-mail: info@huseyinkandulu.com

Ethics Committee Approval
Ethical approval was obtained from the Atlas University institutional review board. Since this was a cross-sectional questionnaire study, written informed consent was obtained from the participants.
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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 27

How to cite: Kandulu H. Revision rhinoplasty with free diced cartilage grafts: Outcome evaluations with the Nasal Obstruction Symptom Evaluation (NOSE) scale. J Surg Med. 2023;7(10):700-704.

Introduction

Rhinoplasty is one of the most prevalent facial surgeries performed in an attempt to improve breathing difficulties or facial structure. Alongside the increasing number of primary procedures, the number of cases requiring secondary surgery has also risen [1,2]. Residual and iatrogenic aesthetic deformities following the procedures, which were not well organized or performed under emergency conditions, constitute a secondary surgical indication. Hence, secondary rhinoplasty, also called revision rhinoplasty, is performed to correct such complications and ameliorate the initial outcomes of primary surgery and patient dissatisfaction. Revision rhinoplasty has an incidence rate of 5-15% [3,4].

In addition to major complications, namely dysfunction, deformities due to grafts or implants used include skin and soft tissue disease and infection, the collapse of the nasal bridge, irregularities of the nasal bridge, and asymmetries, which also cause aesthetic problems [5]. In cases where the results of the primary surgery are not satisfactory to the patient, revision surgery might be mandatory. Revision rhinoplasty is a complicated and challenging operation because of the scar tissue and changes in nasal structure that occurred during the primary surgery. In cases where revision is required, a detailed preoperative evaluation is needed to identify deformities, and further surgical techniques should be well planned. It should be determined whether grafts are needed, and on which part of the nose the operation should take place [6]. Graft material selection among the autografts (bony, cartilage), homografts, and allografts is critical for successful aesthetic and functional results [7,8].

Rhinoplasty surgery should not compromise nasal functions and nasal physiology while providing aesthetic improvement. Patient satisfaction after rhinoplasty depends mainly on two factors. One is the patient's expectation regarding cosmetic aspects, and the other is nasal obstruction, which affects functional satisfaction [9]. While evaluating surgical outcomes, the opinions of the surgeon and the patient do not always coincide. For this reason, patient expectations and nasal airflow should be evaluated in addition to the preoperative and postoperative clinical analysis [10]. Furthermore, revision rhinoplasty is considered a complex procedure due to the traumatization and scarring of the tissues following the primary procedure.

There are several subjective and objective methods for the evaluation of functional and aesthetic outcomes. Acoustic rhinometry, measurement of nasal inspiratory flow, and computed tomography are among the objective methods. However, performing these procedures is not feasible under clinical conditions; thus, subjective methods may be more practical and informative [11].

The Nasal Obstruction Symptom Evaluation (NOSE) scale developed by Stewart et al. is a simple, easy to use, noninvasive, and durable quality of life questionnaire. It is available in different languages, including Spanish, Chinese, Italian, French, Greek, Portuguese, Dutch, and Turkish. The questionnaire consists of five questions to assess the status of nasal obstruction through patient feedback [12,13].

This study aims to evaluate patient satisfaction before and after revision rhinoplasty with free diced cartilage (fDC) autografts using the NOSE scale.

Materials and methods

The study was conducted in a private plastic surgery clinic from August 2021 to May 2022.

A power analysis revealed that a minimum of 26 participants was required to be able to evaluate the statistical significance with 80% power (alpha=0.05) Thirty-six individuals over the age of 18 with a history of previous rhinoplasty who had septal deviation, septal fracture, crooked or saddle nose deformities accompanied with chronic nasal blockage were enrolled. Ethical approval was obtained from the local board. Since this was a cross-sectional questionnaire study, written informed consent was obtained from the participants. The study was conducted in accordance with the Declaration of Helsinki.

Exclusion criteria included the presence of one or more of the following conditions: primary surgery, chronic sinusitis, allergic rhinitis, nasal polyp, acute nasal trauma, and asthma.

The Turkish NOSE (T-NOSE) scale validated by Karahatay et al. [13] was filled out by patients, both before and six months after the surgery. The English version of the scale is shown in Table 1.

Table 1: The English version of the T-NOSE scale; patient survey

	not a problem	very mild problem	moderate problem	fairly bad problem	Severe problem
1. Nasal congestion or stuffiness	0	1	2	3	4
2. Nasal blockage or obstruction	0	1	2	3	4
3. Trouble breathing through my nose	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Unable to get enough air through my nose during exercise or exertion	0	1	2	3	4

Over the past 1 month how much of a blend were the following conditions for you? Please circle the most correct response

The total NOSE score was calculated for each questionnaire by summing the scores of all questions and multiplying them by 5, with a total score ranging between 0-100.

According to the calculated total score, the severity of nasal obstruction was classified as mild (5-25), moderate (30-50), severe (55-75), and extreme (80-100).

All patients were operated on with an open rhinoplasty technique using conventional endotracheal intubation under general anesthesia.

fDC, harvested from the septum, rib, or ear cartilage was prepared and placed according to Kreutzer et al. [14].

Patients were hospitalized for one day after surgery. Cold compresses for 24 hours, oral antibiotics and analgesic treatments were applied. Sutures and splints were removed on the seventh day of the operation.

Statistical analysis

SPSS.v18 for Windows (IBM, New York, USA) was used for statistical analyses. Normality distribution of NOSE scores was tested by Kolmogorov–Smirnov test. The Mann Whitney U-test was applied to compare mean NOSE scores. A *P*-value of <0.05 was accepted for statistical significance.

Results

The baseline demographic and clinical characteristics of 36 patients have been summarized in Table 2. According to this table, saddle nose was a common condition among the patients. All patient underwent secondary surgery procedures.

Table 2: Baseline demographic and clinical characteristics of patients

Demographic data	
Total patients, n	36
Age (years), mean (SD)	33.64 (9.36)
Gender (n; male/female) - (%; male/female)	27/9 - 75/25
Deformity	
Saddle nose, n (%)	23 (63.88)
Deviated septum, n (%)	5 (13.88)
Septal fracture, n (%)	5 (13.88)
Crooked nose, n (%)	3 (8.33)

SD: standard deviation

The calculated means of pre-op and post-op NOSE scores, standard deviations, confidence intervals (95% CI) and p-value are given in Table 3. We observed a significant difference between the pre- and postoperative NOSE scores.

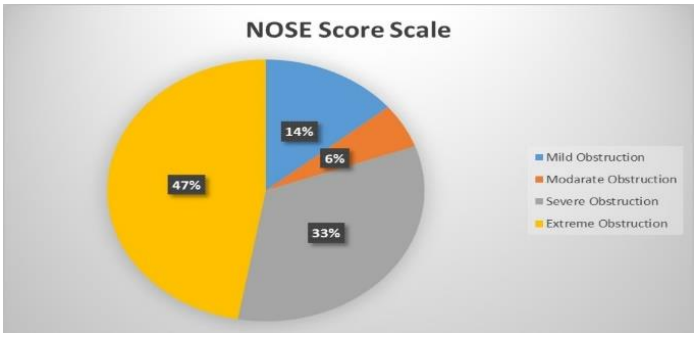
Table 3: Calculated means of pre-op and post-op NOSE scores, standard deviations, confidence intervals and the *P*-value

	Mean	**SD**	**95% CI**	***P*-value**
Pre-operative NOSE Score	68.06	26.44	60-80	<0.001
Post-operative NOSE Score	8.47	7.44	5-10	

SD: standard deviation, CI: confidence interval

Classification of patients according to their nasal obstruction status depending on pre-op NOSE scores is shown in Figure 1. The frequency of extreme obstruction was the highest with a frequency of 47%. This was followed by severe, mild, and moderate levels of obstruction (33%, 14%, and 6%, respectively).

Figure 1: Classification of patients according to their nasal obstruction status depending on pre-op NOSE scores



Mean values of the NOSE score of each question in the questionnaire are presented in Table 3. The mean score of air flow during exercise was higher than other conditions for the pre-operative status, and exhibited the highest improvement following the surgery.

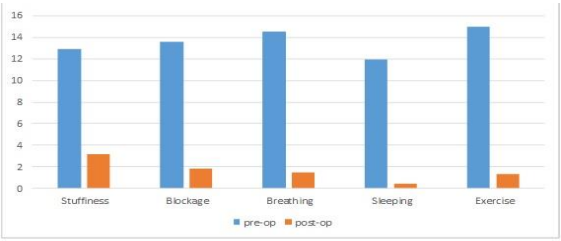
Table 1: Mean values, standard deviations and confidence intervals of NOSE score of each question in questionnaire

	Pre-op			**Post-op**			
	Mean	**SD**	**95% CI**	**Mean**	**SD**	**95% CI**	***P*-value**
Stuffiness	12.92	5.52	11.05-14.79	3.19	2.43	2.37-4.01	<0.001
Blockage	13.61	6.04	11.56-15.66	1.86	2.71	0.88-2.72	<0.001
Breathing	14.58	5.91	12.59-16.58	1.38	2.56	0.52-2.25	<0.001
Sleeping	11.94	6.57	9.71-14.17	0.44	1.44	0-0.94	<0.001
Exercise	15	5.85	13.02-16.98	1.28	2.24	0.52-2.04	<0.001

SD: standard deviation, CI: confidence interval

Patients' satisfaction six months after surgery on each situation in the questionnaire is depicted in Figure 2.

Figure 2: Improvement of patients' satisfaction six months after surgery according to NOSE scores



Discussion

Since rhinoplasty is a more demanding operation when compared to other facial aesthetic surgeries, patient satisfaction is an indicator of the performance and surgical approach [15,16]. Hence, in this study we aimed to evaluate the quality of life using the NOSE scale in patients who underwent revision rhinoplasty with fDC grafts. The use of fDC grafts is an efficient and easily applicable method in rhinoplasty surgery, with no cost. It is adequate for the personal tailoring and shaping of the nose regions, especially the dorsum. In addition, the autologous nature of these grafts is associated with lower complication rates, and higher chondrocyte viability, enabling the diffusion of supplementary chemicals inside the graft material [14].

In this study, we used fDC grafts in all patients in an attempt to reduce the patient burden from the initial surgery and provide a better-shaped and functioning nose, which would not require an additional rhinoplasty procedure in the future.

The NOSE scale is a practical instrument that has been used to evaluate the final outcomes of rhinoplasty surgery by several authors [17,18]. In a meta-analysis conducted by Rhee et al. [18], 19 study groups consisting of 725 patients reported an improvement of NOSE scores following the surgery, which is similar to our findings. They further reported a mean NOSE score of 15 for patients who were asymptomatic and had no history of nasal airway obstruction. This score could overlap with that of a healthy population with no complaints, concluding that, despite the concordancy of the published data, postoperative scores might be biased or placebo-influenced, as they had the similar mean NOSE score of the asymptomatic population.

