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Research Article

trial

The effects of sugammadex on cognitive functions in bariatric surgery

Ülkü Sabuncu, Hatice Selçuk Kuşderci , Mesut Öterkuş , Ruslan Abdullayev , Öznur Uludağ , Sabri Özdaş

383-386

The relationship of KDIGO classification and incidence & mortality of acute kidney injury in sepsis patients in intensive care unit: A retrospective cohort study

Acute kidney injury in sepsis patients in ICU

Bilge Banu Taşdemir Mecit, Mustafa Deniz

387-390

Pan-immune-inflammation value and systemic immune-inflammation index: Are they useful markers in sarcoidosis?

SII and PIV in sarcoidosis

Adem Ertürk , Aydın Balcı

391-397

Case Report

Radiological approach to multinodular and vacuolating neuronal tumor: Two case report

Radiological approach to MVNT: Two case report

Şükrüye Firuze Ocak Karataş, Murat Beyhan, Erkan Gökçe

398-400

A case of necrotizing fasciitis developing after cesarean section

Necrotizing fasciitis & cesarean section

İsa Kaplan

401-403

J Surg Med. 2023;7(6):364-368.
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Research article

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Genital hiatus measurements predict cuff prolapse risk in prolapse surgery

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Ethics Committee Approval
The study was approved by the Istanbul Prof. Dr. Cemil Tascıoglu City Hospital Clinical Research Ethics Committee on 23/01/2020 with approval number 28.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Recognition and assessment of apical vaginal support defects remains a significant challenge in the evaluation and management of prolapse because there are no consensus or guidelines address the degree of apical support loss at which an apical support procedure should routinely be performed. The aim of this study was to evaluate whether preoperative genital hiatus (GH), perineal body (PB), and total vaginal length (TVL) are associated with prolapse recurrence after apical prolapse surgery.
Methods: Our cohort study included 98 patients who underwent vaginal hysterectomy apical suspension due to uterovaginal prolapse of grade 2 or higher according to Pelvic Organ Prolapse Quantification (POP-Q) staging between 2020 and 2021. Patients with a history of gynecologic malignancy, those who could not tolerate surgery or anesthesia, those who had previously undergone pelvic organ prolapse surgery, those with concomitant stress urinary incontinence, and those with abnormal cervical smear results were excluded. Patients were followed for 2 years at intervals of 3 months in the first year after the surgery. The last POP-Q was performed 24 months after surgical intervention. Surgical failure or recurrence was defined as apical descent greater than one third of the total vaginal length, anterior or posterior vaginal wall past the hymen, subsequent surgery, or bothersome vaginal bulge. Patients were given the Pelvic Organ Prolapse Symptom Score (POP-SS) questionnaire before surgery and 6 months postoperatively, and the severity of symptoms was compared between the groups with and without postoperative recurrence. Logistic regression (LR) analysis was performed to determine the factors affecting recurrence. Areas under the ROC curve were calculated as a differential diagnosis for the presence of recurrence, and the predictive value (cut-off) of variables was determined using sensitivity, specificity, positive predictive value, negative predictive value, and LR (+) values.
Results: While surgery was successful in 80 patients, genital relapse was seen in 18 patients. The mean preoperative perineal body was 3.05 (0.28) cm, mean preoperative GH was 3.9 (0.39) cm, and mean preoperative TVL was 8.54 (1.33) cm. The mean GH of the group with recurrence was significantly higher than the group without recurrence (P=0.004). The mean preoperative POP-SS score was 15.14 (1.86), and the postoperative POP-SS score was 4.01 (3.74). The postoperative POP-SS score mean of the recurrence (+) group was significantly higher than the group without recurrence (P<0.001). For the genital hiatus, the cut-off >4 cm had a sensitivity of 61.11%, specificity of 76.25%, positive predictive value of 36.70%, negative predictive value of 89.70%, and LR (+) value of 2.57. For POP-SS Preop-Postop Change %, the cut-off <60 had a sensitivity of 94.44%, specificity of 98.75%, positive predictive value of 94.40%, negative predictive value of 98.80%, and LR (+) value of 75.56.
Conclusion: Apical vaginal support loss is highly associated with genital hiatus size. In particular, according to all study definitions, a Pelvic Organ Prolapse-Quantification measurement genital hiatus of >4 cm is a strong predictor of apical support loss. This simple measurement can be used to screen for apical support loss and further evaluate apical vaginal support before planning a hysterectomy or prolapse surgery.

Keywords: sacrospinous ligament fixation, pelvic organ prolapse, uterosacral ligament suspension

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Introduction

The herniation of the apical vaginal compartment through the vaginal introitus can result in the inclusion of either the bowel or uterus, which is indicative of either an enterocele or uterovaginal prolapse, respectively. The risk of undergoing pelvic organ prolapse (POP) surgery for a woman ranges from 11% to 19% in her lifetime [1]. The likelihood of surgical intervention increases with age [2]. Recognizing the association between the more common anterior wall prolapse and apical descent, many gynecologists still prefer vaginal hysterectomy (VH) with apical suspension as the preferred surgical approach for uterine prolapse [3]. A randomized controlled trial (RCT) showed that there is a high surgical failure rate of up to 35% within 2 years despite apical suspension [4]. The risk of reoperation for cuff prolapse after hysterectomy ranges from 4.6% to 18% [5].

Genital hiatus (GH) is the measurement of the distance between the middle of the external urethral meatus and the posterior midline hymen [6]. GH has been identified as an indicator of underlying pelvic floor muscle damage [7] and has been shown to be significant in the evaluation of POP. It is a predictor of outcomes after surgical intervention [8]. When GH is 3.75 cm or greater, it is associated with and predictive of apical vaginal support loss [9]. An enlarged genital hiatus is an independent risk factor for the development of POP [10]. Here, we investigated whether preoperative genital hiatus is a predictor factor for prolapse recurrence after vaginal hysterectomy.

Materials and methods

Between 2020 and 2021, a total of 98 patients who underwent vaginal hysterectomy + apical suspension due to uterovaginal prolapse with a POP-Q stage of grade 2 or higher were included in this prospective study. Eighteen patients were excluded from the study due to insufficient follow-up. Patients with a history of gynecologic malignancy, those who could not tolerate surgery or anesthesia, those who had previously undergone pelvic organ prolapse surgery, those with concomitant stress urinary incontinence, and those with abnormal cervical smear results were excluded. A detailed physical examination was performed after recording the demographic information of all patients included in the study. The ICS/IUGA documents provide a detailed description of how to perform the Pelvic Organ Prolapse Quantification (POP-Q) technique [11]. Six points are identified in the vagina during the POP-Q: Aa and Ba for the anterior vagina, Ap and Bp for the posterior vagina, and C and D for the cervix/vault; point D is excluded in women who have undergone a hysterectomy. The patient is instructed to strain, preferably in a lithotomy position, to achieve maximum POP. Three additional measurements are taken to provide a comprehensive assessment: the genital hiatus length, perineal body length, and total vaginal length [12]. GH is measured from the middle of the external urethral meatus to the posterior margin of the hymen, while TVL is the length of the vagina (in cm) from the posterior fornix to the hymen when Point C or D is in its fully normal position. PB is measured from the posterior margin of the hymen to the mid-anal opening. This preoperative assessment was conducted by two trained gynecologists who were not a part of the initial surgical team. The Pelvic Organ Prolapse Symptom Score (POP-SS) questionnaire was administered to study participants twice: before surgery and six months after the operation. The Turkish version of POP-SS is a valid and reliable tool for Turkish women with POP [13]. The total score calculated by POP-SS is based on seven questions asked with a range of 0 to 28. A higher score indicates more severe prolapse symptoms—it reflects a greater frequency and variety of reported symptoms [14]. Various surgical treatments are available, and there are no guidelines to recommend the best. Patients scheduled for apical compartment prolapse surgery uterosacral ligament suspension (USLS), sacrospinous ligament fixation (SSLF), McCall's culdoplasty and Iliococcygeal Fascia Suspension (ICG) + Perineoplasty were eligible for inclusion.

In transvaginal hysterectomy with sacrospinous ligament fixation (SSLF), the patients who required uterine removal underwent TVH with sacrospinous ligament fixation per standardized requirements. Prior to closing the peritoneum, the uterosacral ligament and cardinal stumps were tied together in the midline. After closure of the peritoneum, unilateral SSLF of the right sacrospinous ligament was performed for all patients via a posterior approach. Finally, the non-absorbable sutures were tied to bring the vaginal vault back to the ligament. At our institution, common practices for TVH USLS include two sutures through each bilateral uterosacral ligament (permanent or delayed absorbable) for a total of four sutures. These are then attached to the vaginal cuff. Once the vaginal cuff has been suspended, any necessary anterior and posterior repairs are typically performed simultaneously.

Raymond Lee of the Mayo Clinic described the technique used for vaginal hysterectomy with McCall's culdoplasty [15]. Following vaginal hysterectomy, one or two internal McCall's sutures were inserted utilizing Vicryl-1. The external McCall's sutures were positioned anterior cephalad to the internal McCall's sutures and inserted through the posterior vaginal wall. The suspension technique utilizing the fascia of the iliococcygeus muscle (ICG) was initially developed by Inmon in 1963 for patients in whom identification of the uterosacral ligament was challenging or inadequate to provide support to the vaginal vault. Shull et al. further modified the technique in 1993 [16]. Its development aimed to prevent potential vessel and nerve injuries linked to SSLF. The technique of initial pararectal dissection in ICG is comparable to that in SSLF except for the suture site for attaching the vaginal vault. ICG involves using the fascia of the iliococcygeus muscle, which is located just below the ischial spine and lateral to the rectum where there are fewer major nerves and vessels. Perineorrhaphy with native tissue was performed as follows: Depending on the size of the vaginal outlet, a transverse incision is made at the musculocutaneous border of the posterior hymen followed by removal of a triangular posterior epithelial flap. The procedure usually involves recto- and enterocele repairs or repairs of other compartments based on individual defect patterns. The tissues proximal and distal to the hymen are included depending on intraoperative findings. Proximal to the hymen, one to three deep interrupted sutures are used to approximate the perirectal connective fascia tissue over the distal part of the rectocele, depending on the size of the vaginal outlet and the extent of the

posterior compartment defect. Levator plication is not performed. The bulbocavernosus muscles are re-approximated with one or two sutures where they deviate. In most cases, re-approximation of the transverse perineal muscles may be appropriate. Finally, the skin is trimmed and closed. All surgeries were performed by five surgeons. Patients were followed up for 2 years at intervals of 3 months in the first year after the surgery. The last POP-Q was performed 24 months after surgical intervention. During each follow-up visit, all patients were examined for any recurrence or de novo urinary incontinence. Pelvic examination was performed under maximum strain to assess for recurrence. Surgical failure or recurrence was defined as apical descent greater than one-third of the total vaginal length, anterior or posterior vaginal wall past the hymen, subsequent surgery, or bothersome vaginal bulge.

In this study, ethical approval was obtained from the Istanbul Prof. Dr. Cemil Tascıoglu City Hospital Clinical Research Ethics Committee on 23/01/2020 with approval number 28. In addition, written permission was obtained from the institutions where the research was conducted. All patients gave informed consent. The study was conducted in accordance with the Principles of the Declaration of Helsinki.

Statistical analysis

Statistical analyses in this study were performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program.

Descriptive statistical methods (mean, standard deviation, median, interquartile range) were used, and the distribution of variables was examined by the Shapiro-Wilk normality test. A paired t-test was used for the evaluation of variables and showed normal distribution in pre-op and post-op assessments. Independent t-tests were used for comparison of binary groups. The Wilcoxon test was used to evaluate variables that did not show normal distribution in pre-op and post-op assessments. The Mann Whitney U test was used for the comparison of binary groups. A Chi-squared test was used to compare qualitative data. Logistic regression analysis was performed to determine the factors affecting the presence of recurrence. The areas under the ROC curve were calculated for differential diagnosis in the presence of recurrence, and the variables' prediction (cut off) value was determined by sensitivity, specificity, positive predictive value, negative predictive value, and LR (+) values. The results were evaluated at the significance level of P <0.05.

Results

The mean age of the 98 patients included in the study was 62.5 (10.05) years, the mean gravidity was 5.18 (3.17). The mean parity of the patients was 4.12 (2.89), the mean body mass index (BMI) was 27.88 (3.63), the mean number of normal deliveries was 4.09 (2.93), the mean preoperative perineal body length was 3.05 (0.28), the mean preoperative genital hiatus was 3.9 (0.39), and the mean preoperative total vaginal length was 8.54 (1.33). Demographic and patient data are summarized in Tables 1 and 2, and the POP-Q parameters between relapse (+) and relapse (-) groups are summarized in Table 3.

Table 1: Baseline patient characteristics

	Mean (SD)
Age	62.5 (10.05)
Gravidity	5.18 (3.17)
Parity	4.12 (2.89)
Height	161.3 (5.83)
Weight	72.32 (8.31)
BMI	27.88 (3.63)
NSD	4.09 (2.93)
CS	0.13 (0.47)
Perineal Body	3.05 (0.28)
Genital Hiatus	3.9 (0.39)
POP-Q	2.58 (0.75)
Aa	0.13 (2.24)
Ba	2.06 (3.87)
C	1.29 (3.44)
Ap	-0.59 (1.9)
Bp	1.02 (3.01)
TVL	8.54 (1.33)

SD: Standard Deviation, TVL: Total Vaginal Length, POP-Q: Pelvic Organ Prolapse Quantification, BMI: Body Mass Index, NSD: Normal Spontaneous Delivery, CS: Cesarean Section

Table 2: Characteristics of women studied in this analysis

		Relapse (-) n=80		Relapse (+) n=18		*P*-value
Age	Mean (SD)	63.19 (9.88)		59.44 (10.48)		0.154*
Operation	VAH+Culdoplasty	22	27.50%	3	16.67%	0.391+
	VAH+Iliococcygeal Fascia Suspension + Perineoplasty	24	30%	5	27.78%	
	VAH+USLS	21	26.25%	4	22.22%	
	VAH+SSLF	13	16.25%	6	33.33%	
Gravidity	Mean (SD)	5.19 (3.28)		5.17 (2.68)		0.904†
Parity	Mean (SD)	4.1 (3)		4.22 (2.46)		0.488†
BMI	Mean (SD)	27,64 (3.51)		28.91 (4.06)		0.182*
NSD	Mean (SD)	4.06 (3.03)		4.22 (2.46)		0.471†
CS	Mean (SD)	0.14 (0,47)		0.11 (0.47)		0.678†
De Novo Urinary Incontinence	Absent	75	93.75%	12	66.67%	0.001+
	Present	5	6.25%	6	33.33%	
Groin Pain	Absent	74	92.50%	14	77.78%	0.062+
	Present	6	7.50%	4	22.22%	
Dyspareunia	Absent	79	98.75%	15	83.33%	0.003+
	Present	1	1.25%	3	16.67%	

*Independent t test † Mann Whitney U test, SD: Standard Deviation, BMI: Body Mass Index, NSD: Normal Spontaneous Delivery, CS: Cesarean Section, VAH: Vaginal Hysterectomy, USLS: Uterosacral Ligament Suspension SSLF: Sacrospinous Ligament Fixation

Table 3: Preoperative POP-Q parameters between relapse (+), relapse (-) groups

		Relapse (-) n=80	Relapse (+) n=18	*P*-value
POP-Q	Mean (SD)	2.53 (0.69)	2.83 (0.92)	0.113*
Aa	Mean (SD)	0.05 (2.24)	0.5 (2.28)	0.457†
Ba	Mean (SD)	1.91 (3.83)	2.72 (4.1)	0.437†
C	Mean (SD)	1.33 (3.18)	1.11 (4.54)	0.555†
Ap	Mean (SD)	-0.6 (1.85)	-0.56 (2.18)	0.925†
Bp	Mean (SD)	1 (2.89)	1.11 (3.58)	0.903†
TVL	Mean (SD)	8.66 (1.35)	8 (1.09)	0.065*
Perineal Body	Mean (SD)	3.04 (0.26)	3.07 (0.35)	0.748*
Genital Hiatus	Mean (SD)	3.85 (0.35)	4.14 (0.48)	0.004*

*Independent t test † Mann Whitney U test, SD: Standard Deviation, POP-Q: Pelvic Organ Prolapse Quantification, TVL: Total Vaginal Length

The average preoperative POP-SS score for the patients was 15.14 (1.86), and the postoperative POP-SS score was 4.01 (3.74). There was no statistically significant difference in the average preoperative POP-SS score between the groups with and without recurrence (P=0.870). However, the postoperative POP-SS score in the group with recurrence was significantly higher than in the group without recurrence (P<0.001).