On the other hand, Mondina et al. [19] reported that the NOSE scale was moderately correlated with patient satisfaction, with a significant difference between baseline days and six months after surgery for each variable of the questionnaire. In our study, we observed a similar improvement for each question and the total NOSE score, setting the duration between the two surveys at six months. Although Gerecci et al. [17] reported that one to three months was sufficient for the recovery of nasal airway blockage, they also mentioned that the recovery period could last up to ten months. Rhee et al. [18] reported a general follow-up period extending from one month to longer than three years to evaluate the NOSE score. While they subdivided the postoperative follow-up period into three different time ranges from one to six months after the operation, Kumar et al. [20] reported a significant amelioration of NOSE score baseline means, with a decreasing trend of the mean value from 71 to 19 within the first month, 10 on the third month, and 9.50 on the sixth month. Implementing similar time intervals, Saratziotis et al. [21] embraced a study duration of 18 months; however they obtained similar results. In our study, we did not construct the follow-up period into time intervals; however, despite this difference, we also observed that the mean value of the NOSE score significantly changed within the six months following the surgery.

The rate of revision rhinoplasty is increasing due to the unsatisfactory and inefficient results obtained from the initial surgery. Alsubeah et al. [22] conducted a prevalence study in Saudi Arabia involving 1,370 individuals, and reported that the prevalence of individuals who considered undergoing revision

rhinoplasty was 44.7% in the Saudi population. They also concluded that in half of these cases, the main reason for undergoing revision rhinoplasty was an aesthetic concern. In another study including 3,525 patients, Sibar et al. [4] reported that the revision rhinoplasty rate was 10.8% in their patient group. Unlike Sibar's study but similar to Alsubeah's, our revision rate was 63.88%, and we observed that the most common causes for revision surgery were saddle nose or a deviated septum.

Kotzampasakis et al. [23] conducted a study to assess the NOSE score of patients who underwent classical rhinoplasty for aesthetic concerns, and without functional interventions to the nasal cavity, septum or conchas. They observed a significant difference between pre-and post-operative NOSE scores, suggesting that an aesthetic rhinoplasty procedure could result in functional satisfaction. In their study, 59 out of 100 patients were smokers; hence, there was no difference between smokers and non-smokers. There were no smokers in our study, thus we could not achieve a comparison among this group.

Several authors have reported the finesse of the fDC grafts in rhinoplasty, with an emphasis on the low complication rate and donor site morbidity [24-26]. In our study, we did not observe graft-related complications, and graft survival was at its highest for all cases. We also suggest that, the use of fDC grafts is the primary source of the study findings, since the improvement rates in the NOSE scores were significantly higher after the surgery for the entire study population, regardless of the deformity.

Bezerra et al. [27] advised that it is essential to use the native language-adapted and validated version of the NOSE scale to compare the questionnaire responses with other studies. Therefore, one of the strengths of our study is the use of a native language adapted and validated questionnaire to ensure the consistency of the responses. The T-NOSE, adapted and validated by Karahatay et al. [13], was a reliable, valid, and responsive version, with Cronbach's alpha coefficient values of 0.938 and 0.942 for test and re-test, respectively. This indicated a robust internal reliability, showing the efficiency of T-NOSE in evaluating septal deviation and nasal obstruction.

Several studies reported that the best improvement after rhinoplasty was in spontaneous nasal breathing (Question 3), whereas in our report, it was the adaptation to exercise (Question 5) [20,28,29]. This variation could depend on the complaints and expectations of patients, age, profile, presence of concomitant diseases (diabetes, hypertension) or conditions as well as the surgical techniques used for rhinoplasty [29].

Limitations

Our study has two essential limitations to declare. Firstly, we had a small number of patients, indicating that the surgeon who performed the surgeries conducted the questionnaires in person with a face-to-face approach. Therefore, we limited the number of patients and the follow-up time in an attempt to keep a stable and qualified surgical practice and questionnaire. Secondly, we did not make a comparison with other available patient satisfaction questionnaires such as the Rhinoplasty Outcome Evaluation (ROE) or the FACE-Q rhinoplasty module. However, our reason for not performing the ROE questionnaire was to investigate functional recovery after rhinoplasty, whereas for the FACE-Q, it was due to the lack of a Turkish-validated version.

Conclusion

The T-NOSE scale is a useful and subjective tool for the evaluation of functional outcomes and patient satisfaction after revision rhinoplasty. The severity of nasal obstruction significantly decreased six months after the procedure. Despite the need for future studies from different parts of the globe with larger number of individuals and a longer follow-up period, a secondary rhinoplasty surgery with the use of fDC grafts contributes to the improvement of the quality of life by eliminating patient dissatisfaction following the primary surgery.

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J Surg Med. 2023;7(10):705-708.
DOI: 10.28982/josam.8000

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Evaluation of risk factors for anal human papillomavirus infection in heterosexual women diagnosed with human papillomavirus associated cervical dysplasia

Utku Özgen

Department of General Surgery, Pamukkale University School Of Medicine, Denizli, Turkey

ORCID ID of the author(s)
UÖ: 0000-0002-6481-1473

Corresponding Author
Utku Özgen
Department of General Surgery, Pamukkale University School Of Medicine, Denizli, Turkey
E-mail: dr_utkuozgen@yahoo.com

Ethics Committee Approval
The study was approved by the Pamukkale University Medical Ethics Committee (May 5, 2019 / 05).
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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 27

Abstract

Background/Aim: Cervical dysplasia is a well-recognized precursor to cervical cancer, and human papillomavirus (HPV) infection is the primary causative agent in its development. The intricate relationship between cervical and anal HPV infections remains understudied. There have been no established risk factors determined for anal HPV infection in women without a history of anal intercourse. This study aims to address this critical knowledge gap by evaluating the risk factors for anal HPV infection in a homogeneous population of heterosexual women with HPV-associated cervical dysplasia.

Methods: This retrospective cohort study was carried out in a single tertiary center and comprised women between the ages of 30 and 65. Women diagnosed with either low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL) and without a history of anal intercourse were included in the analysis. Participants without a histological or colposcopic diagnosis were excluded from the analysis. Women with a history of prior cervical therapeutic intervention, previous cervical or genital dysplasia, known immunosuppressive disorders, current immunosuppressive medication use, a past cancer diagnosis, or a history of HPV vaccination were also excluded. Anal sampling was performed for HPV infection within the first year after the initial diagnosis of cervical dysplasia. Patient characteristics including smoking status were extracted from patient files.

Results: Overall, 186 women who met the inclusion criteria were tested for active anal HPV infection of the anal canal. Active anal HPV infection was found in 96 (51.6%) of the patients. In women with active anal HPV infection, 31 (32.3%) were found to have only HPV 16/18 genotypes, and 22 had HPV16/18 along with other high-risk types. When risk factors were analyzed, only current smoking was found to be associated with anal HPV infection in this group of women. Overall, 40.6% of the women with active anal HPV infection were smokers; however, only 25.6% of the women without anal HPV infection were current smokers (P=0.029).

Conclusion: Women had a high risk of active anal HPV infection during the diagnosis of cervical intraepithelial neoplasia. Current smoking was the only identifiable risk factor for anal HPV infection in women without anal intercourse history.

Keywords: anal cancer, cervical intraepithelial neoplasia, human papillomavirus, screening

Introduction

Human papillomavirus (HPV) is one of the most prevalent sexually transmitted infections worldwide, representing a main cause of cervical and anal cancer [1]. While the association between HPV and cervical dysplasia in women has been extensively studied, the simultaneous presence and impact of anal HPV infection in this population, specifically among heterosexual women diagnosed with HPV-associated cervical dysplasia, have received comparatively limited attention [2].

Cervical dysplasia is a well-recognized precursor to cervical cancer, and HPV infection is the primary causative agent in its development [3,4]. However, the intricate relationship between cervical and anal HPV infections remains understudied, even though the co-occurrence of these infections can have profound implications for disease progression and management. Emerging evidence suggests that women with cervical dysplasia may be at an elevated risk for anal HPV infection due to shared risk factors, such as sexual behavior and immune status [5]. The potential consequences of concurrent cervical and anal HPV infections, including an increased risk of invasive cervical cancer and anal cancer, underscore the importance of elucidating the risk factors and epidemiological patterns associated with this dual infection.

In the literature, most studies on the presence of anal HPV have been conducted on men or HIV-positive patients. Research in women, especially those that include anal HPV screening along with cervical cancer screening, is quite limited. Moreover, there have been no established risk factors for anal HPV infection in women without a history of anal intercourse. This study aims to address this critical knowledge gap by evaluating the risk factors for anal HPV infection in a homogeneous population of heterosexual women with HPV-associated cervical dysplasia. The analysis in this specific population will shed light on the risk factors and natural history of these infections. These results may also provide critical insights for our understanding of concurrent anal HPV infection and, therefore, provide a foundation for the development of anal cancer screening in high-risk patients.

Materials and methods

Study population

This retrospective cohort study was carried out in a single tertiary center. Approval was obtained by the Institutional Ethics Review Board from the same center (Pamukkale University Medical Ethics Committee May 5, 2019 / 05). The study cohort comprised women between the ages of 30 and 65.

The study's inclusion criteria were: women over 30 years of age who had previously tested positive for high-risk cervical human papillomavirus (HR HPV) prior to their colposcopy admission, and those with a histological diagnosis of either low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL). LSIL cases underwent conservative management, while standard cervical excision procedures were performed for initial HSIL diagnoses.

Participants without a histological or colposcopic diagnosis were excluded from the analysis. Women with a history of prior cervical therapeutic intervention, previous cervical or genital dysplasia, known immunosuppressive disorders, current immunosuppressive medication use, a past cancer diagnosis or a history of HPV vaccination were also excluded. Collected data for each participant included age, number of sexual partners, age at first sexual encounter, parity status, smoking habits, and HPV genotypes upon admission. Based on histopathological examination results, patients were classified into either the LSIL or HSIL group. Presence of the HPV infection was grouped into three sections: only HPV16/18; only other high-risk HPV; and HPV 16/18 along with other HPV types.

Specimen collection and HPV genotyping procedure

Anal sampling was performed within the first year after the initial diagnosis of cervical dysplasia. To obtain these samples, Dacron swabs were gently inserted into the anal canal and rotated in a circular manner. Subsequently, these swabs were preserved in a liquid transport solution and sent to the microbiology laboratory. The Advanced XL NA Purification-EZ1® device from Qiagen Inc. in Valencia, CA, was used for DNA extraction. HPV DNA amplification was carried out using the 14 Real-TM Quant kit from NLM in Settala MI, Italy. In cases where the initial sample was deemed inadequate for analysis, additional anal swabs were collected. Laboratory staff was blinded to the cervical HPV results of the patients.

Statistical analysis

Statistical analyses were conducted using PSPP 1.0.1 and R software (with the EasyR plugin). The distribution of continuous variables was assessed using the Shapiro-Wilk test to determine normality. Parametric t-tests were applied to normally distributed continuous variables, while nominal variables were analyzed using Pearson's chi-square or Fisher's exact tests when applicable. Continuous variables were presented as the mean (SD), and categorical variables were reported as the number of cases and their respective percentages. A *P*-value of less than 0.05 was considered statistically significant.

Results

Overall, 186 women who met the inclusion criteria were tested for active anal HPV infection of the anal canal. All patients had previously undergone colposcopic evaluation after being referred from the national HPV-based cervical cancer screening program. A diagnosis of high-grade or low-grade cervical lesions was extracted from the histopathological examination reports of the cervical biopsy materials and the colposcopic examination results. Since patients were initially referred after the cervical cancer-screening program, all of them had active cervical HPV infections. Baseline characteristics of the study population are presented in Table 1.

Table 1: Characteristics of the study population with respect to their cervical pathology

	Low-grade cervical intraepithelial lesion (n=64)	High-grade cervical intraepithelial lesion (n=122)	*P*-value
Age (years)	45.3 (9.3)	43.8 (8.8)	0.302
Parity	1.8 (0.9)	2.0 (1.0)	0.153
Presence of menopause	24 (37.5%)	40 (%32.8)	0.520
First coital age (years)	19.9 (3.8)	20.4 (4.3)	0.582
Active smoking	15 (23.4%)	47 (38.5%)	0.038

HPV: Human Papilloma Virus

Initially, 101 (54.3%) patients were referred with cervical HPV16/18 genotypes. Overall 96 (51.6%) women were

found to have active anal HPV infection. In women with active anal HPV infection, 31 (32.3%) were found to have only HPV 16/18 genotypes, and 22 had HPV16/18 along with other high-risk types. Distribution of the HPV genotypes in cervical and anal samples in women with and without active anal HPV infection is presented in Table 2.

The association of possible risk factors for active anal HPV infection including age, parity, presence of menopause, first coital age, presence of high-grade cervical lesion, and active smoking is summarized in Table 3. No association was found except for active smoking. Overall, 40.6% of the women with active anal HPV infection smoked; however, only 25.6% of the women without anal HPV infection were active smokers (*P*=0.029).

Table 2: Distribution of the HPV genotypes in cervical and anal samples in women with and without active anal HPV infection

	Active anal HPV infection (n=96)		**No active anal HPV infection (n=90)**	
	Cervical HPV test	Anal HPV test	Cervical HPV test	Anal HPV test
Only HPV 16/18	31 (32.3%)	22 (22.9%)	37 (41.1%)	0
Only other HPV types	43 (44.8%)	58 (60.4%)	42 (46.7%)	0
HPV 16/18 along with other HPV types	22 (22.9%)	16 (16.7%)	11 (12.2%)	0
Total	96 (100%)	96 (100%)	90 (100%)	0

HPV: Human Papilloma Virus

Table 3: Evaluation of risk factors for active anal HPV infection

	Active anal HPV infection (n=96)	**No active anal HPV infection (n=90)**	***P*-value**
Age (years)	44.3 (9.3)	44.3 (8.6)	0.980
Parity	1.9 (1.1)	2.0 (0.9)	0.962
Presence of menopause	35 (36.5%)	29 (32.2%)	0.543
First coital age (years)	19.7 (4.1)	20.9 (4.2)	0.073
Presence of high-grade cervical lesion	66 (68.8%)	56 (62.2%)	0.349
Active smoking	39 (40.6%)	23 (25.6%)	0.029*

HPV: Human Papilloma Virus

Discussion

Anal HPV infection is a major risk factor for anal cancer. Since HPV screening programs have become more frequently used worldwide, the investigation of anal HPV in the management of patients diagnosed with cervical HPV infection has also emerged as an important issue for investigating the future risk of anal cancer in this group of women. However, in this population, there is no universally defined risk factor for anal HPV infection apart from anal intercourse. In this study, we aimed to investigate several possible risk factors for active anal HPV infection in heterosexual women without an anal intercourse history who were referred because of active cervical HPV infection. Our results documented a high risk of active anal HPV infection in this group of women. Possible risk factors were evaluated including age, parity, presence of menopause, first coital age, presence of high-grade cervical lesion, and active smoking. Only smoking was found to be associated with active anal HPV infection in the first year of high-grade or low-grade cervical lesion diagnosis.

D'Hauwers et al. [6] previously reported a similarly high rate (56.3%) of active anal infection in women referred to colposcopy. Interestingly, that study documented a relatively low anal intercourse history (16.9%), implying that most of the women having anal HPV infection may have other risk factors. However, there has been a lack of evidence for defining the risk factors of anal HPV infection in women with low-risk sexual behavior (heterosexual and/or without anal intercourse)

Over the years, with the increasing application of HPV-based cervical cancer screening programs, data related to concurrent anal HPV infection in this group of patients has also started to increase. Another interesting finding among these results is that discrepancies can be relatively commonly observed between anal and cervical HPV genotypes. For example, Guler et al. [7] showed a partial concordance rate of 58.3% between the anal and cervical HPV genotypes. This result can be interpreted as follows: Some women may present with relatively low risk cervical HPV genotypes; however, they may have an active anal HPV infectivity with HPV16/18 that has the highest oncogenic potential [8]. There has been no prospective data to allow us to comment on the long-term consequences of this discrepancy in HPV genotypes. Another research topic about which we do not have sufficient information regarding its long-term effects is the importance of persistence of the anal HPV infection. Valari et al. [9] indicated that 12 months following surgical procedures for cervical intraepithelial neoplasia, 53% of the women tested negative for HPV in the cervix; yet among these, 25% continued to show HPV presence in the anus. There is not ample information about the significance of this finding in terms of long-term risk of developing anal cancer.

HPV vaccination, which is the primary and probably the definitive preventive strategy for anal cancer, is still underutilized in many countries and might not be beneficial for older individuals [10]. Therefore, many researchers have been seeking an effective anal cancer screening strategy that has the ability to reach the success of cervical cancer screening protocols. A recent meta-analysis regarding the accuracy of anal cancer screening modalities in different groups at a higher risk of anal cancer concluded that triage of high-risk groups with HPV testing can reduce referral to anoscopy with adequate sensitivity and specificity rates [11]. The main limitation in this meta-analysis is that it mainly included men who have sex with men (MSM), which does not provide information about our study population. The argument can be made that there is also a need for risk defining information regarding the heterosexual women without anal intercourse history but who have high-risk cervical HPV infection. The most frequently encountered group that needs assessing of anal cancer risk is, in fact, this group.

Several studies have investigated the role of smoking in HPV-related anal disorders. Umutoni et al. [12] focused on HIV negative men who have sex with women (MSW) group and reported that active smokers have a higher risk of anal HPV prevalence and persistence compared to non-smokers. Another study on men, however, documented that smoking is a risk factor for high-grade anal lesions but not for HPV infection [13]. A Hawaiian HPV cohort study also found that smoking is associated with longer persistence of anal HPV infection [14]. To our knowledge, no study has investigated the risk of anal HPV infection in heterosexual women without a history of anal intercourse and have been referred with high-risk cervical HPV infection. The strength of our study is that we focused on a homogeneous group of women who recently attended a screening program. The advantage of such a population is that

besides cervical cancer screening, anal cancer screening can easily be performed via anal HPV screening.

Limitations

The limitation of this study is the lack of prospective follow-up of this group of women, which is needed to draw definitive conclusions regarding the value of anal HPV testing in triage procedures. However, we documented that current smoking is a risk factor for active anal HPV infection in our study population. Further studies are needed to understand the clinical value of high-risk anal HPV infection for both the prognosis of cervical dysplasia and for the long-term risk of anal cancer in women diagnosed with cervical intraepithelial neoplasia. In this research, all patients meeting the inclusion criteria were admitted into the study. According to the results, the "1 - β" value calculated based on the occurrence rates determined in the power analysis was found to be 86%. This calculation indicates that the study has sufficient power. However, since this study was planned using a retrospective cohort design, prospective studies are needed for long-term follow-up results of these patients.

Conclusion

In conclusion, active anal HPV infection is common in patients with cervical intraepithelial neoplasia, even if they do not have a history of anal intercourse. Current smoking is the only identifiable risk factor for anal HPV infection in this group of women. Therefore, testing for anal high-risk HPV infection in women with cervical dysplasia may be valuable for defining the future anal dysplasia risk. Current smoking status should also be asked of these patients, since it is major risk factor for co-existing anal HPV infection. The co-existence of anal HPV infection has the potential to lead to a paradigm shift in the future, where anal cancer screening may be included in cancer screening programs for high-risk women, similar to HPV screening for cervical cancer. Prospective studies are needed to define the clinical value of anal HPV screening in women with cervical intraepithelial neoplasia.

Acknowledgements

I would like to acknowledge the help and effort of Dr. Omer Tolga Guler in conducting this research and assisting with the writing of this manuscript.

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J Surg Med. 2023;7(10):709-715.
DOI: 10.28982/josam.8002

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Factors associated with quality of life in caregivers of patients with multiple myeloma

Esma Evrim Doğan, Naciye Demirel

Department of Hematology, University of Health Sciences, İstanbul Prof. Dr. Cemil Tascıoğlu City Hospital, İstanbul, Turkey

ORCID ID of the author(s)

EED: 0000-0003-0635-2966
ND: 0000-0002-1372-5735

Corresponding Author
Esma Evrim Doğan
University of Health Sciences, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Hematology, Darülaceze Cad. No:27 34384 Şişli, İstanbul, Turkey
E-mail: md.esmaevrimdogan@outlook.com

Ethics Committee Approval
Ethical approval was obtained from University of Health Sciences, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee, Date: 9 March 2023, No: 60.
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.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 27

Abstract

Background/Aim: Advances in the therapeutic treatment of multiple myeloma have continuously led to better prognoses. However, longer lives for patients include complications due to both potential comorbidities and the possible severe side effects of specific treatments. These issues make caring for such patients exhausting. In this study, we investigated the most important factors that negatively affect the quality of life (QoL) of non-professional caregivers of patients with multiple myeloma (MM).

Methods: This study was a cross-sectional study conducted between March 2023 and August 2023. The caregivers of 144 patients with MM were assessed for inclusion/exclusion. The demographics of caregivers, their familial relation to the patient, and their socioeconomic status (education, both marital and financial status, and occupations) were recorded. Additionally, data from MM patients were retrieved: (1) clinical and demographic data, (2) light and heavy chain types, (3) disease stage, (4) lytic lesions, and (5) treatment(s). The Caregiver Quality of Life Index-Cancer (CQOLC) questionnaire contains four sub-scores and a total score and was administered to all caregivers who volunteered to participate.

Results: A total of 73 patients and their caregivers were included in the study. For patients, their mean age was 65.7 (11.4) years, 52% were female, and the mean value of the disease duration was 30.5 (16.0–66.5) months. For caregivers, their mean age was 47.2 (12.8) years, and 63% were females. Multivariable linear regression revealed that higher (>40 years) caregiver age was independently associated with a higher CQOLC Burden and Positive adaptation score. Being a female caregiver was independently associated with a higher CQOLC Disruptiveness score. Having university-level or higher education status was independently associated with a lower CQOLC Financial Concerns score. In terms of the overall score, we found that higher (>40 years) caregiver age and the gender of the caregiver (female) appear to be factors that are independently associated with higher CQOLC total scores, whereas being a second-degree relative to the patient independently lowered the total score.

Conclusion: Among caregivers of MM patients, those who were older, female, and/or the first-degree relative of the patient (versus second-degree) with having lower education (versus university or higher) resulted in an improved caregiver QoL. The gender bias among caregivers is also a novel finding.

Keywords: multiple myeloma, caregiver, quality of life, female, high age, educational level, relatives

How to cite: Doğan EE, Demirel N. Factors associated with quality of life in caregivers of patients with multiple myeloma. J Surg Med. 2023;7(10):709-715.