Regression analysis used the variable of genital hiatus to determine the factors affecting the presence of recurrence. There was a statistically significant increase in recurrence with an increase in preoperative genital hiatus measurement (P=0.008).

In the differential diagnosis of recurrence, the area under the ROC curve was 0.705 (0.604-0.771) for the variable of GH, and 0.947 (0.882-0.982) for the variable of percentage change in POP-SS (P=0.01). For genital hiatus, a cut-off value

of >4 cm yielded a sensitivity of 61.11%, specificity of 76.25%, positive predictive value of 36.70%, negative predictive value of 89.70%, and LR (+) value of 2.57. For POP-SS Preop-Postop % Change, a cut-off value of <60 yielded a sensitivity of 94.44%, specificity of 98.75%, positive predictive value of 94.40%, negative predictive value of 98.80%, and LR (+) value of 75.56. Sensitivity and specificity analysis for GH and POP-SS percentage change are summarized in Table 4.

Table 4: Sensitivity and specificity analysis for GH and POP-SS Change %

	Criterion	Sensitivity%	Specificity%	PPV%	NPV%	LR (+)
Genital Hiatus	>4	61.11	76.25	36.7	89.70	2.57
POP-SS Change (%)	<60	94.44	98.75	94.4	98.80	75.56

Discussion

In patients presenting with apical prolapse, recurrence of prolapse can occur despite suspension operations. It is unclear which patients may develop recurrence. Here, prolapse recurrence was 2.57-fold more common in patients with a genital hiatus measurement greater than 4 cm versus those with a measurement of less than 4 cm. We previously showed that urogenital hiatus prolapse was increased in women with POP versus those without, but the Baden Walker classification system was used instead of the POP-Q examination; therefore, the PB measurements were not reported in that study [17]. We found no difference in PB and TVL between the groups with and without recurrence. Similarly, a study of 1037 women evaluated POP severity based on levator hiatus size and function. Prolapse severity was positively correlated with GH but not with PB [18]. Another study found that a GH measurement above 3.75 cm was strongly associated with apical prolapse [9]. Numerous studies have shown that an enlarged pre- and/or postoperative GH is associated with an increased risk of recurrent prolapse following repair surgery [19]. Publications also exist that associate GH size with prolapse symptoms and severity of discomfort [20]. We found that the likelihood of recurrence in a patient with a preoperative-postoperative POP-SS score change percentage value of >60 was 75.56 times higher than in a patient with a value of <60.

Early postoperative genital hiatus measurements <4 cm have been associated with long-term success without increasing dyspareunia in surgeries involving apical suspension such as USLS and robotic sacrocolpopexy [21]. Another study has associated both preoperative and postoperative enlarged GH with increased surgical failure after SSLF [22]. In a randomized controlled trial comparing suspension surgeries for apical prolapse, there was no significant difference in surgical failure rates between USLS and SSLF [23].

HUSLS had better outcomes in a study comparing high uterosacral ligament suspension (HUSLS) and McCall's culdoplasty for vaginal cuff suspension, [24]. In our study, there was no superiority observed in terms of surgical success for USLS, SSLF, ICG fascia fixation, and McCall's culdoplasty. Similar studies in the literature have shown that transvaginal repair using native tissue procedures is safe and effective for correcting vaginal vault prolapse after hysterectomy [25]. Surgeons frequently perform perineorrhaphy during POP surgery to reduce GH size [26]. However, evidence supporting this practice is lacking. Although there is evidence showing a relationship between GH and POP, there is no evidence that surgically correcting GH is effective in preventing POP recurrence [27]. Some publications suggest that perineorrhaphy may not be necessary [28]. In contrast to the aforementioned studies, a different study discovered that incorporating perineorrhaphy in POP repair resulted in Level III support as indicated by decreased genital hiatus size [29]. Here, there was no significant difference in surgical failure rate between adding perineoplasty to ICG fascia fixation and other apical prolapses; however, the correction of the genital hiatus or the reduction of its measurements does not ensure the maintenance of the apical correction. It is not possible to establish a cause of recurrence or that only taking care to reduce the genital hiatus can guarantee the maintenance of the apical correction. The pathophysiology of recurrence is complex, and other factors may be involved with the need for further studies with long-term follow-up.

Similar studies in the literature have shown that the diagnosis of prolapse is preceded by a larger GH, and the risk of prolapse differs significantly depending on the GH values [30]. This cohort did have a few limitations. While we followed women for up to 2 years, this duration of follow up may be insufficient to accurately predict outcomes many decades from surgery. The strengths of this study include its prospective nature, standardized methods for collecting medical history, and POP-Q examinations. All POP-Q values were collected by two individuals who were well trained in obtaining POP-Q measurements.

Although there is still no definitive proof of a causal link between GH size and prolapse, these results imply that a larger GH is a crucial factor in predicting future prolapse risk.

Conclusion

Apical vaginal support loss is highly associated with genital hiatus size. In particular, according to all study definitions, a Pelvic Organ Prolapse-Quantification measurement genital hiatus of >4 cm is a strong predictor of apical support loss. This simple measurement can be used to screen for apical support loss and further evaluate apical vaginal support before planning a hysterectomy or prolapse surgery.

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The relationship of stress, self-efficacy and sociodemographic factors among physicians during the COVID-19 pandemic

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The study was approved by Harran University Scientific Research Ethics Committee, 13.04.2020 and 10.
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Abstract

Background/Aim: During the COVID-19 pandemic, many health care workers had to perform jobs that were not in their area of expertise. That the disease is a newly defined disease and that it required health care workers to work outside of their fields may have affected their stress levels. In this study, we aimed to determine the relationship among sociodemographic characteristics, the sense of self-efficacy in the diagnosis and treatment of COVID-19, and perceived stress levels of physicians working in a university hospital.

Methods: This was a cross-sectional study. The population included in this study was 327 physicians working in a university hospital at the time of the pandemic. No sampling was performed for this study. This study was completed by a total of 108 physicians (participation level: 33.03%). After being informed about this study, the physicians were asked whether they agreed to participate. Research data were collected with a questionnaire and the Perceived Stress Scale. The questionnaire included questions about physicians' sociodemographic characteristics and feelings of self-efficacy in the diagnosis and treatment of COVID-19.

Results: The total number of skills physicians reported they could perform was higher among specialist physicians and faculty members, those 34 years and older, and those who received training on the diagnosis and treatment of COVID-19 and virus prevention (P=0.04; P=0.01; P<0.001; P<0.001; P<0.001, respectively). In addition, perceived stress levels (PSLs) were found to be lower among those who reported a high total number of skills they could perform, as assessed by the self-efficacy questions (P=0.04).

Conclusion: Although the PSLs of physicians were high, this is expected in a state of emergency such as the pandemic. The sense of self-efficacy regarding COVID-19 improved with training and professional experience. In-service training and shared experiences can both decrease PSLs and improve self-efficacy.

Keywords: COVID-19, physician self-efficacy, stress

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a newly discovered type of coronavirus that spread worldwide, with over 200,800,000 cases and over 4,260,000 confirmed deaths [1]. COVID-19 was introduced worldwide with the reporting of pneumonia cases of unknown etiology in Wuhan city, China, in December 2019.

Spreading to nearly 230 countries and regions worldwide, COVID-19 has become a major public health problem, with more than 5,500,000 cases and approximately 50,000 deaths in Turkey alone [1,2]. In the fight against this disease, health care professionals have been at the forefront; they have been infected with the virus and have even lost their lives. Given physical and mental fatigue due to harsh working conditions, separation from families, stigmatization and the pain of losing colleagues, health care professionals have also had to deal with the intense stress of this tough fight [3,4]. Stress is common among physicians. Many studies have reported that the rate of physicians experiencing moderate and high levels of stress varies between 43% and 91%. Stress levels are known to be higher among women, younger people, hospital workers and single individuals [5-7]. Many studies have been conducted examining the mood of health workers during the pandemic. Depression, anxiety, insomnia, posttraumatic stress disorder, somatization, and obsessive-compulsive symptoms are common problems [8-11]. In studies conducted during the pandemic that examined stress and stress-related factors among physicians, there was no relationship between stress and age, but the stress levels of women were higher [12,13]. It has been reported that an increase in the level of education and professionalization are factors that reduce stress, while working in a pandemic clinic increases stress [14]. In studies that investigated stress and related factors among health care workers during the pandemic period in Turkey, women and single people experienced higher levels of stress, and stress decreased with increasing age and professional experience [15,16].

Stress is defined as a condition that causes the deterioration of individuals' physiological and psychological adjustment capabilities as a result of their interaction with their environment and changes in their daily lives [17]. Life- and work-related stressors are triggered by a stimulus and generate the perception of stress in the brain [18]. Self-efficacy, on the other hand, is defined as an individual's self-belief and confidence that he or she can take the necessary action to achieve their desired goals. According to self-efficacy theory, the main factor that motivates an individual to take action that results in a desired behavior is the belief that the individual has the power to exhibit this behavior. Self-belief in one's ability to deal with a situation affects one's moods and stress levels [19,20].

Exposure of individuals to stressors causes many behavioral and psychological responses. Self-efficacy plays a very active role in the body's fight against stressors [21]. High self-efficacy acts as a buffer to many stress-related diseases, such as the stress experienced by individuals that causes burnout syndrome. Both a general sense of self-efficacy and a professional sense of self-efficacy reduce an individual's level of stress. It is very important to promote self-efficacy as a part of health promotion programs, especially in high-risk occupations [19,22-24].

During the COVID-19 pandemic, many health care workers had to perform jobs that were not in their area of expertise. That the disease is a newly defined disease and that it required health care workers to work outside of their fields may have affected their stress levels. In this study, we aimed to determine the relationship among sociodemographic characteristics, the sense of self-efficacy in the diagnosis and treatment of COVID-19, and perceived stress levels of physicians working in a university hospital. The hypotheses of this study are as follows:

H0: Physicians' sense of self-efficacy in the diagnosis and treatment of coronavirus and their sociodemographic variables are not related to their perceived stress level (PSL).

H1: Feelings of low self-efficacy in the diagnosis and treatment of coronavirus among physicians cause an increase in PSL.

H2: Some sociodemographic variables of physicians are associated with PSLs.

Materials and methods

Research design

This was a cross-sectional study. The population included in this study was 327 physicians working in a university hospital at the time of the pandemic. No sampling was performed for this study. This study was completed by a total of 108 physicians (participation level: 33.03%). After being informed about this study, the physicians were asked whether they agreed to participate. Written consent was obtained from those who agreed to participate and were included in the current study. The questionnaire developed by the researchers and the Perceived Stress Scale were given to the physicians, and they were asked to complete it. It was explained that they had to fill in each question for the scale to be scored correctly.

Participants

Physicians who worked in the hospital during the pandemic were included. Physicians who were on maternity leave or on annual/health leave for more than 2 weeks and who did not work during the pandemic were excluded from this study. A total of 202 (61.77%) of 327 physicians in the study population were assistant physicians. Similarly, 66.6% (72 people) of the participants included in this study were resident physicians.

Measures

Research data were collected using a questionnaire and the Perceived Stress Scale.

A questionnaire consisting of two parts was administered to the participants. The first part of the questionnaire included questions about sociodemographic characteristics such as age, sex, marital status, title, hospital unit and professional experience. The second part included questions to determine physicians' feelings of self-efficacy in the diagnosis and treatment of COVID-19. More specifically, this part of the questionnaire consisted of 3 questions about whether the physicians received training on the diagnosis of COVID-19, the treatment for COVID-19, and the use of personal protective measures against COVID-19 infection and 10 questions about whether they felt qualified in the diagnosis, treatment and patient management of COVID-19. The questions were as follows:

1. Can you perform initial evaluation/triage for COVID-19?
2. Can you differentiate between possible/confirmed cases of COVID-19?
3. Can you perform emergency/outpatient management of COVID-19 cases?
4. Can you perform follow-up of patients diagnosed with COVID-19 at home?
5. Can you plan services for the treatment of patients diagnosed with COVID-19?
6. Can you plan intensive care treatment for patients diagnosed with COVID-19?
7. Can you plan services for the treatment of children diagnosed with COVID-19?
8. Can you plan intensive care treatment for children diagnosed with COVID-19?
9. Can you adjust the dosage of drugs used in the treatment of COVID-19?
10. Can you correctly use the materials/equipment in an isolation area for COVID-19?

Those who answered "yes" to these self-efficacy questions were considered to also perform those skills. The total number of skills the physicians could perform, as reflected by the self-efficacy questions, ranged from 0 to 10. Although the questions were not designed as a scale, the item total correlation value was greater than .30. The Kuder-Richardson 20 (KR-20) coefficient was 0.86. When explanatory factor analysis was performed, the questions clustered in one dimension and explained 44.53% of the variance. The Kaiser-Mayer-Olkin (KMO) value was 0.81, and the Bartlett's test of sphericity result was $P<0.001$.

The Perceived Stress Scale is a scale developed to measure the level of stress perceived by individuals in the last month. This 5-point Likert-type scale consists of 14 questions [25]. The Turkish validity-reliability of the scale was assessed by Eskin et al. in 2013, and the Cronbach's alpha internal safety coefficient of the scale was found to be 0.84. The total scores that can be obtained using the scale range from 0 to 56. The higher the score is, the higher the PSL. In this study, physicians' scores were made dichotomous by defining two groups based on the scale's median score. Those who scored 28 and below were coded as having low stress levels, and those who scored 29 and above were coded as having moderate-high stress levels.

Procedure

This study included all physicians who agreed to participate between 1 April 2020 and 30 April 2020. Both verbal and written consent were obtained from the participants after they had been informed about this study. Regarding the use of the Perceived Stress Scale in this study, permission was obtained from the authors who conducted the validity and reliability study of the scale. Approval was obtained from the Harran University Clinical Research Ethics Committee at session no. 07 dated 13.04.2020 with decision number 10. Institutional permission was obtained from the hospital for this study, and all procedures were carried out in accordance with ethical rules that must be followed in human studies.

Data analysis

After the hospital units were listed based on the answers from the physicians, the coronavirus quarantine unit, the emergency department and the intensive care unit were grouped as high-risk units; inpatient services and outpatient clinics were grouped as moderate-risk units; and laboratories and radiology and administrative units were grouped as low-risk units. The professional experience and age variables were treated as dichotomous by taking the median value as the cutoff point.

Statistical analysis

Statistical analyzes were performed using IBM SPSS 18.0 (SPSS Inc., Chicago, USA). The significance level for this study was set at $P<0.05$. The variables used in this study fit a normal distribution. Frequencies and distributions of the data were determined by performing univariate analyses. The chi-square test was used for categorical variables, while the t test and one-way ANOVA were used for continuous variables.

After this study was completed, its strength was evaluated. The PSL was made categorical by taking the median score as a cutoff. Physicians were divided into two groups: low and moderate/high PSLs. The relationship between PSLs and the total number of skills the physicians could perform, as measured by the self-efficacy questions, was evaluated. The average and standard deviation of the total number of skills physicians in the low PSL group could perform, based on the self-efficacy questions, were compared with the average and standard deviation of the total number of skills physicians in the moderate/high PSL group could perform. According to G power analysis, the power of this study was calculated as a 0.52 effect size, a 0.05% margin of error and 84.40%.

Results

A total of 108 physicians participated in this study. The mean age of the physicians was 33.2 (6.4) years, and the mean duration of their professional experience was 7.9 (6.4) years. A total of 64.8% of the participants were male, 62.0% were married, and 66.7% were resident physicians. The sociodemographic characteristics of the physicians are shown in Table 1.

Table 1: Sociodemographic characteristics of the physicians

Variables	Categories	Number	Percentage
Age	31 years and under	55	50.92
	32 years and over	53	49.08
Sex	Female	38	35.18
	Male	70	64.82
Marital status	Single	41	37.96
	Married	67	62.04
Position	Assistant physician	72	66.66
	Faculty member	32	29.62
	Specialist physician	4	3.72
Work unit	Inpatient services	33	30.56
	Polyclinic	26	24.08
	Intensive care	25	23.15
	COVID-19 quarantine unit	8	7.41
	Emergency	7	6.48
	Administrative unit	6	5.55
	Laboratory/radiology unit	3	2.77
Total		108	100.00

When the stress levels of the physicians who participated in this study were examined according to the Perceived Stress Scale, 42.6% had a low stress level, and 57.4% had a moderate/high stress level. The relationship between PSL and self-efficacy is shown in Table 2. The total number of skills the physicians could perform based on the self-efficacy questions of those with low PSLs was 4.32 (3.04), and that of those with moderate-high PSLs was 3.16 (2.82). The difference was statistically significant ($P<0.05$).

Table 2: Relationship of self-efficacy with physician PSLs

		Self-Efficacy	
Variables	**Categories**	**Mean (Standard deviation)**	**Statistical analysis**
PSL	Low	4.32 (3.04)	T=2.04 *P*=0.04
	Moderate-high	3.16 (2.82)	

Among the physicians, PSLs decreased with increasing age and professional experience ($P<0.001$ and $P<0.001$, respectively). The perceived stress level was found to be lower among specialist physicians or faculty members and those who had received training on the treatment of coronavirus ($P<0.001$ and $P=0.01$, respectively). The relationship of PSLs with the sociodemographic characteristics of the physicians is shown in detail in Table 3.

Table 3: Relationship of PSLs with the sociodemographic characteristics of the physicians

Variables	**Categories**	**PSL Low**		**PSL Moderate-High**	
		Number	**Percentage**	**Number**	**Percentage**
Age	31 years and under	13	28.26	42	67.74
	32 years and over	33	71.74	20	32.26
		$X^2=14.92$	$P<0.001$		
Sex	Female	15	32.60	23	37.09
	Male	31	67.40	39	62.91
		$X^2=0.23$	$P=0.62$		
Marital status	Single	16	34.78	25	40.32
	Married	30	65.22	37	59.68
		$X^2=0.34$	$P=0.55$		
Position	Assistant physician	22	47.82	50	80.64
	Faculty member/Specialist physician	24	52.18	12	19.36
		$X^2=12.79$	$P<0.001$		
Work unit	High-risk unit	25	54.34	33	53.22
	Moderate-risk unit	16	34.78	25	40.32
	Low-risk unit	5	10.88	4	6.46
		$X^2=0.83$	$P=0.65$		
Duration of professional experience	5 years and under	16	34.78	38	61.29
	Over 5 years	30	65.22	24	38.71
		$X^2=6.40$	$P=0.01$		
Diagnosis of COVID-19	Trained	24	52.18	24	38.70
	Untrained	22	47.82	38	61.30
		$X^2=1.93$	$P=0.13$		
Treatment of COVID-19	Trained	19	41.30	12	19.36
	Untrained	27	58.70	50	80.64
		$X^2=6.21$	$P=0.01$		
Protection against COVID-19	Trained	22	47.82	27	43.54
	Untrained	24	52.18	35	56.46
		$X^2=0.19$	$P=0.40$		

Of the physicians, 63.0% stated that they could perform initial evaluation/triage for COVID-19 cases, 44.4% stated that they could differentiate between possible/confirmed cases of COVID-19, 50.0% stated that they could perform emergency/outpatient management of COVID-19 cases, 53.7% stated that they could perform follow-up of patients diagnosed with COVID-19 at home, 38.0% stated that they could plan the service treatment of patients diagnosed with COVID-19, and 18.5% stated that they could plan the intensive care treatment of patients diagnosed with COVID-19. A total of 11.1% stated that they could plan the treatment of children diagnosed with COVID-19, 5.6% stated that they could plan the intensive care treatment of children diagnosed with COVID-19, 29.6% stated that they could adjust the dosage of drugs used in the treatment of COVID-19, and 51.9% stated that they could correctly use the materials/equipment in an isolation area for COVID-19.

Regarding the questions that assessed self-efficacy in the diagnosis and treatment of COVID-19, the total number of skills physicians reported they could perform was 3.6 (2.9). The relationship between physicians' sense of self-efficacy and their sociodemographic characteristics is shown in Table 4.

The total number of skills physicians reported they could perform was found to be higher among specialist physicians and faculty members, those 34 years and older, and those who received training on the diagnosis and treatment of COVID-19 and virus prevention ($P=0.04$; $P=0.01$; $P<0.001$; $P<0.001$; $P<0.001$, respectively). In addition, PSLs were lower among those who reported a high total number of skills they could perform, as assessed by the self-efficacy questions ($P=0.04$).

Table 4: Relationship of self-efficacy with the sociodemographic characteristics of the physicians

		Self-Efficacy	
Variables	**Categories**	**Mean (Standard deviation)**	**Statistical analysis**
Age	31 years and under	2.94 (2.69)	T=-2.60 *P*=0.01
	32 years and over	4.39 (3.07)	
Sex	Female	3.65 (3.33)	T=0.01 *P*=0.99
	Male	3.65 (2.77)	
Marital status	Single	3.56 (3.12)	T=-0.26 *P*=0.79
	Married	3.71 (2.89)	
Position	Assistant physician	3.23 (2.75)	T=-2.12 *P*=0.04
	Faculty member/Specialist physician	4.50 (3.22)	
Work unit	High-risk unit	3.82 (3.19)	F=0.49 *P*=0.61
	Moderate-risk unit	3.60 (2.63)	
	Low-risk unit	2.77 (3.03)	
Duration of professional experience	5 years and under	3.12 (2.77)	T=-1.87 *P*=0.06
	Over 5 years	4.18 (3.08)	
Diagnosis of COVID-19	Trained	4.81 (2.85)	T=3.84 *P*<0.001
	Untrained	2.73 (2.74)	
Treatment of COVID-19	Trained	5.96 (2.52)	T=5.85 *P*<0.001
	Untrained	2.72 (2.61)	
Protection against COVID-19	Trained	5.06 (2.73)	T=4.94 *P*<0.001
	Untrained	2.49 (2.64)	

Discussion

Two-thirds of the physicians who participated in this study were male. Approximately 60% of the physicians were resident physicians, the mean age was approximately 33 years, and the mean duration of professional experience was approximately 8 years. Similarly, in their study among physicians working at a university hospital, Unver et al. found the mean age to be 36.3 (10.1) years. In that same study, a total of 61.9% of the participants were resident physicians, and 55.7% were male [26]. Health care is an area in which the advanced age of physicians is often reflected in studies. However, it can be speculated that the mean age of the physicians in our study was low since our study was conducted in a training hospital.

In our study, the majority of physicians experienced moderate to high levels of stress. Younger age, little professional experience, being in the early stages of an academic career and a

lack of training led to increased PSLs. The profession of medicine is a branch of work that amplifies both physical and mental burdens caused by workload, long working hours, busy shifts and limited hours of rest. Many studies have revealed that physicians experience high levels of stress and burnout [27-31]. Many studies have demonstrated that gaining professional experience is a stress-relieving factor among health care professionals [32-34]. Increased knowledge and professional experience are thought to help physicians cope with emerging situations and events in work life, thereby reducing PSLs.

The answers to the self-efficacy questions about COVID-19 showed that nearly half of the physicians stated that they could perform initial evaluation/triage for COVID-19 cases, differentiate between possible/confirmed cases, perform emergency/outpatient management of the cases and perform the follow-up of diagnosed patients at home. In general, the physicians reported lower levels of self-efficacy with regard to the service and intensive care treatment planning of adults and children and the dosage adjustment of drugs. The mean of the total number of skills they could perform, based on the self-efficacy questions, was approximately 3.5. Considering that the total number of skills assessed by the self-efficacy questions ranged from 0 to 10, the mean number of skills physicians reported they could perform with regard to COVID-19 was below the median. In a study by Citak et al. [35] among resident physicians in 2012, physicians stated that they were overwhelmed by the service burden and that they went through a nonstandardized and unsatisfactory training process. In addition to harsh working conditions and a lack of training, the fact that COVID-19 is a newly identified disease and that the literature on the subject has just begun to emerge can help us better understand why the mean number of skills physicians reported they could perform, based on their self-efficacy answers, was low.

In this study, physicians' sense of self-efficacy regarding COVID-19 was found to increase with age, academic progress and training. Although self-efficacy is an inner sense, it is a concept that can be shaped by external factors. Further training and gaining experience are known to increase feelings of self-efficacy [36].

Those physicians with high self-efficacy regarding COVID-19 had lower PSLs. The relationship between the sense of self-efficacy and PSLs shows that self-confidence is a stress-relieving factor. Based on the relevant literature, increasing professional self-efficacy can improve psychological resilience [37-39].

Limitations

The study group comprised 33.03% of the total number of physicians. A limitation of this study is that not all physicians were included. To evaluate the individual skills of physicians in diagnosing and treating COVID-19, they were asked whether they felt competent in those areas and were asked to evaluate themselves subjectively. The questions were formulated by the researchers, but they were not a standard measurement tool or designed as a scale. As the questions did not constitute a scale, their validity and reliability were not evaluated. The questions were prepared to make a subjective and rapid assessment of competence in diagnosis and treatment, which was a variable that could not be measured directly.

Conclusion and recommendations

Although the PSLs of physicians were high, this is expected in a state of emergency such as the pandemic. Young physicians and those with little professional experience had higher PSLs. The sense of self-efficacy regarding COVID-19 improved with training and professional experience. In-service training and shared experiences can reduce PSLs and improve self-efficacy.

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Elective cesarean section versus induced vaginal delivery: Do any differences in terms of neonatal respiratory morbidities exist?

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Ethics Committee Approval
This study was approved by İzmir Bakırçay University, Ethical Committee on Noninvasive Clinical Research. (Date: 16.01.2019, Number: 3811-5317).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Transient tachypnea of the newborn (TTN) is mostly a benign and self-limiting common physiological disorder. Certain factors, such as elective cesarean section (CS) not preceded by spontaneous labor, delivery before 39 gestational weeks, and perinatal asphyxia, interfere with the fetal–neonatal transition. In our study, we aimed to review the results of hospitalized newborns who receive a diagnosis of TTN and investigate the possible relationship between the implementation of labor induction and the occurrence of this disorder.

Methods: This study used a case-control study design. We scanned the hospital records of 156 term newborns hospitalized between January 2017 and January 2018 who received a diagnosis of TTN and who did not have any additional fetal and/or maternal risk factors. Demographic features, mode of delivery, and implementation of labor induction in vaginal deliveries were recorded and compared to the data from 150 healthy term infants. Infants were then split into two groups according to their type of labor induction, and a separate subgroup analysis was performed in terms of the risk of TTN development.

Results: The incidence of TTN was 2.9% in vaginal deliveries and 8.5% in CSs. Differences between groups regarding gestational age, birth weights, gender, elective induction in vaginal deliveries, interventions in the delivery room, and types of intervention were found ($P<0.05$). The risk of developing TTN was 2.5 times higher in the induction group compared to those who did not receive induction but still developed TTN ($P<0.001$). Also, the risk was significantly higher in the induction group compared to those who did not receive induction and did not develop TTN ($P<0.001$). After applying a logistic regression analysis, labor induction (odds ratio: 1.005; 95% confidence interval: 1.003–1.008, $P<0.001$) was found to be an independent significant risk factor for developing TTN.

Conclusions: This study indicates that infants born via electively induced vaginal delivery had significantly higher rates of TTN. Therefore, elective labor induction can be added as a new risk factor for TTN development. In our opinion, labor induction without valid medical and obstetric indications should be avoided due to maternal and fetal complications.

Keywords: transient tachypnea of the newborn, induced vaginal delivery, elective cesarean section, fetal complications

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Introduction

Transient tachypnea of the newborn (TTN) is a benign and self-limiting common physiological disorder resulting from pulmonary edema secondary to inadequate or delayed clearance of fetal alveolar fluid [1–3]. Activation of the epithelial sodium channels after birth is the primary mechanism for formation of functional residual capacity (FRC) and prevents alveolar collapse upon expiration. Other studies have demonstrated that fetal alveolar fluid is continuously secreted during pregnancy through an epithelial chloride secretion mechanism, and the secretion rate decreases a few days before delivery [2, 4–6]. At birth, a surge in catecholamines and steroid hormones occurs, and the balance of fluid movement in the alveolus switches from chloride secretion to sodium absorption, an process that causes the resorption of intra-alveolar fluid [5, 6]. Certain factors, such as elective cesarean section (CS) not preceded by spontaneous labor, delivery before 39 gestational weeks, and perinatal asphyxia, interfere with the fetal–neonatal transition by interrupting absorption of the fetal alveolar fluid [7–9].

In elective CSs, the delivery time is determined apart from physiological mechanisms. This procedure occurs without spontaneous labor thus preventing the fetus from preparing for the transition to the neonatal period and preventing the anticipated rise of catecholamines and other hormones, a process that causes a delay in the clearance of alveolar fluid [10]. In recent years, the dramatic increase in the rate of elective induction of labor without cervical maturation is thought to cause neonatal respiratory complications with a similar mechanism of action. Joseph et al. [11] investigated the effect of CS on TTN and examined 4576 deliveries performed at their hospital. The authors determined that the relative risk of CS is 3.78 when compared with normal vaginal deliveries.