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy with an incidence that has steadily increased over the past ten years [1]. MM is marked by abnormal clonal plasma cells in the bone marrow that potentially lead to destructive bone lesions, kidney damage, and cytopenia [2]. Despite therapeutic advances leading to better patient prognoses, MM is ultimately a fatal disease [3,4]. MM causes long-term complications, and its treatment can cause severe side effects. Most MM patients suffer from debilitating conditions, including fatigue, bone pain, frequent infections, renal failure, and peripheral neuropathy, all of which reduce health-related quality of life (QoL) for the patients [1,4,5]. Moreover, considering that MM is often diagnosed in older adults, patient comorbidities may cause worsening of MM-related morbidities (1, 3, 5). A growing number of studies have demonstrated the severe impact of MM on QoL, leading to dependency on caregivers [1,6,7] and necessitating long-term care.

Long-term care for MM patients is sometimes provided by professional caregivers, patient's relatives, or rarely, other acquaintances. Due to the long-term nature of MM treatment, patients and caregivers often devote a significant portion of their time to managing the disease, which can affect their QoL and psychological well-being [8,9]. Regrettably, the QoL and the experiences of caregivers caring for MM individuals are largely unknown [7]. Improving the QoL of caregivers must be an important aspect of healthcare policies since an efficient and compassionate performance will improve the QoL of both the patient and caregiver. The ability to process the demands of caregiving can contribute to better prognosis and therapeutic success. Hence, pinpointing the factors impacting caregivers' QoL and addressing these issues can help alleviate the adverse effects of MM on both caregivers and patients. Nevertheless, research is scarce on this topic [7,10,11], and we do not have enough data to draw definitive conclusions about issues affecting either population.

The Caregiver Quality of Life Index-Cancer (CQOLC) questionnaire, a self-administered rating scale, was developed by Weitzner et al. in 1999 to evaluate the QoL of caregivers with cancer [12]. In this study, we aimed to report the QoL of non-professional caregivers of MM patients in our population and to identify the most important factors that may have an impact on QoL based on CQOLC questionnaire.

Materials and methods

Setting and ethical statement

This cross-sectional study was conducted at the Hematology Department of Prof. Dr. Cemil Taşcıoğlu City Hospital in Istanbul, Turkey. The study procedure was thoroughly explained to all participants, and written informed consent was obtained from both caregivers and patients before inclusion in the study. The study was designed with due consideration for ethical principles, adhered to the Declaration of Helsinki and its subsequent amendments, and received approval from the Ethics Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (Date: 9 March 2023, No: 60).

Study population

The study assessed the principal caregivers of 144 MM patients who were diagnosed between January 2008 and July 2021 and who were not receiving professional care and regularly presenting for follow-up at our hospital. Caregivers eligible for inclusion were defined as those who had been providing care to the patient from the time of the diagnosis until the questionnaire was administered. Using the method, we were able to avoid uncoupling of patient–caregiver data and prevent biased outcomes at both ends of the spectrum (long-term and recent caregivers). We are aware that this approach introduces a secondary concern, namely that the challenges faced by caregivers working for 15+ years would not resemble those providing caregiving for only two years. Exclusion criteria included caregivers below the age of 18, individuals unwilling to participate, caregivers whose patients had passed away, those with known psychiatric or cognitive disorders, individuals with a known history of cancer diagnosis, individuals who were not the primary caregivers, and/or professional caregivers.

Data collection

Patient data

MM was diagnosed according to current international guidelines [13-15]. The following data of the patients about demographical features, diagnosis, and follow-up were obtained from the hospital computer database and patient files. Patients' ages, genders, and comorbidity information, duration of the disease, light and heavy chain types at the first diagnosis, highest disease stages detected at the diagnosis or during the follow-ups, whether lytic lesions developed at the time of diagnosis or during follow-up, and treatment information including whether they received radiotherapy, whether autologous stem cell transplantation was applied, the type of treatment (primary or advanced), and treatment response (progression, stable disease, partial response, very good partial response, or complete response) were collected. The patients were categorized into two age groups: (1) those aged 60 years or younger and (2) those older than 60 years. To calculate the disease duration (in months), we considered the period from the initial diagnosis to the time of questionnaire completion. Based on disease duration, patients were further divided into two groups: (1) those with a disease duration of 60 months or less and (2) those with a duration exceeding 60 months. Additionally, we classified patients receiving three lines of therapy or fewer as undergoing primary treatment, while those receiving four or more lines of therapy were categorized as undergoing advanced treatment [7].

Caregiver data

Between March and August 2023, the relatives of the patients with MM received phone calls, were informed about the study, and then asked whether the patients received/did not receive professional care. During the initial follow-up examination, face-to-face interviews were conducted with the primary caregivers of the patients. These caregivers were generally family members and expressed their willingness to participate in the study. Information collected during these interviews included caregivers' ages, genders, relationship degrees with the patient, marital status (single, married, widowed), educational backgrounds (literate, primary school, secondary school, high school, university, postgraduate),

employment statuses (unemployed, employed), and income levels (equal or below minimum wage, above minimum wage). Caregivers were categorized into two age groups: (1) those aged 40 years or younger and (2) those older than 40 years. Caregivers who were children, spouses, or siblings of the patient were classified as first-degree relatives, while other relatives serving as caregivers were designated as second-degree relatives.

The Turkish version of the CQOLC (CQOLC-T) questionnaire [16] was administered to all non-professional caregivers. CQOLC measures the effect of caring for cancer patients on the quality of the caregiver's life. The original CQOLC is designed to assess how caregiving for cancer patients impacts the caregiver's quality of life. It encompasses four functional sub-dimensions: (1) physical, (2) emotional, (3) family, and (3) social for a total of 35 items. These items cover various aspects with 10 related to burden, seven related to disruptiveness, seven related to positive adaptation, three related to financial concerns, and eight related to additional factors, such as sleeplessness, satisfaction with sexual functions, daily focus, mental strain, being informed about the disease, protection of the patient, management of the patient's pain, and family interest in caregiving [12]. Each item was rated on a 5-point Likert-type scale: (1) 0 (not at all), (2) 1 (a little bit), (3) 2 (somewhat), (4) 3 (quite a bit), and (5) 4 (very much). CQOLC subscale scores were determined by summing the scores of the items in the subscales. Total CQOLC scores were determined based on the sum of 35 items. The scores of items with negative expressions were reversed in which 0 is converted to 4, 1 to 3, 3 to 1, and 4 to 0. The total CQOLC scale score could range from 0 to 140 with a higher score indicating a better QoL [12].

Validation of the Turkish scale was done by Bektas et al. [16] and Ozer et al. [17]. As a result of this validity study, items 4, 10, 12, 16, 22, 23, 27, 28, 34, and 35 were removed from the scale based on the factor analysis.

The CQOLC-T has the same four sub-dimensions as the original scale (burden represents psychological distress based on 10 items), disruptiveness (represents disruption in daily life based on six items), positive adaptation (represents caregiving responsibility based on six items), and financial concerns (three items). Again, each item (n=25) was scored using a 5-point Likert scale to reach a total score range of 0 to 100 points.

Outcomes

The primary outcome of the study was to investigate patient- and caregiver-related factors that affect the total CQOLC-T score and its four subscale scores.

Statistical analysis

The statistical procedures were performed using SPSS. To assess the normality of data, the Shapiro–Wilk test was used. Descriptive statistics encompassed mean and standard deviation (SD) for normally distributed continuous variables, while non-normally distributed variables were expressed as median (1^{st}–3^{rd} quartiles), and categorical variables were presented as frequencies (percentages). Comparative analyses for normally distributed variables were performed using the Student's t-test, whereas the Mann–Whitney U test was used for non-normally distributed variables. To identify the factors independently associated with CQOLC-T scores, multivariable linear regression was applied by incorporating the stepwise selection method. Variables that exhibited statistical significance based on the outcomes of between group analyses were included as predictors in the regression analysis. The significance threshold was set at *P*-values <0.05, indicating statistical significance.

Table 1: Summary of patients' and caregivers' characteristics and index scores

Age, patients	**65.68 (11.38)**
≤60	24 (32.88%)
>60	49 (67.12%)
Sex, patients	
Male	35 (47.95%)
Female	38 (52.05%)
Duration of disease, months	30.5 (16.0 - 66.5)
≤60	53 (72.60%)
>60	20 (27.40%)
Type, heavy chain	
IgG	47 (70.15%)
IgA	20 (29.85%)
Type, light chain	
Kappa	46 (63.89%)
Lambda	26 (36.11%)
Stage	
Stage I	11 (15.28%)
Stage II	13 (18.06%)
Stage III	48 (66.67%)
Lytic lesions	44 (60.27%)
Radiotherapy	14 (19.18%)
Autologous stem cell transplantation	30 (41.10%)
Treatment	
Primary	55 (75.34%)
Advanced	18 (24.66%)
Response to treatment	
Progression	4 (5.48%)
Stable disease	12 (16.44%)
Partial response	18 (24.66%)
Very good partial response	21 (28.77%)
Complete response	18 (24.66%)
Comorbidity, patients	35 (47.95%)
Diabetes mellitus	6 (8.22%)
Hypertension	15 (20.55%)
Heart diseases	7 (9.59%)
Respiratory diseases	5 (6.85%)
Renal diseases	10 (13.70%)
Other malignancies	3 (4.11%)
Others	9 (12.33%)
Age, caregivers	47.19 (12.76)
≤40	19 (26.03%)
>40	54 (73.97%)
Sex, caregivers	
Male	27 (36.99%)
Female	46 (63.01%)
Relationship of caregivers	
First degree	62 (84.93%)
Second degree	11 (15.07%)
Marital status, caregivers	
Single	14 (19.18%)
Married	58 (79.45%)
Widow	1 (1.37%)
Education status, caregivers	
Literate	1 (1.37%)
Primary school	27 (36.99%)
Secondary school	6 (8.22%)
High school	24 (32.88%)
University	13 (17.81%)
Postgraduate	2 (2.74%)
Working status, caregivers	
Not working	40 (54.79%)
Working	33 (45.21%)
Income, caregivers	
Equal or below minimum wage	35 (47.95%)
Above minimum wage	38 (52.05%)
Caregiver Quality of Life Index-Cancer scores	
Burden	24 (17 - 28)
Disruptiveness	9.56 (5.93)
Positive adaptation	8.36 (5.53)
Financial concerns	3 (1 - 6)
Total	43.49 (21.26)

Data are given as mean (standard deviation) or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. IgA: Immunoglobulin A, IgG: Immunoglobulin G

Results

A total of 73 patients and their caregivers were included study. All data are summarized in Table 1. The mean age of the patients was 65.68 (11.38) years, and 38 (52.05% of the) patients

Table 2: Analysis results of Caregiver Quality of Life Index scores with regard to patients' and caregivers' characteristics