Even though one of the risk factors for developing TTN was shown to be CS versus a normal vaginal delivery, no information regarding induced vaginal delivery is available. Therefore, this study aimed to review the results of hospitalized newborns with the diagnosis of TTN and investigate the possible relationship between the implementation of labor induction and the occurrence of this disorder.

Materials and methods

Participants

This retrospective case-control study was conducted in the Department of Pediatrics, Division of Neonatology, Cigli Regional Training and Research Hospital. The Noninvasive Research Ethics Board of Bakırçay University approved the study protocol (16.01.2019/Number: 3811-5317). All procedures performed in the study followed the provisions of the Declaration of Helsinki (as revised in Brazil in 2013), and informed consent was obtained from the parents of all newborns involved in the study.

We scanned the hospital records of 156 term newborns hospitalized between January 1, 2017 and January 1, 2018 who had received a diagnosis of TTN and who did not have any fetal or maternal additional risk factors (such as prolonged labor, fetal distress, preeclampsia, maternal diabetes, multiparity, small or large for gestational age, prematurity, and others). All records were scanned by a neonatologist who was blinded to the presence of TTN.

Outcome measures

Demographic features, modes of delivery, and implementation of labor induction in vaginal deliveries were recorded and compared to the data from 150 healthy term infants. Infants were then split into two groups according to type of labor induction, and a separate subgroup analysis was performed for the risk of developing TTN.

Sample size

Due to the study's retrospective design, post hoc power analyses were performed. The TTN ratio in both groups was used to calculate the effect size. Using the following information, the study population was 306, effect size was 0.479, α=0.05, and the power of the study was determined as 100%.

Statistical analysis

Data were analyzed using the IBM SPSS (Version 25.0. Armonk, NY: IBM Corp.) program. Normal distribution was determined using the Kolmogorov–Smirnov/Shapiro–Wilk tests and analysis of graphs. Since the variables showed a normal distribution, all analyses were performed with parametric methods. All results were presented as numbers (percentages) and mean (standard deviation). Paired sample T- and chi-squared tests were used to analyze differences in outcome measures between groups for continuous and categorical variables, respectively. Cohen's d effect size was calculated and interpreted as small (d=0.2), medium (d=0.5), and large (d=0.8). A logistic regression analysis was performed to determine whether or not labor induction is a risk factor for TTN development.

Results

In the study group involving 156 newborns with TTN, mean gestational age was 38.2 (1.4) weeks, and the mean birth weight was 3243.8 (539.6) g. Thirty-five percent of infants were born vaginally (n=54), and 65% underwent CS (n=102). When proportioned to the number of vaginal and CS deliveries performed in our hospital over the same time interval, the incidence of TTN was 2.9% for vaginal deliveries and 8.5% for CS. Elective labor induction was used in 74% (40/54) vaginal delivery babies who developed TTN. The rate of elective labor induction for all vaginal deliveries during that year was 53% (n=972). Difference between groups in terms of gestational age and birth weight with a medium effect, gender, elective induction in vaginal deliveries, intervention in the delivery room with a large effect, and type of intervention were found (P<0.05). Detailed information regarding the groups' comparison is presented in Table 1.

When the results of 40 infants who underwent induction and developed TTN were compared to those of 14 infants who did not undergo induction but developed TTN, the risk of developing TTN was 2.5 times higher in the induction group (P<0.001). When the same comparison was applied to the infants who did not receive induction and did not develop TTN, the risk was found to be significantly higher in the induction group (P<0.001) as shown in Table 2.

After applying a logistic regression analysis, labor induction (odds ratio [OR] 1.005; 95% confidence interval [CI]:

1.003–1.008, $P<0.001$) was an independent significant risk factor for the development of TTN.

Table 1: Demographic features and clinical findings of neonates with transient tachypnea of the newborn (TTN) and healthy controls

	TTN (n=156) mean (SD)	Control (n=150) mean (SD)	*P*-value	Cohen's d
Gestational age (weeks)	38.2 (1.4)	39.3 (1.6)	0.038	0.73
Birth weight (g)	3243.8 (539.6)	3581 (435.5)	0.046	0.69
Mode of delivery, n (%) CS/Vaginal	102/54 (65/35)	63/87 (42/58)	0.012	
Gender, n (%) Female/Male	54/102 (35/65)	86/64 (57/43)	0.056	
Elective induction in vaginal deliveries, n (%)	40/54 (74)	46/87 (53)	<0.001	
Apgar 1′	9.0 (0.78)	9.02 (0.9)	0.542	0.02
Apgar 5′	9.37 (0.71)	9.41 (0.8)	0.641	0.05
Intervention in the delivery room	121 (77.6)	16 (10.6)	<0.001	1.90
Type of intervention, n (%)				
Aspiration	5 (4.2)	10 (62.5)	0.346	
Oxygen	58 (47.9)	6 (37.5)	<0.001	
nCPAP	58 (47.9)	0 (0)	<0.001	
CPR	0 (0)	0 (0)	0	

CS: cesarean section, nCPAP: nasal continuous positive airway pressure, CPR: cardiopulmonary resuscitation, SD: standard deviation

Table 2: Comparison of infants born vaginally in terms of developing TTN and in those who underwent labor induction

	Induction present n (%)	Induction absent n (%)	Total n (%)	*P*-value
TTN present, n (%)	40 (4)	14 (1.6)	54 (3)	<0.001
TTN absent, n (%)	932 (96)	848 (98.4)	1780 (97)	0.647
Total, n (%)	972 (100)	862 (100)	1834 (100)	-

TTN: transient tachypnea of the newborn

Discussion

TTN is mostly a benign and self-limiting disorder with a good prognosis. However, it may cause severe morbidities, such as hypoxemia, respiratory failure, and air leak syndromes [12,13]. Even if no complications occur, the rate of hospitalization increases. Due to separation of the infant from the mother and prolonged hospital stay, problems regarding mother–infant attachment are experienced. It is already known that compared to normal vaginal delivery, respiratory distress, and neonatal intensive care unit (NICU) admissions are 5–7 times more prevalent in infants born via elective CS not preceded by spontaneous labor [14–17]. In the current literature, the incidence of TTN is reported as 0.3% to 3% in vaginal deliveries and 0.9% to 12% in elective CSs [3,7]. In our study, the incidence of TTN according to the mode of delivery was compatible with the upper limits reported in the literature. When compared with healthy controls, infants in the TTN group had lower gestational ages, lower birth weights, higher CS rates, and higher requirements for additional oxygen and nasal continuous positive airway pressure (nCPAP) in the delivery room.

Recently, iatrogenic stimulation of uterine contractions before the onset of spontaneous labor to achieve vaginal delivery has become a common method of labor induction [18–20]. Generally, it must be selected in case of medical and obstetric indications. Nevertheless, induction may be applied without any valid indication for logistic and psychosocial reasons and is called "elective induction" [19,21,22]. In recent years, the rate of elective induction of labor has risen dramatically throughout the world and in our country. Initiating vaginal delivery, especially before cervical maturation, has caused significant maternal and neonatal morbidity [19,23]. Although no study has investigated the effects of induced vaginal delivery on the development of TTN, one study examined the relationship between precipitous labor and TTN. Jegard et al. [24] divided the vaginal delivery according to duration as precipitous labor (<3 h) and the reference group (>3 h). Although the TTN rate was lower in the precipitous labor group than in the reference group, this difference was not observed after adjustment for the risk factors. In our study, we demonstrated that infants born via electively-induced vaginal delivery had significantly higher rates of TTN. In such infants, the underlying mechanisms for TTN development are not fully understood. However, similar to the mechanisms in elective CS, the most probable explanation for TTN development in electively-induced vaginal deliveries is the determination of delivery time apart from physiological mechanisms and prevention of the fetus from preparing for the transition to the neonatal period; it seems that catecholamines and other hormones do not have the necessary time to increase in such infants and just as in elective CSs, epithelial sodium channels cannot be activated resulting in a delay in alveolar fluid clearance.

Strengths and Limitations

Some study strengths and limitations should be discussed. The major strength of the study is the large sample size. Also, we scanned a short period to avoid the changes in obstetrics methods that could impact the study's homogeneity. Another strength of the study is exclusion of the cases with maternal risk factors that may have impacted perinatal outcomes. Along with the study's strength, our limitation was that we needed to evaluate long-term results. Consequently, the need the future studies with prospective and long-term designs is present.

Conclusion

In conclusion, elective induction of labor can be added as a new risk factor for TTN development to the already known risk factors, such as elective CS, premature birth, and perinatal asphyxia. Also, considering the TTN presence results in requirements for more oxygen and nCPAP than in the control group, labor induction without valid medical and obstetric indications should be avoided due to associated maternal and fetal complications.

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Research article

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Efficacy of Taraxacum officinale in liver damage caused by doxorubicin in rats

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Abstract

Background/Aim: The use of doxorubicin is limited due to its toxic effects on normal cells. A substance containing antioxidant properties, such as taraxacum officinale, would be useful in preventing doxorubicin toxicity. This study aimed to evaluate the effect of taraxacum officinale on doxorubicin-induced damage in the rat liver.

Methods: Forty Wistar albino rats were allocated into four groups. In group 1 (control group), no treatment was given. In group 2 (Taraxacum officinale, group T), 100 mg/kg Taraxacum officinale was administered via the gavage route for 10 days. In group 3 (doxorubicin, group D), a single intraperitoneal dose of 40 mg/kg doxorubicin was given. In group 4 (doxorubicin + Taraxacum officinale, group D+T), a single intraperitoneal dose of 40 mg/kg doxorubicin was administered on the eighth day, and 100 mg/kg Taraxacum officinale was administered for 10 days. Blood malondialdehyde (MDA) levels and the activities of catalase (CAT) and superoxide dismutase (SOD) were measured. Histopathology was assessed by examining preparations of hepatic tissue with light microscopy and immunohistochemistry.

Results: MDA levels were significantly higher, and the activities of SOD and CAT were lower in group D than in group D+T (P=0.04). Tissue damage was significantly higher in group D than in group D+T (P=0.03).

Conclusion: Our short-term results indicate that oxidative stress could be responsible for the damage to liver tissue due to doxorubicin, and Taraxacum officinale might reverse these harmful effects.

Keywords: doxorubicin, toxicity, taraxacum officinale, rat, liver

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Ethics Committee Approval
The study was approved by the Erciyes University Animal Experiments Local Ethics Committee (date: 07.12.2022, number: 22/258).

Conflict of Interest
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Introduction

Doxorubicin, an anthracycline derivative antineoplastic, has toxic effects on many tissues and organs, especially the liver [1]. Although doxorubicin is widely used to treat malignancies, its usage is limited due to its harmful effects on normal cells [2]. While doxorubicin is primarily cardiotoxic, it also has severe effects on the liver, which is mainly responsible for its clearance and excretion via bile [3]. The exact mechanism of liver damage remains controversial, with apoptosis, oxidative stress, and inflammation being the most commonly suggested underlying factors responsible for the hepatotoxic effect [4]. Additionally, doxorubicin forms a complex by interacting with cell DNA [5]. Wang et al. [6] reported that 40% of patients receiving doxorubicin experienced liver toxicity. Doxorubicin increases reactive oxygen species and free radicals, which affect the cell membrane in liver tissue, causing lipid peroxidation and inflammation [7,8]. No substance is known to have been clinically proven to reverse liver damage caused by doxorubicin.

Taraxacum officinale (TO) is a herbal substance that belongs to the *Asteraceae* family. It has been suggested that TO has immunostimulating and cancer-protective properties [9]. TO has been used to treat liver diseases and diabetes mellitus [10]. TO exhibits antioxidant properties dependent on the phenolic compounds in its content [11]. Although TO has been widely used worldwide for years, its hepatoprotective effect is poorly understood. Moreover, to the best of our knowledge, no study demonstrates the effect of TO on liver toxicity caused by cisplatin.

Materials and methods

Forty female Wistar albino rats weighing 150–220 g were included in the study. The animals were fed a standard regimen with free access to water and food and were kept under standard conditions at a temperature of 20–22 °C. Doxorubicin was obtained from a drugstore, and TO was purchased from a herbal medicine store. Ethical approval for the study was obtained from the Erciyes University Animal Experiments Local Ethics Committee, with the document of ethical approval dated 07.12.2022 and numbered 22/258.

The animals participating in the study were divided into four groups: Group 1 (control group) received nothing, group 2 (Taraxacum officinale, group T) was given 100 mg/kg TO for 10 days, group 3 (doxorubicin, group D) received a single dose of 40 mg/kg doxorubicin, and group 4 (doxorubicin+TO, group D+T) received a single intraperitoneal dose of 40 mg/kg doxorubicin and 100 mg/kg TO.

The animals were anesthetized using ketamine hydrochloride (45 mg/kg, Ketalar, Eczacibasi, Istanbul, Turkey) and xylazine hydrochloride (5 mg/kg, Rompun, Bayer, Leverkusen, Germany). Blood samples were taken by entering the heart with a needle, and then cervical dislocation was performed for euthanasia. The liver tissues of the rats were removed.

The levels of blood MDA and activities of SOD and CAT were analyzed using a spectrophotometer (Shimadzu UV 1800, Kyoto, Japan). MDA levels were detected using the thiobarbituric acid test [12]. SOD and CAT enzyme activities were measured based on previous studies [13,14].

Macroscopic evaluation of liver

The liver tissue was fixed in 10% formalin, and all specimens were sliced along their long axis and kept for microscopy.

Histopathologic evaluation of liver

The tissues were embedded in paraffin blocks and sliced to a thickness of 4 micrometers. Staining was performed using hematoxylin and eosin (H&E) dye. Immunohistochemical staining was also performed for p53 and c-kit (CD117). The degree of damage was determined based on histopathological scoring according to the highest area, using the following semi-quantitative analysis: 0: None (0%), 1: Minimal (0–10%), 2: Mild (10–30%), 3: Moderate (30–50%), 4: Severe (more than 50%). Parameters were scored accordingly, using the following parameters: hepatocyte damage (cellular changes), disorganization in the hepatic cords, inflammation, congestion, hemorrhage, fibrosis, and necrosis. CD117 expression levels were graded on a 0-3+ range: 0: no staining, 1: less than 10% membranous/cytoplasmic staining in hepatocytes, 2: 10–30% membranous/cytoplasmic staining in hepatocytes, and 3: membranous/cytoplasmic staining of more than 30% of hepatocytes. p53 expression levels were also graded on a 0–3+ range: 0: no staining, 1: nuclear staining of less than 10% of hepatocytes, 2: nuclear staining of 10–30% of hepatocytes, and 3: nuclear staining of more than 30% of hepatocytes.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, version 22.00) was used for statistical analyses. The levels of blood MDA and activities of SOD and CAT were analyzed using a one-way analysis of variance (ANOVA) test. Tissue damage scores were compared using the nonparametric chi-square test. A *P*-value less than 0.05 was considered statistically significant.

Results

The biochemical parameters are presented in Table 1. The MDA levels in group D were significantly higher than those in group D+T (18.41 [2.29] vs. 12.65 [1.58]; $P=0.04$). In contrast, both SOD and CAT enzyme activities were significantly lower in group D than in group D+T ($P=0.03$).

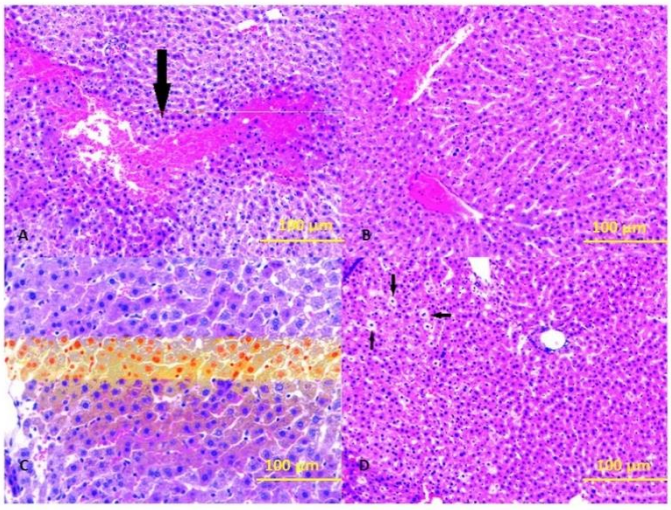
Table 1: Distribution of malondialdehyde (MDA), superoxide dismutase (SOD), and catalase (CAT) in the experimental groups.

Groups (n=10)	MDA (nmol/mg)	SOD (U/mg)	CAT (U/mg)
Control	7.22 (0.42)	64 (7.2)	78.24 (6.47)
Taraxacum officinale (100 mg/kg)	7.73 (0.44)	59 (4.56)	80.53 (8.83)
Doxorubicin (40 mg/kg)	18.41 (2.29)*	32.01 (3.5)*	41.38 (4.66)*
Doxorubicin+Taraxacum officinale (100 mg/kg+40mg/kg)	12.65 (1.58)*	47.24 (4.08)*	62.57 (6.94)*

MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase. Data are presented as mean (SD).
* Significant difference ($P<0.05$) between groups 2 and 3.

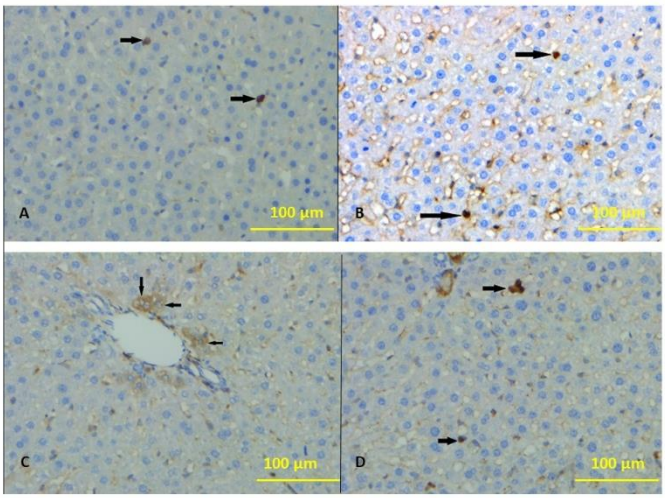
The morphology and parenchymal structures of liver tissues in the control and T groups were normal and intact, as shown in Figures 1A and 1B. In the group D, hepatocytes and parenchymal tissue exhibited signs of injury, as depicted in Figure 1C. Group D showed more severe liver damage than the other groups. Compared to group D, the group D+T showed a decrease in hepatocytes with disorganization of the hepatic cords and damage, as illustrated in Figure 1D.

Figure 1: A) Normal histological architecture in the liver of rats from the control group (H&E, x100). B) Focal mild degenerative findings in the rat liver from group T (H&E, x200). C) Hepatocytes with degenerative changes in the group D; There is granular appearance in the cytoplasm, darkening of the nucleus, binucleolization, nuclear contour irregularity, slight focal distortions of the trabeculae, as well as single-cell necrosis (arrows) (H&E, x200). D) Although cellular degenerative changes are less in hepatocytes in the group D+T than group D, vacuolar degeneration is present in some hepatocyte cytoplasms (arrows) (H&E, x100).



There was no significant difference observed in p53 immunostaining among the groups. When hepatocytes and liver parenchyma were examined, no difference was observed between the groups in terms of p53 staining. After CD117 immunostaining, histopathological damage was re-evaluated. Mild cytoplasmic immunoexpression of CD117 was observed in the group D, as shown in Figure 2.

Figure 2: A) Immunoexpression in two cells with CD117 in the liver of a rat from the control group (x200). B) Rare cell immunoexpression with CD117 in the liver of a rat from group T, similar to the control group (x200). C) Mild cytoplasmic immunoexpression by CD117 in a focal area in the liver of a group D rat (x200). D) Mild cytoplasmic immunoexpression with CD117 in relatively fewer cells in the liver of a rat from the group D+T compared to the group D (x200).



The histopathologic damage scores were significantly higher in the group D than in the group D+T, and the difference was statistically significant (P=0.03) (Table 2).

Table 2: Distribution of histopathologic findings.

Groups (n=10)	Hepatocyte damage	Disorganization of the Hepatic Cords	Inflammation	Congestion	Hemorrhage	Necrosis	p53	CD117 Expression
Control	0	0	0	1	0	0	0	0
Taraxacum officinale (100 mg/kg)	0	0	1	1	0	0	0	0
Doxorubicin (40 mg/kg)	2*	1	1	1	1*	0	0	1
Doxorubicin+Taraxacum officinale(100 mg/kg+40mg/kg)	1*	0*	1	1	0	0	0	0*

* Significant difference (P<0.05) between groups D and group D+T. Histopathological scoring was done by determining the highest area. Four categories (0=None; 1=Minimal, 2=Mild, 3=Moderate, 4=Severe) were determined by making a semi-quantitative analysis, and the parameters were scored accordingly.

Discussion

Doxorubicin is commonly used to treat various malignant diseases, including solid tumors and blood cancers. However, its effectiveness is limited due to its negative impact on both normal and cancerous cells [15]. Bilgic et al. [16] demonstrated that a single dose of doxorubicin could lead to acute liver damage. Therefore, in our study, we also administered a single dose of doxorubicin. Our results indicated that doxorubicin increased MDA levels and decreased SOD and CAT activities in the treated group. However, we hypothesized that TO could mitigate these effects by reducing MDA levels and increasing SOD and CAT activities. Our study concluded that TO could improve the biochemical and histopathological damage caused by doxorubicin. To the best of our knowledge, this study is the first to demonstrate the positive impact of TO on the liver's adverse reactions to doxorubicin.

Prasanna et al. [17] have reported that oxidative stress is the primary cause of doxorubicin-induced liver damage. As a result of doxorubicin-induced oxidative stress, electrons are lost from oxygen, leading to the production of superoxide radicals and reactive oxygen species (ROS). The elevated levels of ROS, in turn, cause an increase in lipid peroxidation, ultimately causing damage to hepatocytes and the liver [18]. Our study found that the D group had more hepatocyte damage indicators, such as inflammation and hemorrhage, than other groups. Furthermore, the D group showed more pronounced biochemical parameters indicating liver damage. However, the addition of TO was observed to reverse these adverse effects.

TO is a plant commonly found in nature, and its leaves can be eaten raw or used in tea, while its roots can be cooked and consumed. For centuries, TO has been a key component in traditional medicine for treating gout, diarrhea, and liver ailments [19]. It has been shown that TO can prevent oxidative stress in neurons, and it is believed that the protective effect is due to its phenols and hydroxycinnamic acid components [20]. Many studies have also demonstrated that TO possesses antioxidant, anti-inflammatory, antibacterial, and anticancer properties [21,22]. Therefore, we hypothesized that the antioxidant properties of TO could effectively prevent liver damage caused by doxorubicin.

In our study, we observed that TO increased the activities of SOD and CAT while reducing the levels of MDA. Histopathological analysis confirmed the protective effects of TO. The scores indicating tissue damage were significantly lower in the D+T group than in the D group. While there was no significant difference in p53 immunohistochemical staining, CD117 dye showed similar findings as H&E.

Limitations

Our study has certain limitations, such as the small sample size and the fact that animal experiments may not perfectly replicate the effects seen in humans.

Conclusions

In conclusion, our study found that TO can reduce hepatic injury and may be a useful treatment option for managing the oxidative stress caused by doxorubicin. We hope that our findings will inspire further research in this field. However, large prospective randomized trials are necessary to evaluate the efficacy of TO in preventing hepatic injury caused by doxorubicin.

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Comparison the effects of sugammadex and neostigmine/atropine on cognitive functions in bariatric surgery patents: Randomized controlled trial

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Ethics Committee Approval
The study was approved by Malatya Inonu University Clinical Studies Ethics Committee (2015/178).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: A recently introduced drug, sugammadex, can be a good alternative to conventional neuromuscular blockade reversal agents, such as neostigmine. This choice is of great importance, especially in the patients in whom it would be wise to avoid cholinergic side effects. The aim of this study was to compare the effects of sugammadex and the combination of neostigmine/atropine on post-operative cognitive dysfunction in bariatric surgery patients.

Methods: This randomized controlled trial included a total of 90 patients with American Society of Anesthesiologists (ASA) I–III physical status and body mass index >30 who were scheduled for elective sleeve gastrectomy were recruited for the study after obtaining ethics committee approval. Written consent was obtained from each patient. The exclusion criteria consisted of several parameters: lack of consent, co-existing muscular diseases, and severe cardiovascular diseases (New York Heart Association [NYHA]). The patients were randomly divided into two groups, and the randomization was performed by the investigator using previously prepared envelopes. In both groups, Mini Mental State Examination (MMSE) was performed before the operation. The patients' memory, attentive executive functions, and motor skills were evaluated as part of a control cognitive evaluation. After the operation while in the post-anesthesia care unit and when the Modified Aldrete Recovery Score was ≥9, the MMSE evaluation was repeated one and six hours later.

Results: The pre-operative MMSE results were similar in both groups. In the post-operative period, MMSEpo, MMSEpo1, and MMSEpo6 values were not significantly different between the groups. When a detailed examination of MMSEpo data was performed, it was determined that the MMSE scores were 20–25 in 14 patients (32.6%) in Group N/A and six patients (14.6%) in Group S. In Group N/A, the percentage of patients with MMSE 20–25 was significantly higher than that of Group S ($X2=3.807$; $P=0.046$).

Conclusion: In this study, sugammadex produced less effects on cognitive functions when compared with neostigmine/atropine combination. The neostigmine/atropine combination produced mild effects on cognitive functions in the first hour of recovery.

Keywords: sugammadex, neostigmine, atropine, cognitive dysfunction, bariatric surgery

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Introduction

Sugammadex is a γ-cyclodextrin that is used to encapsulate aminosteroidal non-depolarizing neuromuscular blocking drugs (NMBDs), such as rocuronium and vecuronium. With hydrophobic cores and hydrophilic peripheral chains, NMBDs becomes trapped inside the sugammadex molecule, and a rocuronium–sugammadex complex is formed. This inert complex leads to a reduction in the concentration of rocuronium in the neuromuscular cleft without affecting muscarinic functions and is mainly excreted via urine [1]. It has a high molecular weight, so it has a very low blood-brain barrier transfer [2]. It also has no direct effects on cholinergic transmission [3].

Neostigmine is an anticholinesterase that is used for reversal of NMBDs for over 40 years. It consists of a quaternary ammonium group and provides a covalent bonding to acetylcholinesterase which is lipid insoluble and cannot pass through the blood-brain barrier (BBB) [4]. They cause a rise in the level of acetylcholine (Ach) in the postsynaptic membrane by inhibiting acetylcholinesterase reversibly [5]. It causes some muscarinic effects that can be prevented by adding an anticholinergic drug during blockade reversal [4]. Atropine can rapidly cross the BBB and has been associated with mild post-operative memory deficits; its toxic doses are associated with excitatory reactions [6].

Post-operative cognitive dysfunction (POCD) refers to an impairment in a person's concentration, memory, language use, and social communication and is especially common after major surgery [7,8]. The etiology of POCD remains unclear, but many factors are blamed to be its cause. Recently, it's emphasized that the imbalance of the neurotransmitters, such as acetylcholine (Ach), serotonin, and glutamate during the peri-operative period can be a cause of POCD [9]. Ach, especially, has serious effects on cognitive functions, and it is thought that the defect in the acetylcholinergic system can be the reason behind POCD [10]. The effect of the nicotinic system on learning, memory, and cognition has previously been shown in human and animal studies [11].

The mini mental state examination (MMSE) is a widely used test among the elderly population to evaluate the cognitive status of these patients. It was first described in 1975 by Folstein et al. [12] and designed as a screening test for evaluating cognitive status. The test measures, orientation to time and place, short term memory, attention span, ability to solve problems, language, comprehension, and motor skills. The scoring is straight forward and even can be done at home.

In this study, we hypothesized that sugammadex may yield better cognitive functions with less adverse airway effects in bariatric surgery patients when compared with neostigmine/atropine combination, which are the most commonly used reversal agents for neuromuscular blockade.

Materials and methods

After obtaining the local ethics committee approval (Malatya Inonu Unıversity Clinical Studies Ethics Committee, 015/178), 90 patients with American Society of Anesthesiologists (ASA) I–III physical status who were scheduled for elective sleeve gastrectomy were recruited for this randomized controlled study. Written informed consent was obtained from all the patients. The sample size was determined due to power analysis. It was carried out using the G*power program 3.1.9.4 version. According to the mean difference and standard deviation in MMSE scores during the post-operative period and at baseline, to achieve the power of the study as 80% with 0.05 alpha error and 0.50 effect size, 44 and 45 patients should have been included in the neostigmine/atropine and sugammadex groups, respectively. The closed envelope method was used for the patient assignment, and the patients were divided into two groups with 45 patients in each group.in terms of the use of neuromuscular block reversal: (1) Group N/A and (2) Group S. Neostigmine/atropine combination was used in the Group N/A, and sugammadex in the Group S for reversal. Patients under the age of 18 and those with congestive heart failure, history of previous neuropsychiatric disorder, cardiac arrest, and/or stroke were excluded. Patients with ASA physical status IV and above patients who met difficult intubation criteria were also excluded from the study. Two patients in Group N/A and four in the Group S did not complete the study because of surgical complications. Each patient was pre-medicated with intravenous (IV) metochlopramide 10 mg and ranitidine 50 mg 30 min prior to the surgical procedure. An 8-h fasting period was ensured for the patients.

In the surgical theatre, routine monitoring, including electrocardiography (ECG), pulse oximetry (SpO_2) and non-invasive blood pressure (NIBP), was provided. Neuromuscular block monitoring was performed by a TOF-WATCH®SX (Organon Teknika B V, Netherlands). Forehead temperature probes were used for patients' temperature measurements. During the entire procedure, fluids were warmed, and an underbody warming blanket (Bair Hugger 63500, 3M Health Care, Nauss, Germany) was used to keep patients' body temperature at 36 to 36.5 °C. Anesthesia was induced with propofol 2 mg kg^{-1}, fentanyl 1 µg kg^{-1}, and rocuronium 0.6 mg/kg. The dosing regimen was selected according to ideal body weight. An endotracheal tube with an internal diameter of 8.5 and 7.5 mm was used for males and females, respectively. Following intubation, an orogastric tube was inserted and free drainage was allowed after aspiration.