	Burden	*P*-value	Disruptiveness	*P*-value	Positive adaptation	*P*-value	Financial concerns	*P*-value	Total	*P*-value
Age, patients										
≤60	21 (12 - 27.5)	0.290	8.04 (6.44)	0.126	6.33 (4.57)	**0.028**	4 (0 - 6.5)	0.868	38.04 (22.03)	0.126
>60	25 (17 - 29)		10.31 (5.58)		9.35 (5.73)		3 (1 - 6)		46.16 (20.58)	
Sex, patients										
Male	24 (16 - 29)	0.916	10.17 (6.26)	0.403	8.63 (5.91)	0.689	4 (1 - 7)	0.772	44.71 (22.55)	0.641
Female	24.5 (17 - 28)		9.00 (5.64)		8.11 (5.23)		3 (1 - 6)		42.37 (20.25)	
Duration of disease, months										
≤60	23 (15 - 27)	0.136	9.21 (6.07)	0.410	7.85 (5.65)	0.205	3 (0 - 6)	0.399	41.53 (21.76)	0.201
>60	26 (20 - 31.5)		10.50 (5.58)		9.70 (5.09)		4 (2 - 6)		48.70 (19.46)	
Type, heavy chain										
IgG	24 (17 - 28)	0.337	10.17 (6.52)	0.129	8.51 (5.40)	0.441	4 (1 - 7)	0.196	45.68 (20.84)	0.138
IgA	24 (7.5 - 26.5)		7.70 (4.57)		7.35 (6.05)		2.5 (0 - 5)		37.15 (22.38)	
Type, light chain										
Kappa	24 (14 - 29)	0.902	9.93 (6.63)	0.485	8.17 (6.03)	0.770	3 (0 - 6)	0.632	43.35 (23.91)	0.924
Lambda	24 (20 - 28)		9.00 (4.60)		8.58 (4.73)		4 (1 - 6)		43.81 (16.51)	
Stage										
Stage I & II	21 (14.5 - 28)	0.437	7.83 (5.43)	0.086	6.92 (5.17)	0.128	3.5 (0 - 5)	0.281	38.54 (18.98)	0.169
Stage III	24.5 (17 - 28.5)		10.40 (6.10)		9.04 (5.68)		3.5 (1 - 7)		45.94 (22.31)	
Lytic lesions										
No	22 (15 - 27)	0.584	8.03 (5.36)	0.074	7.59 (5.17)	0.338	3 (1 - 5)	0.366	39.79 (18.84)	0.230
Yes	24 (17 - 28.5)		10.57 (6.13)		8.86 (5.77)		3.5 (1 - 7)		45.93 (22.60)	
Radiotherapy										
No	25 (15 - 28)	0.950	9.22 (5.65)	0.316	8.17 (5.49)	0.558	4 (1 - 7)	0.358	42.95 (21.13)	0.657
Yes	21.5 (17 - 30)		11.00 (7.04)		9.14 (5.87)		2.5 (0 - 6)		45.79 (22.49)	
Autologous stem cell transplantation										
No	25 (17 - 29)	0.174	10.19 (5.43)	0.285	9.42 (5.44)	**0.049**	3 (0 - 7)	0.905	46.49 (20.78)	0.151
Yes	20.5 (14 - 28)		8.67 (6.57)		6.83 (5.40)		3.5 (1 - 6)		39.20 (21.56)	
Treatment										
Primary	25 (17 - 29)	0.305	9.84 (5.66)	0.493	8.38 (4.99)	0.955	3 (1 - 6)	0.732	44.38 (19.93)	0.536
Advanced	20.5 (14 - 27)		8.72 (6.80)		8.28 (7.10)		3.5 (1 - 6)		40.78 (25.36)	
Response to treatment										
PD & SD & PR	21.5 (13 - 27)	0.155	9.53 (6.42)	0.966	8.59 (6.13)	0.740	5 (1 - 7)	0.124	42.06 (24.80)	0.594
VGPR & CR	24 (17 - 29)		9.59 (5.55)		8.15 (5.03)		2 (1 - 4)		44.74 (17.87)	
Comorbidity, patients										
No	21.5 (14 - 28)	0.304	8.55 (6.20)	0.131	7.21 (4.96)	0.065	2.5 (0 - 6)	0.263	39.95 (20.71)	0.139
Yes	25 (17 - 29)		10.66 (5.50)		9.60 (5.92)		4 (1 - 7)		47.34 (21.48)	
Caregivers										
Age										
≤40	17 (7 - 25)	**0.002**	6.89 (5.76)	**0.022**	5.21 (5.29)	**0.003**	3 (0 - 6)	0.612	31.42 (22.15)	**0.003**
>40	25 (20 - 29)		10.50 (5.75)		9.46 (5.23)		3.5 (1 - 6)		47.74 (19.42)	
Sex										
Male	21 (13 - 26)	**0.009**	6.81 (4.98)	**0.002**	7.00 (5.37)	0.109	3 (1 - 5)	0.333	35.30 (18.84)	**0.011**
Female	25 (17 - 30)		11.17 (5.90)		9.15 (5.53)		3.5 (1 - 7)		48.30 (21.32)	
Relationship										
First degree	24 (17 - 29)	0.097	10.10 (5.63)	0.067	8.82 (5.38)	0.087	4 (1 - 6)	**0.022**	45.92 (19.11)	**0.020**
Second degree	17 (2 - 26)		6.55 (6.95)		5.73 (5.92)		0 (0 - 2)		29.82 (28.04)	
Marital status										
Not married	17 (10 - 25)	**0.010**	7.07 (5.99)	0.067	6.47 (6.55)	0.139	4 (1 - 7)	0.420	34.20 (23.11)	0.057
Married	25 (19 - 29)		10.21 (5.79)		8.84 (5.19)		3 (1 - 6)		45.90 (20.28)	
Education status										
High school or below	24.5 (19 - 29)	**0.009**	10.34 (5.96)	**0.025**	9.21 (5.26)	**0.009**	4 (1 - 7)	**0.044**	47.09 (20.29)	**0.004**
University or above	17 (2 - 25)		6.53 (4.87)		5.07 (5.50)		1 (0 - 4)		29.60 (19.71)	
Working status										
Not working	25.5 (20 - 29)	**0.019**	11.03 (6.21)	**0.019**	9.38 (5.44)	0.083	4 (1 - 7)	0.204	48.90 (20.48)	**0.016**
Working	21 (13 - 26)		7.79 (5.12)		7.12 (5.48)		3 (0 - 6)		36.94 (20.63)	
Income										
Equal or below minimum wage	26 (21 - 30)	**0.008**	11.11 (6.43)	**0.031**	9.69 (5.76)	**0.048**	4 (0 - 8)	0.190	49.57 (23.21)	**0.018**
Above minimum wage	21 (15 - 26)		8.13 (5.11)		7.13 (5.09)		3 (1 - 5)		37.89 (17.82)	

Data are given as mean (standard deviation) or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. IgA: Immunoglobulin A, IgG: Immunoglobulin G

were female. The median disease duration was 30.5 (16.0–66.5) months with <60 months in 72.60% (n=53). The mean age of caregivers was 47.19 (12.76) years, and 46 (63.01%) were females. Fifty-four (73.97%) of the caregivers were older than 40 years, while 19 (26.03%) were 40 years or younger. According to the CQOLC-T survey, the median Burden score was 24 (17–28), Disruptiveness was 9.56 (5.93), Positive adaptation was 8.36 (5.53), Financial concerns 3 (1–6), while the total CQOLC-T score was 43.49 (21.26) points.

Univariate analysis of the relationship between CQOLC-T scores and other variables is presented in Table 2. Accordingly, for patient-related data, age greater than 60 years (P=0.028) and not undergoing autologous stem cell transplantation (P=0.049) were associated with higher Positive adaptation scores. For caregivers, age greater than 40 years was associated with higher Burden (P=0.002), Disruptiveness (P=0.022), Positive adaptation (P=0.003), and total scores (P=0.003). Being a female caregiver was associated with higher Burden (0.009), Disruptiveness (P=0.002), and Total score (P=0.011). Being a first-degree relative of the patient was significantly associated with higher Financial concerns (P=0.022) and total scores (P=0.020). Married couples (caregiver/patient) translated to higher Burden scores (P=0.010). Caregivers who had received university-level or higher education had significantly lower Burden (P=0.009), Disruptiveness (P=0.025), Positive adaptation (P=0.009), Financial concerns (P=0.044), and total scores (P=0.004). Being an employed caregiver was associated with lower Burden (P=0.019), Disruptiveness (P=0.019), and total score (P=0.016). Having an income exceeding minimum wage was associated with lower Burden (P=0.008), Disruptiveness (P=0.031), Positive adaptation (P=0.048), and total scores (P=0.018).

Multiple linear regression analysis (stepwise selection) revealed that high (>40 years) caregiver age (P=0.001) was independently associated with a high CQOLC-T Burden score. Other variables in the analysis, including caregiver sex (P=0.056), caregiver marital status (P=0.526), caregiver education status (P=0.105), caregiver working status (P=0.106),

and caregiver income (P=0.126) were found to be non-significant (Table 3). A female caregiver (P=0.002) was independently associated with a higher CQOLC-T Disruptiveness score. Other variables in the analysis included caregiver age (P=0.066), caregiver education status (P=0.156), caregiver working status (P=0.188), and caregiver income (P=0.153), all of which were found to be non-significant (Table 4). High (>40 years) caregiver age (P=0.003) was independently associated with a higher CQOLC-T Positive adaptation score. Other variables included in the analysis were patient age (P=0.075), autologous stem cell transplantation (P=0.064), caregiver education status (P=0.096), and caregiver income (P=0.130) were found to be insignificant (Table 5). Having a university-level or higher education (caregiver; P=0.036) was independently associated with a lower CQOLC-T Financial concerns score. The other variable included in the analysis, namely, the family relationship of the caregiver to the patient (P=0.122), was found to be non-significant (Table 6). Finally, high (>40 years) caregiver age (P=0.008) and being a female caregiver (P=0.026) were independently associated with higher CQOLC-T Total score, while being a second-degree relative of the patient (P=0.012) was independently associated with a lower CQOLC-T Total score. Other variables in the analysis, including caregiver education status (P=0.276), caregiver working status (P=0.258), and caregiver income (P=0.143), were found to be non-significant (Table 7, Figure 1).

Table 3: Significant factors independently associated with Caregiver Quality of Life Index Burden score, multivariable linear regression analysis

	Unstandardized β	Standard error	Standardized β	*P*-value	95% Confidence interval for β	
(Constant)	15.579	2.063		<0.001	11.465	19.693
Age, caregivers (>40)	8.273	2.399	0.379	**0.001**	3.489	13.057

R^2=0.143, F=11.891, P=0.001

Table 4: Significant factors independently associated with Caregiver Quality of Life Index Disruptiveness score, multivariable linear regression analysis

	Unstandardized β	Standard error	Standardized β	*P*-value	95% Confidence interval for β	
(Constant)	2.456	2.299		0.289	-2.128	7.040
Sex, caregivers (Female)	4.359	1.352	0.357	**0.002**	1.663	7.055

R^2=0.128, F=10.392, P=0.002

Table 5: Significant factors independently associated with Caregiver Quality of Life Index Positive adaptation score, multivariable linear regression analysis

	Unstandardized β	Standard error	Standardized β	*P*-value	95% Confidence interval for β	
(Constant)	5.211	1.202		<0.001	2.813	7.608
Age, caregivers (>40)	4.252	1.398	0.340	**0.003**	1.465	7.040

R^2=0.115, F=9.251, P=0.003

Table 6: Significant factors independently associated with Caregiver Quality of Life Index Financial concerns score, multivariable linear regression analysis

	Unstandardized B	Standard error	Standardized β	*P*-value	95% Confidence interval for β	
(Constant)	6.421	1.258		<0.001	3.912	8.930
Education status, caregivers (University or above)	-2.110	0.990	-0.245	**0.036**	-4.084	-0.137

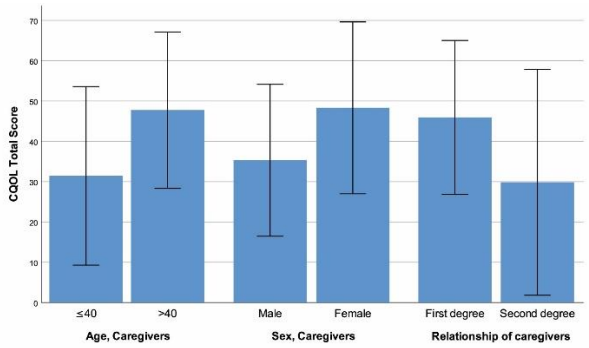
R2=0.060, F=4.547, P=0.036

Table 7: Significant factors independently associated with Caregiver Quality of Life Index Total score, multivariable linear regression analysis

	Unstandardized β	Standard error	Standardized β	*P*-value	95% Confidence interval for β	
(Constant)	34.236	10.791		0.002	12.709	55.764
Age, caregivers (>40)	13.913	5.133	0.289	**0.008**	3.673	24.154
Sex, caregivers (Female)	10.641	4.665	0.243	**0.026**	1.335	19.948
Relationship of caregivers with patient (Second degree)	-15.975	6.179	-0.271	**0.012**	-28.301	-3.649

R2=0.244, F=7.431, P<0.001

Figure 1: Caregiver Quality of Life Index-Cancer Total score, mean and standard deviation, with regard to caregiver age, sex, and familial relationship with patient



Discussion

Cancer is the leading cause of mortality and morbidity in the world [18], and as found with other chronic diseases, cancer has many sequelae and greatly limits self-sufficiency. Patients often require support from other people, usually from their close relatives. These individuals are known as informal or non-professional caregivers. The role of these caregivers is key to providing help and support to such cancer patients, but these caregivers can experience a significant burden on many levels, which can affect their QoL [19]. Due to the challenging characteristics of MM and the palliative approach to treatment, MM has evolved into a chronic disease for numerous patients [1], particularly in relation to the extended life expectancy achieved through improved management [20]. Many patients are living with significant side effects and disabilities and require assistance from caregivers and equipment [20]. MM diagnosis and treatment affects not only the patient but also their relatives, particularly since these relatives are the people who assume the caregiver role [10]. In a pilot study employing the CQOLC scale, the great majority of caregivers reported experiencing heightened levels of stress, possibly in relation to their concerns regarding the health of their loved ones while concurrently witnessing their relative's deterioration [20]. The anxiety experienced by caregivers of MM patients (which originates from concerns about their loved ones), uncertainties regarding patient survival and QoL, and the necessity for frequent visits spanning several years of MM treatment, may contribute to their caregiver-related burden and distress [7,21]. Decreased caregiver QoL may impact the quality of care they provide to MM patients in their care [22]. This decrease is a major concern for both the patient and the caregiver since improving QoL is in fact one of the most important aspects of MM treatment [23].

The study aimed to identify key factors influencing the QoL of caregivers for MM patients. Findings indicate that caregivers over 40 years of age experienced less psychological distress and demonstrated better caregiving capabilities. A minor sex bias was apparent among caregivers with most caregivers being women. Although our data indicate that female caregivers experience fewer disruptions in their daily lives, this reduction in disruptions is likely to be associated with other factors, including employment, education, social functioning, and interpretation of gender roles. Those caregivers with university-level educations or higher expressed more financial concerns. Moreover, caregivers over 40 years of age, females, and first-degree relatives were associated with higher total QoL scores as independent predictors. The results provided by the limited

number of studies on caregivers of MM patients are described. In the multivariate analysis of one study, age, gender, and education status of caregivers and treatment modality of patients with MM were not associated with caregiver QoL or psychological distress. In unadjusted analyses, only older caregiver ages were associated with better caregiver QoL but not with psychological distress [7]. In another study, no correlations were found between assessing unmet needs, caregiver age, patient age, caregiving daily care, caregiving duration, and caregiver QoL [10]. Simoneau et al. suggested that distress did not differ according to caregiver gender, but younger caregivers showed higher distress than older ones [11]. Some studies have shown that the deterioration in the QoL of caregivers of MM patients decreases over time [7,24]. Conversely, research on caregivers of cancer patients in general is notably more abundant. An example from China highlights the significance of caregiver QoL, indicating that it is markedly influenced by the quality of the partner relationship, the presence of chronic illnesses in the caregiver, the patient's daily activities ($r=-0.21$), the duration of cancer ($r=-0.11$), the total number of caregivers ($r=0.21$), and the overall caregiving duration ($r=-0.27$). Notably, the quality of the partner relationship with the patient exerted the most substantial influence on caregiver QoL. However, no noteworthy associations were observed between caregiver age, gender, educational attainment, and QoL in that particular study [25]. The spousal relationship has been documented as a critical parameter affecting QoL of caregivers in other studies [26-28]. Low income, being married, living in rural areas, and other sociodemographic characteristics have also been shown to impact caregiver QoL in other countries [29]. Many studies have shown that family caregivers of advanced cancer patients or allogeneic transplant patients during the peri-transplant period exhibit higher levels of anxiety, depression, and stress [11,24,30].

The caregiver burden can limit all aspects of a caregiver's life, causing anxiety, insecurity, and isolation. These can lead to the loss of social support systems, which can increase the risk of stress and fatigue [31]. Caregivers of MM patients are at risk of higher workload and lower QoL than caregivers of patients with other oncological diseases [32]. Moreover, patients with MM and their caregivers are more likely to suffer from financial problems, including treatment and care costs [22]. In fact, many caregivers are reported to have lost their jobs due to time constraints [24,33]. Metin et al. [22] showed that lower levels of the financial well-being of caregivers of patients with MM negatively affects their QoL, and vice versa. Carreño and colleagues [34] noted that the economic burden of caregivers is not only related to medical services but also to a lack of labor productivity and even job loss. They also reported that this financial burden was linked to higher levels of anxiety and distress experienced by caregivers.

The present findings and literature results demonstrate that older caregivers experience less reduction in overall QoL; however, several other studies did not find a link between age and QoL [7,10,25]. In addition, in contrast to most previous studies [7,11,35], our study also found that female sex, less education, and first-degree relationships were associated with better QoL. In several studies, it was suggested that being a spouse is associated with reduced QoL. It was stated that if the caregiver is a spouse, the reason for the lower QoL may be related to the fact that spouses are less likely to receive help from other people than other non-spouse caregivers. Spouses are the most vulnerable group, and they tend to provide the most comprehensive care [25,36]. The deviation from previous findings concerning first-degree relatives might be attributed to cultural disparities. Additionally, second-degree relatives might be less willing to provide care, while first-degree relatives more readily accept this responsibility. An intriguing discovery in our study was the absence of a significant correlation between QoL results and factors, such as cancer stage, treatment features, and disease duration, all of which are highly peculiar findings in the light of earlier research [11,24,25,30]. This difference may be because our study excluded patients in which the primary caregiver had changed during the study period, thus skewing the population toward younger patients with shorter disease durations. Therefore, the lack of relationships shown for these parameters must be interpreted based on this information.

Caregiving creates physical, emotional, social, and financial problems that burden caregivers and lead to a reduction in their QoL [19,37]. The need for interventions to improve caregiver QoL, reduce their psychological distress, and cultivate adaptive coping strategies that may help improve the shared experience over the MM disease course exists [38]. Unfortunately, supportive care interventions that address the psychological needs of caregivers of patients with MM are lacking [7]. Studies aimed at enhancing the QoL of caregivers have emphasized the significance of social support systems, access to support networks [39,40], implementation of coping strategies [41,42], improvements in economic status [43], training [43,44], exercising practices [19], breathing exercises [19], and counseling sessions [19]. A cross-sectional descriptive study reported that moral support was the most predictive domain for QoL in caregivers of cancer patients followed by practical support and information [44]. These effects have been proven in prior studies. For instance, in a study utilizing a different scale (Quality of Life in Life-Threatening Illness - Family Carer Version), the QoL of family caregivers of patients with advanced cancer was measured before and after multicomponent intervention (Pranayama, yoga relaxation, counseling, and education). Significant improvements were reported in post-intervention test scores [45]. The presented study aimed to highlight potentially correctable factors that may be associated with the QoL of caregivers who care for MM patients. In summary, we can say that caregivers who are younger, male, non-first-degree relatives, and those with higher education levels present a higher risk of lower QoL.

Limitations

The cross-sectional design does not allow for causal relationships, while the exclusive use of self-report measures limits reliability and may have introduced recall bias. The fact that it is a single-center study with a small number of participants might limit the generalizability; however, we employed strict inclusion/exclusion criteria to ensure that the patients and their caregivers were matched in the study. Although limitations from the point of generalizability are present, we believe the results accurately represent the characteristics of our target group.

Laboratory results of patients were not assessed, and we deemed such tests unnecessary for the present hypothesis. Detailed measures that can evaluate the psychiatric conditions of caregivers such as anxiety and depression were not examined. The chronic diseases of caregivers [25] and activities of daily living [25] could have had a threshold effect on QoL-related findings and scores; however, these parameters could not be examined. Finally, it is quite possible that cultural and traditional factors also have an impact on caregiver QoL. Therefore, interpretations of our results should always consider the gender aspect and sociocultural characteristics of the target society.

Conclusion

Our study shows that the caregivers of patients with MM may experience different levels of their QoL. Caregivers who were older, female, first-degree relatives of the patient (versus second-degree), and those with lower education levels (versus university or higher education) had higher QoL. These correlations are evidently caused by multidimensional and multifaceted effects that apply differently to each of the independent factors identified in this study. However, the results suggest that the age, gender, familial relation, and education levels of caregivers should be considered by healthcare professionals to prevent caregiver burnout and adverse mental outcomes. This consideration can make a significant contribution to the QoL of not only caregivers but also the MM patients to whom they are providing essential care.

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J Surg Med. 2023;7(10):716-718.
DOI: 10.28982/josam.7372

Case report

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

A case of laryngeal tuberculosis mimicking supraglottic carcinoma in a pregnant patient and literature review

Deniz Baklaci [1], Anil Cakir Turhan [2], Müge Harma [2]

[1] Department of Otorhinolaryngology, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey
[2] Department of Gynecology and Obstetrics, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey

ORCID ID of the author(s)

BD: 0000-0001-8449-4965
CAT: 0000-0001-7976-4123
HM: 0000-0002-4327-674X

Corresponding Author
Deniz Baklacı
Department of Otorhinolaryngology, Zonguldak Bülent Ecevit University, Faculty of Medicine, Zonguldak, Turkey
E-mail: doktorent@gmail.com

Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 10

Abstract

Tuberculosis (TB) is the most common granulomatous disease, but laryngeal involvement is rare. The risk of developing this clinical form is higher in immunocompromised patients due to primary infection or reactivation of latent TB. Laryngeal TB can be misdiagnosed as laryngeal cancer since they have similar macroscopic lesions, and both cause dysphonia. We present a case of laryngeal TB in a 37-week pregnant patient who complained of dysphonia, odynophagia, and dysphagia. A mass with supraglottic carcinoma findings was discovered during a laryngoscopic examination. The reason for presenting this case is to emphasize the necessity for a high degree of suspicion for laryngeal TB involvement in patients with upper respiratory tract lesions in regions with high TB prevalence, to achieve early diagnosis and treatment.