Anesthesia was maintained with one minimum alveolar concentration desflurane (6%) with 40% oxygen in air. Volume-controlled mechanical ventilation was used for both groups, and the ventilation parameters were set as a tidal volume of 6 mL kg^{-1} according to ideal body weight at a rate of 10 to12 min^{-1} and adjusted to maintain an end-tidal carbon dioxide ($EtCO_2$) between 30 and 45 mm Hg. The high initial fresh gas flow rates (6 L min^{-1}) were reduced to 4 L min^{-1}.

After Veress needle insertion from the lower abdomen pneumoperitoneum was obtained, the intra-abdominal pressure was maintained at 8 to10 mm Hg in the supine position. The patient was put in a reverse-Trendelenburg position with the patient's head raised about 30° from the horizontal line after which the gastrectomy was performed.

In Group N/A, neostigmine 0.04 mg kg^{-1} IV was used to reverse the neuromuscular blockade. Atropine 0.02 mg kg^{-1} IV was given to prevent muscarinic side effects. In Group S,

sugammadex 2 mg/kg was used when a train-of-four of 25% (TOF 25) was reached. Extubation was performed after obtaining a TOF value of 90% (TOF 90). Tenoxicam 20 mg IV and tramadol 1 mg kg^{-1} were used for post-operative analgesia. Heart rates, blood pressures, SpO_2 values, and body temperatures of the patients were closely followed and maintained within physiological ranges.

In both groups, MMSE was performed before the operation: The patients' memory, attentive executive functions, and motor skills were evaluated as a control cognitive evaluation. For MMSE (total score 30) was used orientation (total 10 points), recording memory (total score 3), pay attention and count (total score 5), recursion (total score 3), language (total score 9). After the operation in the post-operative anesthesia care unit (PACU) and when the Modified Aldrete Recovery Score was ≥9, the MMSE evaluations were repeated one and six hours later (MMSEp: mini mental test pre-operative, MMSEpo: mini mental test post-operative, MMSEpo1: mini mental test post-operative 1st h, and MMSEpo6: mini mental test post-operative 6th h). The patients in both groups did not receive any pre-medications.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 20.0 software. Age, BMI, and MMSE were assessed using a Student's t-test between the groups. Assessment of data such as ASA and MMESpo patient numbers was done using a chi-squared or Fisher's exact test. The correlation between MMESpo data and surgical time, ASA, and BMI was assessed by Spearman's correlation. $P<0.05$ was considered significant.

Results

Demographic characteristics of the patients and surgery duration are presented in the Table 1. No significant differences between the groups were found.

Table 1: Demographic characteristics of the patients

	Group N/A (n=43)	Group S (n=41)	*P*-value
BMI (kg m^{-2})	47.69 (4.14) (40-56)	47.39 (5.13) (40-57)	0.770
Operation duration (min)	90.69 (17.71) (65–145)	89.51 (19.39) (65-135)	0.763
ASA (1/2/3)	14/28/1 (32.6/65.1/2.3)	21/19/1 (51.2/46.3/2.4)	0.436

BMI: body mass index, ASA: American Society of Anesthesiologist, Group N/A: Group neostigmine/atropine, Group S: Group sugammadex. BMI and operation duration were presented as mean (standard deviation) (min-max); ASA was presented as number (%).

The MMSE scores of the patients are presented in Table 2. No significant differences between the groups were found..

When a detailed evaluation of the post-operative MMSE scores was obtained, more patients with higher MMSE scores (such as 25–30) in Group S were when compared with Group N/A. This difference was statistically significant ($x^{2=}3.807$; $P=0.046$) as shown in Table 3. No residual cauterization was observed in any patient.

Table 2: MMSE scores of the groups

	Group N/A (n=43)	Group S (n=41)	*P*-value
MMSEp	30.00 (0.00) (30–30)	30.00 (0.00) (30–30)	-
MMSEpo	27.00 (2.93) (21–32)	27.35 (2.77) (21–30)	0.585
MMSEpo1	28.79 (1.54) (25–30)	29.05 (1.32) (26–30)	0.413
MMSEpo6	29.84 (0.37) (29–30)	29.88 (0.33) (29–30)	0.598

MMSEp, MMSEpo, MMSEpo1, and MMSEpo6: mini mental state examination pre-operative, post-operative, post-operative 1st h, and post-operative 6th h, respectively; Group N/A, Group neostigmine/atropine; Group S, Group sugammadex. MMSE data are presented as mean (standard deviation; min–max). The numbers are test points (see text for detailed information).

Table 3: MMSEpo data of the patients

MMSE Score	Group N/A (n=43)	Group S (n=41)	*P*-value
25–30	29 (67.4)	35 (85.4)	$x^{2=}3.807$ 0.046*
20–25	14 (32.6)	6 (14.6)	

MMSEpo: mini mental state examination post-operative. MMSE numbers are test points (see text for detailed information). The data for the groups indicate the patient numbers with percentage of them in the group given in the parentheses. *$P<0.05$.

Discussion

In this study, the effects of neostigmine/atropine combination and sugammadex on cognitive functions in morbidly obese patients who had undergone laparoscopic bariatric surgery were evaluated. Obesity has a significant impact on anesthesia procedures. Obesity and alterations due to obesity, which include changes in metabolic, cardiovascular, and pulmonary functions, can lead to an increase the risk of peri-operative mortality and morbidity [14]. We planned our study involving obese patients as they have greater peri-operative mortality and morbidity. Although the MMSEpo, MMESpo1, and MMSEpo6 scores were not significantly different, the number of patients with a total MMSE score of 20 to 25, a score that indicates minimally affected cognitive functions, was significantly higher in Group N/A when compared with Group S.

The difficulty with studies on cognitive dysfunction is the presence of many risk factors that may contribute to POCD. These risk factors include advanced age, comorbidities that effect cognitive functions, multiple drug usage, duration of anesthesia, level of education, post-operative infections, post-operative respiratory complications, type of surgery, intra-operative ischemia, and impairment in glucose, sodium, and potassium levels [15–17]. ASA I–III patients were included in the study to standardize conditions and risk factors associated with the patients. Body temperature and hemodynamic parameters were kept within physiological ranges throughout the operation. Propofol was used for induction, and desflurane for maintenance of anesthesia as these have been shown to be produce less adverse risks on the cognitive functions [18].

The general incidence of POCD is 5–15%, and it can increase to 62% in high risk patients [16]. The etiology of POCD still remains unclear, but many factors for this uncertainty are to blame. Recently, it was emphasized that imbalance in levels neurotransmitters, such as ACh, serotonin, and glutamate during the peri-operative period can be the cause of POCD. ACh, especially, has serious effects on cognitive functions, and defects in the cholinergic system and/or insufficient ACh production were blamed for POCD development [9]. The effects of the nicotinic system on learning, memory, and cognition were previously shown in human and animal studies [10]. Atropine was previously shown to cause mild cognitive disorder during the post-operative period in addition to causing the central

anticholinergic syndrome. This process can be attributed to easy transfer of atropine across the BBB in addition to central and subcortical muscarinic receptor antagonism. Barbiturates lead two a reduction in Ach release and cause somnolence, amnesia, and hallucinations [19,20]. Thus, atropine may result in a decrease in MMSE scores during the first hour of recovery.

Piskin et al. [21] compared the effects of neostigmine and sugammadex following general anesthesia but could not demonstrate better results in cognitive functions in the sugammadex group. Batistaki et al. [13] concluded that no clinically important differences in the incidence of POCD after neostigmine or sugammadex administration in patients above 40 years could be detected. The results of our study are compatible with these findings, but in the detailed examination of MMSEpo data, more patients with minimally affected cognitive functions were found after receiving neostigmine compared to those receiving sugammadex.

Limitations

One limitation of the study was that sugammadex was used at a of 2 mg/kg. The effect of high dose sugammadex on cognitive functions is unknown. Studies can be initiated in this regard.

Conclusion

In conclusion, sugammadex and conventional neostigmine/atropine combination as reversal agents for neuromuscular blockade result in comparable effects on post-operative cognitive functions. Production of less early post-operative effects favor sugammadex, but whether the differences between the two agents has clinical significance should be questioned.

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The relationship of KDIGO classification and incidence & mortality of acute kidney injury in sepsis patients in intensive care unit: A retrospective cohort study

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Ethics Committee Approval
The study was approved by Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (Decree no: 416, date: 31.12.2021). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Acute kidney injury (AKI) is a common and serious complication associated with morbidity and mortality in patients with sepsis. This study aimed to determine the severity of AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria and evaluate its relationship with mortality in patients who were followed up in the intensive care unit (ICU) due to sepsis and developed AKI.

Methods: We retrospectively analyzed patients diagnosed with sepsis and followed up in the ICU, including all patients with AKI. The severity of AKI was determined for all patients using the KDIGO criteria. The patients were divided into four groups: Stage 1, Stage 2, Stage 3, and without AKI. Patients with missing data, COVID-19 patients, patients with chronic kidney insufficiency, and kidney transplant patients were excluded.

Results: A total of 1,177 sepsis patients were included in the study, of whom 52.4% were male (n=617). The median age of the study group was 78 years (Q1-Q3: 68-85 years). It was determined that 57.9% of the patients (n=681) developed AKI at any stage. According to the KDIGO criteria, the rates of patients in Stage 1, Stage 2, and Stage 3 developing AKI were 23.9%, 16.2%, and 17.8%, respectively. The incidence of hypertension (HT) and diabetes mellitus (DM), which are comorbidities, increased as the patients' KDIGO stage increased (P<0.001).

Conclusion: AKI occurred in 57.9% of sepsis patients in the ICU, and 30.4% received renal replacement therapy (RRT). It was determined that mortality increased as the KDIGO stage of our patients increased.

Keywords: acute renal injury, critical care, KDIGO, mortality

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Introduction

Acute kidney injury (AKI) is a common complication observed in patients undergoing intensive care unit (ICU) treatment. It is associated with adverse outcomes, including prolonged ICU and hospital stays, the development of chronic kidney disease, and an increased risk of short- and long-term mortality [1].

In the intensive care setting, AKI serves as an independent risk factor for mortality, with patients requiring renal replacement therapy (RRT) experiencing mortality rates ranging from 40% to 55%. The elevated mortality is primarily attributed to systemic effects on various organs, such as the lungs, heart, liver, brain, and immune system, rather than mere loss of clearance. Studies have demonstrated that AKI heightens susceptibility to infections, doubles the incidence of respiratory failure, and directly or indirectly compromises cardiac function [2].

Numerous risk factors have been identified in association with the development of AKI, with the most common being renal hypoperfusion, which can arise from conditions such as hypovolemia, heart failure, and arterial hypotension. Additionally, the administration of nephrotoxic drugs and contrast-related AKI are known contributors. Among these factors, sepsis-related AKI is particularly prevalent in the intensive care setting [3]. The prevention of septic AKI primarily revolves around prompt sepsis treatment and early resuscitation. In cases where sepsis resolves, most patients regain normal kidney function. However, even a single episode of septic AKI is linked to an elevated risk of subsequent chronic kidney disease [4].

The Kidney Disease: Improving Global Outcomes (KDIGO) guideline, established in 2012, defines AKI as a rapid decline in kidney function within 7 days or less [5,6].

Managing AKI in the ICU presents significant challenges, necessitating appropriate volume control, careful management of nephrotoxic drugs, and strategic decision-making regarding the timing and type of renal replacement therapy. Effective management of fluid and electrolyte balance is crucial in this regard [7].

In this study, our primary objective was to examine the incidence of AKI, the requirement for RRT, and the association between AKI and mortality among sepsis patients in the ICU. Additionally, our secondary objective was to assess the relationship between the ratios of white blood cell (WBC)/lymphocyte and C-reactive protein (CRP)/albumin with mortality.

Materials and methods

This retrospective study was conducted between January 1, 2018, and December 31, 2020, following approval from the Afyon Health Sciences University Faculty of Medicine Clinical Research Ethics Committee (Decree no: 416, date: 2021). The study aimed to analyze the clinical data of patients over 18 years old who were admitted to the ICU with a diagnosis of sepsis. A total of 1,177 patients diagnosed with sepsis accompanied by organ failure due to infection were included in the analysis. Patients with missing data, COVID-19 patients, those with chronic kidney insufficiency, and kidney transplant patients were excluded from the study. The recorded parameters for all patients included age, gender, comorbidities, Acute Physiology and Chronic Health Assessment (APACHE) II score, duration of intensive care and hospital stay, WBC/lymphocyte ratios, and CRP/Albumin ratios.

In this study, AKI was defined and staged according to the KDIGO (Kidney Disease: Improving Global Outcomes) serum creatinine criteria. According to KDIGO, AKI is defined as an increase of ≥0.3 mg/dl in serum creatinine within 48 hours, or a 1.5-fold increase in serum creatinine from baseline within seven days, or urine output of <0.5 ml/kg/h in the last 6 hours [5]. The baseline creatinine value was determined as the most recent creatinine value available in the pre-hospital system within the past year. The patients were categorized into four groups: Stage 1, Stage 2, Stage 3, and without AKI. A comparison of clinical features was performed among the patients, and subgroup analysis was conducted based on the KDIGO staging criteria and the implementation of RRT.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 20. The data were presented as ratios, medians, and interquartile ranges (IQR). The normal distribution of variables was assessed through visual examination (histogram) and analytical methods (Kolmogorov-Smirnov test). The Kruskal-Wallis test was employed to compare continuous variables, while the Chi-square test was used for categorical variables. Receiver operating characteristic (ROC) curves were utilized to evaluate the predictive power of WBC/lymphocyte and CRP/albumin values for mortality. A *P*-value of less than 0.05 was considered statistically significant.

Results

The study enrolled a total of 1,177 patients, with 52.4% (n=617) being male. The median age of the study group was 78 years (Q1-Q3: 68-85 years). AKI was observed in 57.9% (n=681) of the patients at any stage. The characteristics of the patient groups are presented in Table 1, where Stage 1 AKI was found in 23.9% (n=281) of patients, Stage 2 AKI in 16.2% (n=190), and Stage 3 AKI in 17.8% (n=210). Among those who developed AKI, 69.6% (n=474) did not require RRT, while 23.2% (n=158) received intermittent RRT, and 7.2% (n=49) underwent continuous RRT treatments.