Keywords: pregnancy, larynx, mass, tuberculosis

Introduction

Tuberculosis (TB) is a chronic bacterial infection caused by a species belonging to the *Mycobacterium tuberculosis* complex. In the second half of the 20th century, the incidence of TB significantly decreased due to the development of effective antituberculosis drugs, improved living standards, and various public health interventions. However, the incidence of TB is showing an increasing trend due to the growing prevalence of drug resistance, immunosuppressive conditions, poor living standards in some parts of the world, travel to developing countries, and the spread of human immunodeficiency virus infections. This trend suggests that laryngeal TB may become more common in the coming years [1].

Women are particularly vulnerable to TB during pregnancy, which is often attributed to immunological changes associated with pregnancy that provide an opportunity for mycobacterial infection or reactivation [2,3]. Compared to non-pregnant women, pregnant women are twice as likely to develop TB, and the disease typically progresses more rapidly and aggressively in this population [4-6].

Laryngeal TB is a rare form of extrapulmonary TB, accounting for less than 1% of all TB cases. The clinical presentation of laryngeal TB is similar to that of laryngeal cancer, and it can cause dysphonia, dysphagia, and dyspnea. Laryngeal edema and granulations can mimic laryngeal cancer, making diagnosis difficult.

This paper reports on a 37-year-old pregnant woman with laryngeal TB who presented to our emergency department with dysphonia, odynophagia, and dysphagia. During her laryngoscopic examination, a supraglottic mass was detected. We discuss our clinical approach and treatment management.

How to cite: Baklacı D, Turhan AC, Harma M. A case of laryngeal tuberculosis mimicking supraglottic carcinoma in a pregnant patient and literature review. J Surg Med. 2023;7(10):716-718.

Case presentation

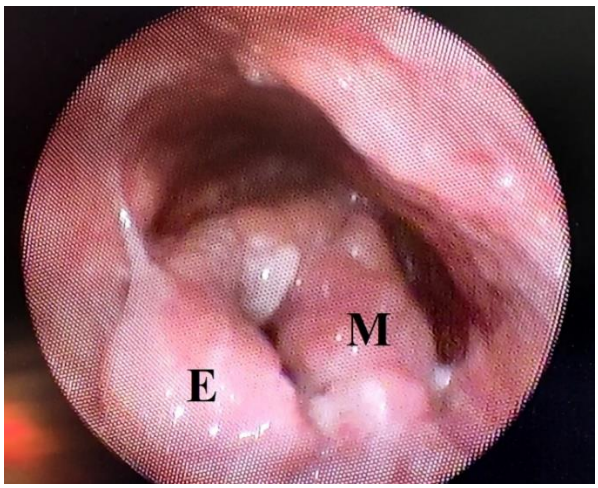
Written informed consent was obtained from the patient. A 37-year-old woman at 37 weeks gestation presented to our clinic with a 10-day history of sore throat, cough, dysphagia, and hoarseness. The patient had no significant medical or family history and had one previous cesarean delivery with a gravida of 2 and parity of 1. She reported no fever, night sweats, weight loss, or hemoptysis; her physical examination was unremarkable.

During rigid laryngoscopy, an ulcerovegetative mass lesion was observed, starting from the epiglottic laryngeal surface and extending to the aryepiglottic folds, arytenoid cartilage, and interarytenoid space. The mass involved the true and false vocal cords and hypopharynx, severely reducing airway patency (Fig. 1). Despite these findings, the patient did not exhibit respiratory distress, and her respiratory rate and blood oxygen saturation were within normal limits. The patient had a smoking history of approximately 20 pack/years. Given the possibility of laryngeal malignancy, direct laryngoscopy and biopsy was planned. After consultation with the obstetrics and gynecology clinic where she was being followed up, the patient was admitted to the hospital. Cold steam and 1 mg/kg steroid treatment were applied for laryngeal edema, and antibiotic treatment was initiated. If necessary, the patient and her relatives were informed about the possibility of emergency tracheotomy, and close respiratory distress monitoring was initiated.

Due to the patient's pregnancy, diagnostic tests such as the tuberculin skin test (purified protein derivative), chest X-ray, computed tomography, and magnetic resonance imaging were not performed. After consulting with the otolaryngology, gynecology, and obstetrics clinics, simultaneous cesarean section and biopsy under direct laryngoscopy were planned. The cesarean section was completed under spinal anesthesia without complications, and a healthy infant with an Apgar score of 9–10, weight of 3.490 g, and height of 50 cm was delivered. The patient was then intubated using a video laryngoscope with a size 5 endotracheal tube, and multiple punch biopsies were taken from many areas of the laryngeal mass under general anesthesia. The histopathological examination revealed necrotizing granulomatous inflammation with no evidence of malignancy.

Based on these findings, the patient was diagnosed with TB with laryngeal involvement, and the chest disease clinic was consulted. Acid-fast bacilli were detected in Ziehl-Neelsen staining of the patient's bronchoalveolar lavage (BAL) fluid, and *M. tuberculosis* was identified in the polymerase chain reaction (PCR) test of the BAL fluid. No pathological findings were observed in the histopathological examination of the placenta. The patient was started on treatment with isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 1,500 mg/day, and ethambutol 1,400 mg/day. No serious side effects were observed during the treatment, and the patient was remotely interviewed once a month. At the end of the 6-month treatment period, follow-up examinations showed the resolution of symptoms and improvement of the mass.

Figure 1: Laryngoscopic image revealing the mass (M) starting from the epiglottis (E) laryngeal surface, extending to the aryepiglottic folds, arytenoid cartilage, and interarytenoid space, involving the true and false vocal cords. E: epiglottis; M: mass.



Discussion

TB is a significant non-obstetric cause of maternal mortality, with an estimated one-third of TB-related deaths occurring in women of childbearing age, predominantly in resource-limited countries [7]. Pregnancy-related changes in the immune system increase the risk of primary TB infection and the reactivation of latent disease. *M. tuberculosis* is the cause of TB, which typically affects the lungs. However, there is also a notable rise in head and neck infections, particularly in developing countries.

Extrapulmonary TB infection commonly affects the cervical lymph nodes (>90%) in the head and neck region, followed by the larynx (2–6%) [8,9]. Involvement of the eye, pharynx, thyroid, sinonasal region, temporal bone, and skull base is less frequent [8-10]. Laryngeal TB typically affects individuals in their 50s or 60s, and initial symptoms include hoarseness, followed by odynophagia, dysphagia, dyspnea, stridor, cough, and hemoptysis [11]. In the case being discussed, the patient's most prominent complaints were odynophagia and dysphonia.

Systemic symptoms are uncommon in laryngeal TB [9,10,12-16]. The primary mode of spread to the larynx and trachea is through expectorated sputum [13,16,17]. Distinguishing between laryngeal TB and laryngeal carcinoma can be challenging, but odynophagia is a significant distinguishing symptom, as it is rarely observed in laryngeal carcinoma [12-16]. During an endoscopic examination of the larynx, laryngeal TB most commonly affects the vocal cords, followed by the epiglottis, ventricular bands and ventricles, arytenoids, posterior commissure, and subglottis [10,15,17]. In addition to edema, hyperemia, or ulcerative lesions, laryngeal TB may also present as a nodule, exophytic mass, or obliteration of an anatomical structure [17]. In the present case, there was an ulceroproliferative mass involving the supraglottic larynx. Due to the absence of pathognomonic features indicative of laryngeal TB and the rarity of the disease in industrialized countries, it can be easily mistaken for laryngeal carcinoma, which is more common [14,18]. The differential diagnosis of laryngeal TB also includes Bartonellosis, syphilis, sarcoidosis, Wegener’s granulomatosis, and fungal infections [8].

Laboratory techniques for detecting *M. tuberculosis* infections include sputum microscopy, sputum culture analysis,

tuberculous PCR testing in sputum or other body fluids, and demonstration of *M. tuberculosis* by histochemical staining in histopathological tissue examination. In the histopathological examination, calcified granulomas in the subepithelial stroma, showing central necrosis surrounded by epithelioid macrophages, Langhans giant cells, and lymphocytes, was a diagnostic finding. Although tomography and chest radiography findings can mimic many other diseases, they cannot diagnose laryngeal TB definitively. In the present case, the histopathological diagnosis revealed a necrotizing granulomatous lesion, and the PCR test of BAL fluid showed M. tuberculosis, which was consistent with laryngeal TB.

The World Health Organization recommends that the treatment of TB in pregnancy should be the same as in non-pregnant women. Exposure of the mother to drug therapy for TB does not pose a risk of congenital anomalies in the fetus, except streptomycin, which can cause ototoxicity [7]. Liver function testing before treatment and frequent follow-ups are essential. Pyridoxine supplementation is recommended for breastfeeding mothers and infants. The infants of mothers taking rifampicin while on isoniazid should also be given vitamin K at birth due to the risk of postpartum hemorrhage [4,19]. Generally, 6 months of treatment is sufficient for complete recovery [20,21]. Methylprednisolone can be used as a supplementary therapy in the presence of lymphadenopathy or laryngeal edema [22,23].

In the present case, cold steam and steroid treatment alleviated laryngeal edema. Tracheotomy may be required in patients with severe dyspnea or those with sequelae after medical treatment. However, a tracheotomy was not performed on our patient, as she responded to steroid and steam treatment, and no oxygenation disorder was observed during close follow-up. During treatment, odynophagia and pain are the first symptoms to resolve, while dysphonia improves as glottic lesions regress. Radiological and endoscopic signs take a few weeks to resolve [22]. If left untreated, laryngeal TB can lead to subglottic stenosis or vocal cord paralysis due to cricoarytenoid joint or recurrent laryngeal nerve invasion [13,17]. The transmission of TB from mother to infant can occur through the utero-hematogenous spread and aspiration of infected amniotic fluid. It can also be transmitted by contact with infected amniotic fluid or genital secretions during the intrapartum period, aerosol spread, or through infected breast milk from an active TB lesion in the breast during the postpartum period. Therefore, the infant should receive the BCG vaccine and isoniazid prophylaxis [7].

Conclusion

TB is a significant non-obstetric cause of maternal mortality, and TB during pregnancy rarely affects the larynx, with laryngeal involvement most commonly associated with pulmonary TB. In this case report, we presented a pregnant patient with pulmonary TB and laryngeal involvement to emphasize the need for a high degree of suspicion for laryngeal involvement in upper respiratory tract lesions to achieve early diagnosis and treatment in regions with high TB prevalence. Adopting a multidisciplinary approach involving relevant medical branches is crucial to prevent complications related to this disease in both the mother and the infant.