Table 1: Characteristics of patients and comparison by groups

Characteristic	Total (n=1177)	No AKI (n=496)	Stage 1 (n=281)	Stage 2 (n=190)	Stage 3 (n=210)	*P*-value
Age (years)	78 (68-85)	76 (66-84)	80 (72-86)	78 (69-84)	75 (67-83)	0.004
Male, %-n	52.4-617	53.2-264	49.8-140	48.9-93	57.1-120	0.297
DM, %-n	20.4-240	14.1-70	21.4-60	25.8-49	29-61	<0.001
HT, %-n	16.6-195	11.3-56	15.3-43	21.1-40	26.7-56	<0.001
COPD, %-n	20.6-243	23-114	19.2-54	19.5-37	18.1-38	0.392
Malignancy, %-n	16.7-197	12.9-64	18.1-51	20-38	21-44	0.021
CHF, %-n	13-153	11.3-56	13.9-39	14.7-28	14.3-30	0.515
RRT, %-n	17.6-207	0	15.7-44	15.8-30	63.3-133	<0.001
Dead, %-n	51.1-602	35.5-176	56.9-160	57.9-110	74.3-156	<0.001
WBC/Lymphocyte	15 (9-22)	12 (8-20)	15 (10-24)	16 (11-25)	18 (12-30)	<0.001
CRP/Albumin	38 (18-51)	31 (12-44)	38 (20-53)	40 (18-57)	49 (34-62)	<0.001
APACHE II	23 (18-30)	20 (16-26)	24 (19-30)	27 (20-32)	30 (24-35)	<0.001

DM: diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, RRT: Renal replacement therapy, APACHE: Acute Physiology and Chronic Health Assessment

The overall survival rates were as follows: 64.5% in the group without AKI, 43.1% in the KDIGO 1 group, 42.1% in the KDIGO 2 group, and 25.7% in the KDIGO 3 group (log-rank

P<0.001). The survival chart of these groups is illustrated in Figure 1. The average duration of ICU stay was 8.4 days (Q1-Q3: 4-11 days).

Figure 1: Survival chart of the groups

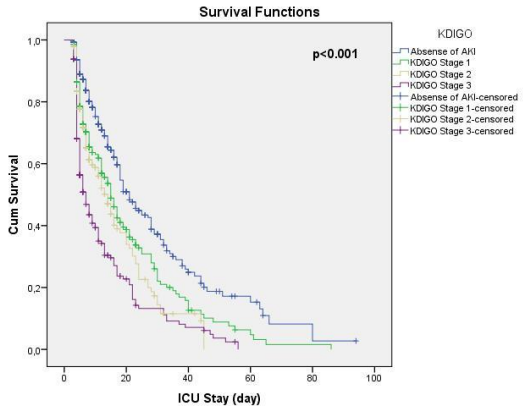
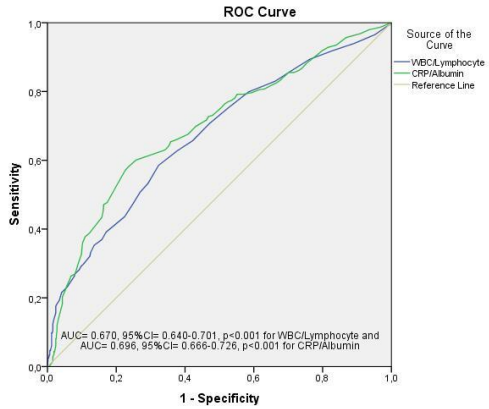


Figure 2 displays the ROC curve depicting the predictive value for mortality of WBC/lymphocyte and CRP/albumin values, along with the corresponding *P*-values at the 95% confidence interval. The area under the curve (AUC) for WBC/lymphocyte was 0.670 (95% CI: 0.640-0.701, [*P*<0.001]), and for CRP/albumin, it was 0.696 (95% CI 0.666-0.726, [*P*<0.001]).

Figure 2: The ROC curve for predicting mortality of WBC/lymphocyte and CRP/alb values



The optimal cutoff value determined by the Youden index was 15.5 for WBC/lymphocyte, with a sensitivity of 58.6% and specificity of 67.7%. For CRP/albumin, a value of 41.5 predicted mortality with a sensitivity of 58.2% and specificity of 76.3%.

Discussion

Sepsis-related AKI is defined as the development of AKI within seven days following the onset of sepsis [8]. The prognosis for sepsis-associated AKI is worse compared to sepsis or AKI alone. Prolonged stays in the ICU and hospital are linked to increased mortality rates and a diminished quality of life [1,9].

In studies examining AKI, it has been reported that AKI classifications can serve as predictors of mortality, with mortality rates rising as the stage of AKI increases [10-12]. Our study found a similar trend, where mortality increased in correlation with the severity of AKI among sepsis patients in the ICU.

In a multicenter study encompassing 15,132 patients in general intensive care, the incidence of AKI development was reported to be 32% [13]. Another study focused on ICU patients and employed the KDIGO criteria to assess AKI, revealing an occurrence rate of 57.3% among 1802 patients [1]. Similarly, our study found that the frequency of AKI among sepsis patients was 57.9%.

In a study investigating the epidemiology of acute kidney injury in intensive care sepsis patients, KDIGO guidelines were utilized for AKI staging and were found to be a reliable measure when compared to Acute Kidney Injury Network (AKIN) criteria. The incidence of AKI was determined to be 47.9%, with a corresponding 28-day mortality rate of 32.7% [14]. In our own study, we similarly employed the KDIGO staging for sepsis patients and observed a 28-day mortality rate of 62%. It is worth noting that our higher mortality rate could be attributed to a significant number of deaths caused by factors other than sepsis.

In a prospective study conducted on sepsis patients in the ICU, it was observed that mortality rates were elevated among patients who experienced recurrent AKI during their stay. Specifically, AKI recurred in 20% of the patients [15]. One limitation of our own study is that we did not investigate or document episodes of recurrent AKI.

Studies have reported AKI-related mortality rates ranging from 30% to 60% among patients with sepsis [16-18]. In our study, the mortality rate among sepsis patients was 51.1%. However, it is important to note that mortality is influenced by various factors beyond AKI. One limitation of our study is that we did not investigate other contributing factors to mortality.

The international AKI-EPI study, which examined the prevalence of AKI in the ICU, revealed a high incidence of AKI among patients with diabetes mellitus (DM) and hypertension (HT) [1], consistent with our findings.

In a multicenter intensive care study conducted in China, focusing on the association between AKI and mortality among general intensive care patients, it was observed that KDIGO Stage-1 patients did not exhibit an elevated 30-day mortality rate [19]. However, in our study, we found a 30-day mortality rate of 72% among our Stage-1 patients. It is important to note that this finding cannot be solely attributed to AKI, as our sample predominantly consisted of sepsis patients, which may contribute to the higher mortality rate observed.

In a study examining AKI in a cohort of 1689 ICU patients, sepsis was identified as the primary cause of acute kidney injury necessitating dialysis [20].

In the study conducted by Hoste et al. [1] in the ICU, RRT was administered to 23.5% of patients with AKI. Similarly, in a study focused on AKI among sepsis patients in the ICU, the rate of RRT utilization was 15%. In our cohort of AKI patients, the rate of RRT utilization was notably higher at 30.4%. This increase may be attributed to the timing of RRT initiation. While we did not have a specific strategy for early or late initiation of RRT, we speculate that RRT might have been initiated early due to the presence of sepsis or septic shock.

The kidneys are among the organs most vulnerable to early injury during sepsis. Approximately two-thirds of patients with septic shock develop AKI [1], with half of them experiencing AKI before even being admitted to the emergency department [21]. Hence, it is appropriate to regard AKI as an early indicator of sepsis. In our study, the mortality rate among patients who developed AKI was 51.1%, whereas the mortality

rate among sepsis patients who did not develop AKI was 62%. Notably, the mortality rates of sepsis patients with and without AKI were comparable [22].

Irrespective of whether sepsis occurs prior to, concurrently with, or after AKI, it is evident that it contributes to additional mortality in AKI cases. A study examining the mortality of ICU patients with AKI compared individuals with and without sepsis, revealing that septic shock resulted in higher mortality rates than sepsis alone [23]. Moreover, other studies have reported significantly elevated rates of AKI among patients with septic shock, ranging from 60% to 70% [24]. One limitation of our study was its retrospective nature, which prevented us from examining the rates of AKI in patients who developed septic shock.

A high CRP/Albumin ratio serves as an indicator of severe inflammation. In a study involving sepsis patients in the ICU, it was observed that the CRP/Albumin ratio yielded more consistent prognostic information than CRP levels alone, and it was also correlated with mortality [25]. Furthermore, the association between CRP/Albumin ratios and hospital mortality has been reported in studies conducted both in general ICUs and among ICU patients with AKI [26,27].

Upon analyzing the WBC/lymphocyte and CRP/albumin values of our patients as predictors of mortality, we observed that the sensitivity and specificity were relatively low. Given the multitude of factors influencing patient mortality, we believe it would be inappropriate to draw conclusions regarding mortality based solely on these indices.

Limitations

This study has several limitations, including the absence of data regarding urine output, fluid administration, and nutritional management. Due to the retrospective nature of our study, we were unable to analyze the occurrence of septic shock, which directly impacts both mortality and the development of AKI. Furthermore, another limitation is our failure to investigate organ failures other than AKI among sepsis patients in the ICU. Future research must address these limitations by conducting prospective and multicenter studies focused on sepsis patients in the ICU.

Conclusion

In this study, we observed the development of AKI in 57.9% of sepsis patients admitted to the ICU. By categorizing patients with AKI according to KDIGO staging, we investigated their respective mortality rates. Our findings demonstrated a correlation between the severity of AKI and mortality, as indicated by the KDIGO criteria. Early identification and appropriate management of sepsis in the ICU can potentially decrease mortality rates and the occurrence of AKI, ultimately leading to improved outcomes for patients with sepsis admitted to the ICU.

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Pan-immune-inflammation value and systemic immune-inflammation index: Are they useful markers in sarcoidosis?

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Ethics Committee Approval
The study was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (date: March 3, 2023, number: 2023/130).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Sarcoidosis is a multisystem inflammatory disease characterized by the infiltration of various organs. Due to the lack of a widely-accepted biomarker, researchers have explored alternative and previously unexplored parameters in sarcoidosis. This study aimed to investigate the utility of various markers, including the systemic immune-inflammation index (SII) and pan-immune-inflammation value (PIV), in patients with sarcoidosis.

Methods: A case-control study was conducted between January 2019 and February 2023. The study included 75 patients diagnosed with sarcoidosis, and 93 healthy individuals matched for age, sex, and body mass index. Sarcoidosis-related features, such as lung stage and extrapulmonary involvement, were recorded. The researchers investigated SII, PIV, procalcitonin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), other biochemical results, and complete blood counts (including neutrophil, lymphocyte, monocyte, platelet counts, hemoglobin, mean platelet volume [MPV], and red cell distribution width [RDW]).

Results: The age and sex distribution were similar in both the case and control groups (P=0.258 and P=0.196, respectively). The patient group had a significantly lower absolute lymphocyte count than the control group (P=0.035). Patients' RDW (P=0.007), platelet-to-lymphocyte ratio (P=0.028), and ESR (P<0.001) values were significantly higher compared to controls. No significant difference was observed between the two groups regarding other variables, including PIV and SII. There was a significant weak positive correlation between PIV and lung stage, as well as between MPV and the presence of erythema nodosum.

Conclusion: PIV and SII values in patients with sarcoidosis were similar to controls. The positive correlations between PIV and lung stage and between MPV and erythema nodosum suggest potential relationships with sarcoidosis-related features and demonstrate the value of these readily available and inexpensive markers in patient management. Comprehensive studies are needed to clarify whether SII and/or PIV can be used to assess the characteristics of patients with sarcoidosis.

Keywords: sarcoidosis, pan-immune-inflammation value, systemic immune-inflammation index, pulmonary sarcoidosis

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Introduction

Sarcoidosis is a multisystem disease characterized by infiltrating various organs with non-necrotizing granulomas [1]. It is estimated to have an annual incidence of approximately 2.3 to 11 cases per 100,000 people [2]. Patients diagnosed with sarcoidosis generally have a shorter life expectancy than the general population [3,4], and certain populations face a particularly high mortality risk [5].

Sarcoidosis exhibits heterogeneous manifestations [1,6]. It can be asymptomatic or present with non-specific symptoms such as fatigue [7], mild-to-moderate respiratory symptoms (cough, dyspnea, and chest pain), lymphadenopathy, fever, weight loss, and night sweats [1,6]. Asymptomatic patients are sometimes incidentally detected through lung X-rays ordered for other reasons. Patients presenting with non-specific symptoms like fatigue and lymphadenopathy require a differential diagnosis to exclude lymphoma, leishmaniasis, toxoplasmosis, and tuberculosis [1,8]. The clinical presentation's heterogeneity and the numerous potential differential diagnoses make the disease challenging to diagnose. Additionally, predicting the disease's course and treatment response appears to be difficult [9].

The etiology and pathogenesis of sarcoidosis remain unclear, but there is increasing research into the mechanisms involved in granuloma formation, including genetic predisposition, environmental factors, and infectious triggers [1,10,11]. While it has been suggested that immune system overactivation may play a significant role in forming granulomas responsible for the disease's clinical manifestations, our understanding of immune-related mechanisms remains limited [10]. Numerous clinical, physiological, radiographic, histological, and serological parameters have been investigated to identify potential disease-specific biomarkers that can aid in the diagnosis, classification, and prognosis of sarcoidosis. Many parameters have shown significant alterations in patients with sarcoidosis [4,12,13]. However, a common characteristic of many of these parameters is their low sensitivity and specificity.

The pan-immune-inflammation value (PIV) has recently emerged as a novel prognostic predictor for certain diseases. PIV is calculated using an equation that incorporates neutrophil, platelet, monocyte, and lymphocyte counts [14]. Studies have demonstrated that PIV serves as an important indicator of mortality and/or prognosis in various conditions, including different cancers [15], myocardial infarction [16], antineutrophil cytoplasmic antibody-associated vasculitides [14], membranous nephropathy [17], chemotherapy response [18], and steroid response in idiopathic IgA nephropathy [19]. Additionally, the systemic immune-inflammation index (SII), which is similar to PIV and derived from neutrophil, platelet, and lymphocyte counts, has shown predictive capabilities for prognosis and/or disease severity in diverse conditions such as various cancers [20], membranous nephropathy [17], subarachnoid hemorrhage [21], carotid stenosis [22], and acute pulmonary embolism [23]. However, to our knowledge, the predictive roles of these two prognostic markers in the diagnosis, clinical features, and severity of sarcoidosis have not been investigated previously.

The absence of a widely-accepted biomarker has prompted research into alternative and previously unexplored parameters in sarcoidosis. In this study, our primary objective was to examine the predictive capabilities of SII and PIV in diagnosing sarcoidosis. Additionally, we aimed to explore potential correlations between various biomarkers, including PIV and SII, and the clinical features and severity of sarcoidosis as secondary objectives.

Materials and methods

Ethical statement

The ethical protocol for this study was approved by the local ethics committee with a decision date of 03.03.2023 and decision number 2023/130. All procedures were conducted in compliance with the ethical standards set forth by the institutional research committee, as well as the Helsinki Declaration and its subsequent amendments.

Study design and setting

This case-control study was conducted at the Department of Rheumatology, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey, spanning from January 2019 to February 2023.

Study population

Based on descriptive statistics from Kemal et al.'s study [24] (effect size=0.577), a sample size of 65 participants per group (total of 130) was determined to achieve 90% power at a two-sided significance level of 0.05. The sample size calculation was performed using a two-sample t-test power analysis (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

The study included a total of 75 patients diagnosed with sarcoidosis (patient group) and 93 healthy individuals (control group). The control group was selected randomly from individuals who visited the internal medicine or rheumatology outpatient clinic for various reasons. These individuals had no known diseases and were not diagnosed with any conditions after undergoing necessary examinations. Age, sex, and body mass index were matched between the control group and the patient group.