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J Surg Med. 2023;7(10):719-721.
DOI: 10.28982/josam.7380

Case report

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

ERCC8-related Cockayne syndrome type-1: A rare entity diagnosed in a Turkish boy

Sinem Kocagil [1], Ali Riza Keklikci [1], Yusuf Aydemir [2], Oguz Cilingir [1], Sabri Aynaci [1], Ebru Erzurumluoglu Gokalp [1], Beyhan Durak Aras [1], Sevilhan Artan [1]

[1] Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Genetics, Eskisehir, Turkey
[2] Eskisehir Osmangazi University, Faculty of Medicine, Department of Pediatrics, Eskisehir, Turkey

ORCID ID of the author(s)

SK: 0000-0003-2595-3919
ARK: 0000-0001-7370-1594
YA: 0000-0003-3318-2747
OÇ: 0000-0002-5593-4164
SA: 0000-0001-8172-7436
EEG: 0000-0002-1275-5174
BDA: 0000-0003-1881-1912
SA: 0000-0001-7658-6309

Corresponding Author
Sinem Kocagil
Department of Medical Genetics, Eskisehir Osmangazi University, Meselik Campus, Professor Dr. Nabi Avci Avenue No:4, 26040, Eskisehir, Turkey
E-mail: sinemkocagil@gmail.com

Informed Consent
The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 October 10

Abstract

Cockayne syndrome (CS, OMIM #216400 and OMIM #133540) is a rare, progressive, multisystemic disorder that results in premature aging and cachectic dwarfism. It is an autosomal recessive disorder with a prevalence of 2-2.5 per million. Pathogenic variants detected in the *ERCC excision repair 6* (*ERCC6*) and *ERCC excision repair 8* (*ERCC8*) genes are responsible for molecular pathogenesis. In this case report, an 11-year-old boy with severe microcephaly, growth retardation, loss of subcutaneous fat tissue, neuromotor developmental delay, bilateral cataracts, and facial dysmorphism but without dermal photosensitivity, who had a novel missense variant in trans configuration with a nonsense variant is presented.

Keywords: Cockayne syndrome, ERCC8 gene, novel variant

Introduction

Cockayne syndrome (CS, OMIM #216400 and OMIM #133540) is an autosomal recessive, multisystemic disorder with a prevalence assumed to be 2–2.5 per million [1]. The main clinical features include microcephaly, growth failure, photosensitivity, developmental delay, cataracts, sensorineural deafness, feeding difficulties, and loss of subcutaneous fat [2]. Three subtypes of CS have been defined based on the clinical expressivity and age of onset of symptoms. In type 1 (classical/moderate), developmental delay and growth failure usually begin in the first 2 years of life. Type 2 is the severe and early-onset form of CS, while type 3 is the mild, late-onset form that may not become apparent until later in childhood [3]. However, the differences between the subtypes are not always clear-cut, and they share a large overlapping spectrum of severity [4]. Most CS cases have increased sensitivity to sunlight because of deficiencies in repairing damaged DNA caused by pathogenic homozygous or compound heterozygous variants in one of two genes: *excision repair cross-complementation 6* (*ERCC6*) (also known as CSB) (OMIM # 609413) or *ERCC8* (also known as CSA) (OMIM # 609412). Although increased sensitivity to sunlight is a common feature, it should be kept in mind that microcephaly and postnatal growth failure are the major findings for CS suspicion in any child.

How to cite: Kocagil S, Keklikci AR, Aydemir Y, Cilingir O, Aynaci S, Gokalp EE, Aras BD, Artan S. ERCC8-related Cockayne syndrome type-1: A rare entity diagnosed in a Turkish boy. J Surg Med. 2023;7(10):719-721.

Case presentation

Our patient was referred to our outpatient clinics by the Pediatric Gastroenterology Department to evaluate dysmorphic features. He was delivered by normal spontaneous vaginal delivery at 36 weeks, resulting in an uneventful pregnancy of non-consanguineous parents. Birth parameters for gestational age were 2360 g (10–25th percentile) and 48 cm (50–75th percentile). He passed the neonatal hearing test. He could sit without support at around 15 months and walk with support at the age of 3. Progressive contractures of the lower extremities developed around age 6, and he became wheelchair-dependent. He could speak only a few words and was diagnosed with bilateral cataracts at the age of 3. His cranial MRI showed posterior fossa dilatation and was reported as a Dandy-Walker malformation variant (Figure 1). Repetitive serum transaminase levels were elevated, so a liver biopsy was performed, which showed non-specific hepatocyte degeneration. Growth hormone replacement therapy was administered at the age of 10 for 1 year, but he did not benefit. At age 11, a physical examination revealed a weight of 11.5 kg (-7.38 SD), a height of 102 cm (-6.6 SD), and an OFC of 45 cm (-6.37 SD). He had deeply set eyes, a prominent nasal bridge, a pointed chin, decreased subcutaneous fat tissue, multiple dental caries, and abnormal-sized and shaped teeth. Thin extremities and spasticity in the lower extremities were noted (Figure 2).

Figure 1: Sagittal T1-weighted MRI of patient showing posterior fossa dilatation.

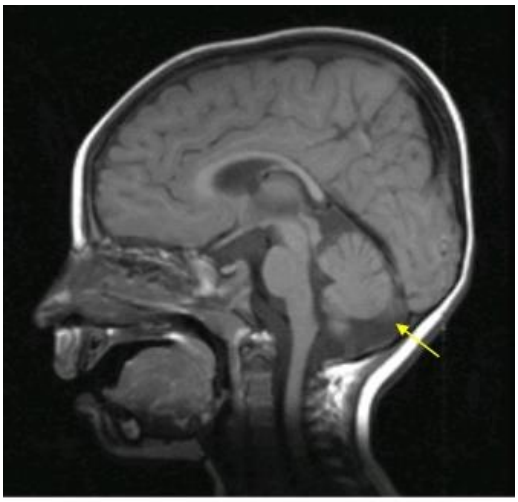
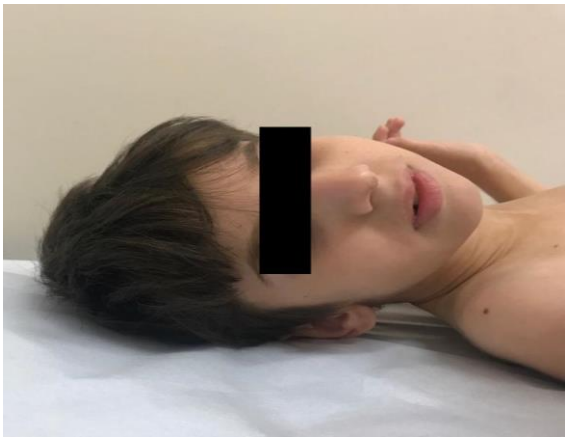


Figure 2: Facial dysmorphic features of the patient comprising deeply set eyes, prominent nasal bridge and pointy chin.



Karyotype analysis revealed a normal male karyotype. Following standard gDNA extraction methods, *ERCC8* and *ERCC6* genes were sequenced using the Illumina Miseq Inc, USA platform, according to the manufacturer's protocols. The detected variants were classified according to the Standards and Guidelines for the Interpretation of Sequence Variants released by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology [5]. A novel c.644A>T variant and a rare c.581G>A (rs76598851) variant in the *ERRC8* gene (NM_000082.3) were detected in the heterozygous state (Figures 3 and 4). Segregation analysis revealed that the c.644A>T allele was paternal, and the c.581G>A variant was of maternal origin. The novel c.644A>T (p.Asp215Val) variant is classified as a "Variant of Uncertain Significance" by ACMG criteria and is assumed to cause rigidification of the protein structure (http://biosig.unimelb.edu.au/dynamut/results_prediction/157676006822) (Figure 5). The c.581G>A (p.Trp194Ter) variant is classified as "Pathogenic"; it is a nonsense variant that leads to premature termination codon and a truncated protein. Informed written consent was obtained from the patient's parents for collecting samples, performing genetic testing, and publishing of patient images.

Figure 3: IGV image of the p.Asp215Val variant detected at the patient.

Figure 4: IGV image of the p.Trp194Ter variant detected at the patient.

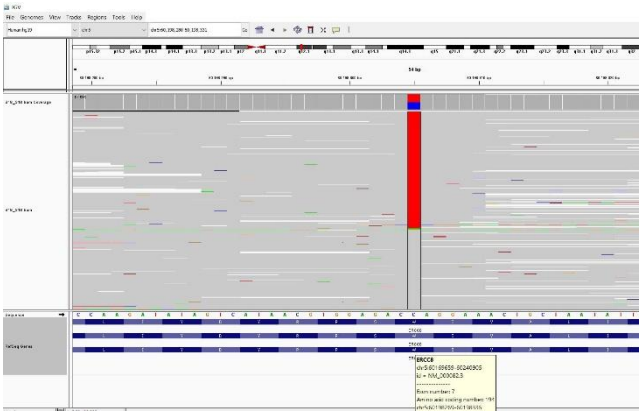
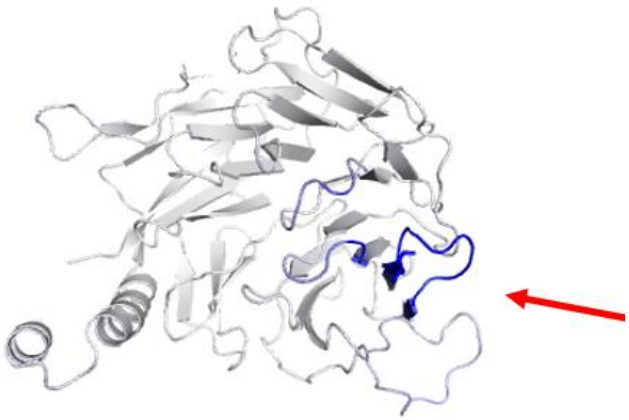


Figure 5: Schematic representation and rigidification site resulting of p.Asp215Val variant at the protein level.



Discussion

CS is a rare disease that was first reported by Sir Edward A. Cockayne in 1936 in two siblings with progressive hearing loss, retinal atrophy, and dwarfism [6].

Cardinal clinical features such as microcephaly and growth retardation were early descriptions of CS. Nance and Berry first defined the diagnostic criteria for CS with their large series of patients in 1992, and Wilson et al. reported comprehensive CS diagnostic criteria in 2016 [7,8]. More recently, in early 2021, Spitz et al. proposed a new quantitative-based method for establishing the diagnosis in early childhood and severity scoring for appropriate evaluation and surveillance of patients [9]. Due to the heterogeneous nature of the disease, it is believed that the frequency of CS may be lower because of difficulties in diagnosis, especially the reliance on dermal photosensitivity, which is thought to be helpful in diagnosis [10,11]. Although our patient manifested both major criteria of microcephaly and growth retardation, we believe that the age of diagnosis was slightly delayed because he did not manifest cutaneous photosensitivity [8].

The *ERCC8* gene (also known as CSA) is responsible for 35% of patients with the CS phenotype. The reported missense variants of the *ERCC8* gene are mostly located at the WD4 domain of the protein, which is an important component for beta-propeller structures functioning in protein-protein interaction. It has been demonstrated that missense variants located around this region can lead to impaired binding and disruption of the protein structure. However, although missense variants are mostly localized in a hotspot region, phenotype-genotype correlations and clinical heterogeneity still remain elusive among patients [12].

Conclusion

Cockayne syndrome is a rare neurodevelopmental disorder with multisystemic involvement, and due to the molecular function of the underlying genes, it is known as one of the DNA repair mechanism dysfunction syndromes. Although cutaneous photosensitivity is assumed to be one of the major features of the syndrome, it should be kept in mind that not all patients manifest this cardinal feature. Reporting a novel variant will enrich the clinical and genetic spectrum of CS and provide insight for further genotype-phenotype analysis. In conclusion, diagnosing rare diseases in advance is essential to prevent unnecessary procedures and provide proper counseling for families.

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