Common exclusion criteria for both groups were under 18 years of age, having an active infection at the time of blood sample collection, having a known immunological or rheumatological disease, and being diagnosed with any confounding comorbidity such as diabetes, hypertension, chronic kidney failure, chronic liver failure, cardiovascular disease, metabolic disease, or malignancy.

Data collection

The age and sex information of the participants was documented. Measurements of height (in cm) and weight (in kg) were taken, and body mass index was calculated using the formula weight/height^2 (in kg/m^2). Smoking status was queried among the patients; however, due to missing data in the smoking information collected from the control group, this variable was not included in the study. Blood test results for all participants and sarcoidosis-related characteristics of the patient group were obtained retrospectively from the computerized database records of our hospital.

Sarcoidosis diagnosis, management, and related definitions

Confirming sarcoidosis diagnosis involved obtaining tissue samples from patients suspected of having sarcoidosis, supported by clinical and radiological evidence. This was achieved through procedures such as endobronchial ultrasound, mediastinoscopy, and biopsies of the skin and axillary lymph nodes. These samples were analyzed to identify the presence of non-caseating granulomas while excluding other potential causes of these granulomas, as previously documented [1,6]. All pathological analyses were conducted in the pathology laboratory of our hospital. In cases where patients did not consent to biopsy and/or presented with Löfgren's syndrome, the diagnosis of sarcoidosis was made based on clinical, radiological, and laboratory findings in accordance with established criteria [25].

Sarcoidosis staging was determined by analyzing radiological images of the lungs using the Siltzbach classification system. This system categorizes sarcoidosis into five stages as follows: Stage 0, which indicates a normal appearance on chest X-ray; Stage 1, characterized by the presence of bilateral hilar lymphadenopathy; Stage 2, where bilateral hilar lymphadenopathy is accompanied by parenchymal involvement; Stage 3, indicating parenchymal involvement without bilateral hilar lymphadenopathy; and Stage 4, denoting the presence of pulmonary fibrosis [26].

Extrapulmonary involvement was diagnosed based on established general and organ-specific guidelines and studies, as mentioned previously [1,27–30].

Sarcoidosis treatment and follow-up management were conducted following the guidance provided by previous studies that describe treatment approaches [6,31].

Blood analysis

All laboratory analyses were conducted at the Biochemistry Laboratory of Afyonkarahisar Health Sciences University Hospital, utilizing calibrated standard measuring devices and adhering to the manufacturer's recommendations and international standards. The study incorporated routine laboratory results of patients following histopathological diagnosis and those of the control group during their outpatient clinic admission. No additional blood samples were collected specifically for the study, and no laboratory analyses exclusive to the study were performed. The measured laboratory parameters encompassed procalcitonin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), calcium levels, and a complete blood count, which involved assessing absolute neutrophil, lymphocyte, monocyte, and platelet counts, as well as hemoglobin level, mean platelet volume (MPV), and red cell distribution width (RDW).

Inflammation-related indexes

The systemic immune-inflammation index was calculated using the following formula: SII=Absolute neutrophil count ($\times 10^3$) × Absolute platelet count ($\times 10^3$) / Absolute lymphocyte count ($\times 10^3$) [32].

Pan-immune-inflammation value was calculated using the following formula: PIV=Absolute neutrophil count ($\times 10^3$) × Absolute monocyte count ($\times 10^3$) × Absolute platelet count ($\times 10^3$) / Absolute lymphocyte count ($\times 10^3$) [14].

Also, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR) were calculated.

Statistical analysis

IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) was employed for all analyses conducted in this study. The normality of the data was assessed using the Kolmogorov-Smirnov test. Continuous variables are presented as mean (standard deviation) or median (1st quartile - 3rd quartile), depending on their distribution, while categorical variables are presented as frequency (percentage). For normally distributed variables, independent samples t-tests were performed, whereas non-normally distributed variables were analyzed using the Mann-Whitney U test. The chi-square test was used to analyze categorical variables. The discrimination performance of variables was evaluated through Receiver Operating Characteristic (ROC) curve analysis, and the optimal cut-off points were determined using the Youden index. Spearman correlation coefficients were calculated to assess the relationships between variables. A *P*-value of <0.05 was considered statistically significant.

Results

The median age of the patient group was 55 years (42–62 years), and that of the control group was 56 years (46–60 years) (P=0.258). Among the patient group, 72.00% (n=54) were female, while 61.29% (n=57) of the control group were female (P=0.196). Table 1 summarizes the differences in variables between the patient and control groups, as well as the distribution of characteristics in the patient group. Accordingly, the absolute lymphocyte count of the patient group was significantly lower than that of the control group (P=0.035). The RDW (P=0.007), PLR (P=0.028), and ESR (P<0.001) of the patient group were significantly higher than those of the control group. No significant difference was observed between the two groups in terms of other variables, including PIV (P=0.204) and SII (P=0.201).

Using a cut-off value of ≥14, the sensitivity of RDW in distinguishing patients with sarcoidosis from healthy individuals was 51.35%, and the specificity was 70.97% [P=0.007, AUC (95.0% CI)=0.621 (0.533–0.708)]. It was observed that PLR exhibited a sensitivity of 36.00% and a specificity of 94.62% with a cut-off value of ≥171 [P=0.028, AUC (95.0% CI)=0.599 (0.509–0.688)] (Table 2, Figure 1).

The present study in patients with sarcoidosis found a significant correlation between PIV and stage (r=0.294, P=0.010), as well as between PIV and erythema nodosum (r=-0.280, P=0.015), and uveitis (r=-0.257, P=0.026). SII also showed a significant correlation with erythema nodosum (r=-0.293, P=0.011). Additionally, PLR was found to be significantly correlated with dactylitis (r=-0.251, P=0.030), MLR with erythema nodosum (r=-0.280, P=0.015), NLR with erythema nodosum (r=-0.319, P=0.005), dactylitis (r=-0.255, P=0.028), and myositis (r=-0.248, P=0.032). MPV showed a positive correlation with erythema nodosum (r=0.308, P=0.008), and procalcitonin showed a correlation with uveitis (r=-0.277, P=0.017). Furthermore, there was a significant moderate positive correlation between PIV and CRP (r=0.477, P<0.001),

PIV and ESR (r=0.439, *P*<0.001), ESR and RDW (r=0.574, *P*<0.001), SII and ESR (r=0.403, *P*<0.001), and SII and CRP (r=0.483, *P*<0.001) (Table 3).

Table 1: Demographic, clinical and laboratory features of patients with sarcoidosis and healthy controls

	Patients (n=75)	Controls (n=93)	*P*-value
Age (years)	55 (42 - 62)	56 (46 - 60)	0.258
Sex			
Male	21 (28.00%)	36 (38.71%)	0.196
Female	54 (72.00%)	57 (61.29%)	
Body mass index (kg/m^2)	30.24 (25.86 - 33.30)	30.06 (24.75 - 32.03)	0.101
Smoking status			
Smoker	8 (10.67%)	-	-
Non-smoker	62 (82.67%)	-	
Ex-smoker	5 (6.67%)	-	
Hemoglobin (g/dL)	13.26 (1.70)	13.54 (1.76)	0.300
Neutrophil (x10^3)	4.76 (3.76 - 5.89)	4.88 (3.67 - 5.98)	0.595
Lymphocyte (x10^3)	1.82 (1.34 - 2.54)	2.11 (1.72 - 2.59)	**0.035**
Monocyte (x10^3)	0.59 (0.44 - 0.70)	0.57 (0.43 - 0.69)	0.991
Platelet (x10^3)	268 (226 - 334)	252 (219 - 293)	0.177
Procalcitonin (ng/mL)	0.27 (0.24 - 0.33)	0.25 (0.23 - 0.31)	0.139
Mean platelet volume (fl)	10.3 (9.7 - 10.8)	10.1 (9.4 - 10.9)	0.897
Red cells distribution width (%)	14.0 (13.1 - 15.1)	13.2 (12.8 - 14.1)	**0.007**
Neutrophil-to-lymphocyte ratio	2.43 (1.74 - 3.41)	2.53 (1.69 - 3.37)	0.509
Monocyte-to-lymphocyte ratio	0.30 (0.22 - 0.40)	0.28 (0.19 - 0.39)	0.245
Platelet-to-lymphocyte ratio	142.79 (104.64 - 202.21)	131.61 (106.12 - 155.92)	**0.028**
Systemic immune-inflammation index (x10^3)	626.24 (443.60 - 1076.04)	582.65 (430.00 - 826.86)	0.201
Pan-immune-inflammation value (x10^6)	350.43 (229.07 - 677.91)	339.70 (197.33 - 531.25)	0.204
Erythrocyte sedimentation rate (mm/h)	24 (11 - 38)	12.5 (7 - 20)	**<0.001**
C-reactive protein (mg/L)	0.7 (0.3 - 3.55)	0.7 (0.3 - 2.4)	0.594
Calcium (mg/dL)	9.40 (9.06 - 9.67)	9.32 (8.97 - 9.63)	0.342
Stage			
Stage 1	15 (20.00%)	-	-
Stage 2	32 (42.67%)	-	
Stage 3	21 (28.00%)	-	
Stage 4	7 (9.33%)	-	
Erythema nodosum	16 (21.33%)	-	-
Uveitis	16 (21.33%)	-	-
Neurosarcoidosis	5 (6.67%)	-	-
Ankle arthritis	25 (33.33%)	-	-
Arthritis in another site from ankle	16 (21.33%)	-	-
Arthralgia	50 (66.67%)	-	-
Dactylitis	3 (4.00%)	-	-
Enthesitis	12 (16.00%)	-	-
Inflammatory waist pain	18 (24.00%)	-	-
Myositis	3 (4.00%)	-	-

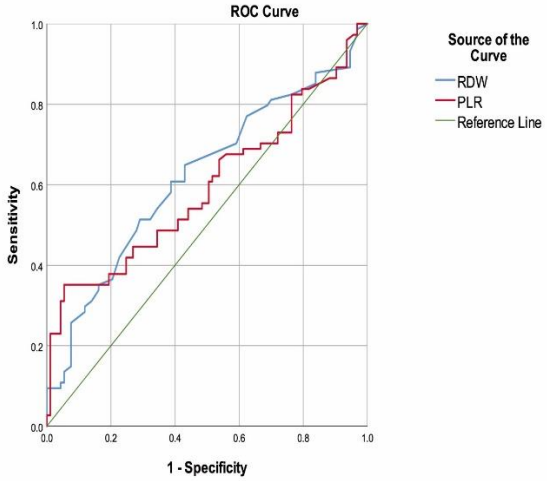
Data are given as mean (standard deviation) or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

Table 2: Performance of RDW and PLR to discriminate patients with sarcoidosis and healthy controls

	RDW	PLR
Cut-off	≥14	≥171
Sensitivity	51.35%	36.00%
Specificity	70.97%	94.62%
Accuracy	62.28%	68.45%
PPV	58.46%	84.38%
NPV	64.71%	64.71%
AUC (95.0% CI)	0.621 (0.533 - 0.708)	0.599 (0.509 - 0.688)
***P*-value**	**0.007**	**0.028**

AUC: Area under ROC curve, CI: Confidence intervals, NPV: Negative predictive value, PLR: Platelet-to-lymphocyte ratio, PPV: Positive predictive value, RDW: Red cell distribution width

Figure 1: ROC curve of the RDW and PLR to discriminate patients with sarcoidosis and healthy controls



PLR: Platelet-to-lymphocyte ratio, RDW: Red cell distribution width, ROC: Receiver Operating Characteristic

Table 3: Correlation between SII, PIV, other hematologic parameters and clinical findings in patients with sarcoidosis

		PCT	MPV	RDW	NLR	MLR	PLR	SII	PIV
Smoking status, Smoker	r	-0.169	0.169	0.022	**0.227**	0.166	0.042	0.132	0.136
	P	0.150	0.150	0.850	**0.049**	0.156	0.721	0.260	0.246
Erythrocyte sedimentation rate	r	**0.328**	-0.082	**0.574**	**0.273**	**0.299**	**0.305**	**0.403**	**0.439**
	P	**0.006**	0.499	**<0.001**	**0.021**	**0.011**	**0.010**	**<0.001**	**<0.001**
CRP	r	0.158	-0.074	**0.264**	**0.393**	**0.319**	**0.335**	**0.483**	**0.477**
	P	0.187	0.540	**0.025**	**0.001**	**0.006**	**0.004**	**<0.001**	**<0.001**
Calcium	r	0.127	-0.139	-0.011	-0.205	-0.193	-0.098	-0.126	-0.108
	P	0.287	0.244	0.924	0.082	0.103	0.407	0.286	0.363
Stage	r	0.168	0.141	0.129	0.144	0.196	-0.067	0.140	**0.294**
	P	0.153	0.230	0.273	0.218	0.092	0.567	0.231	**0.010**
Erythema nodosum	r	-0.077	**0.308**	-0.041	**-0.319**	**-0.280**	-0.186	**-0.293**	**-0.280**
	P	0.515	**0.008**	0.730	**0.005**	**0.015**	0.109	**0.011**	**0.015**
Uveitis	r	**-0.277**	-0.065	-0.218	0.006	-0.114	-0.099	-0.170	**-0.257**
	P	**0.017**	0.584	0.063	0.959	0.329	0.397	0.145	**0.026**
Neurosarcoidosis	r	0.026	-0.117	-0.069	0.089	0.027	0.040	0.148	0.141
	P	0.823	0.319	0.557	0.448	0.817	0.736	0.205	0.228
Ankle arthritis	r	-0.092	-0.086	0.062	-0.052	0.008	0.064	-0.064	-0.131
	P	0.434	0.464	0.598	0.656	0.947	0.585	0.585	0.264
Other arthritis	r	0.043	0.059	0.093	-0.048	-0.090	0.053	0.015	-0.045
	P	0.715	0.620	0.431	0.682	0.442	0.654	0.898	0.701
Arthralgia	r	-0.062	-0.059	0.135	0.149	0.140	0.144	0.106	0.037
	P	0.602	0.618	0.251	0.202	0.232	0.219	0.366	0.755
Dactylitis	r	0.061	-0.010	-0.181	**-0.255**	-0.211	**-0.251**	-0.167	-0.069
	P	0.606	0.935	0.122	**0.028**	0.070	**0.030**	0.153	0.556
Enthesitis	r	0.027	0.013	-0.009	-0.190	-0.190	-0.101	-0.111	-0.163
	P	0.822	0.913	0.936	0.103	0.103	0.390	0.344	0.162
Inflammatory waist pain	r	0.037	-0.006	0.078	-0.085	-0.042	0.036	-0.035	-0.059
	P	0.755	0.960	0.508	0.468	0.722	0.759	0.768	0.614
Myositis	r	0.108	0.074	0.011	**-0.248**	-0.226	-0.176	-0.151	-0.132
	P	0.362	0.531	0.924	**0.032**	0.051	0.131	0.196	0.259

CRP: C-reactive protein, MLR: Monocyte-to-lymphocyte ratio, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, PCT: Procalcitonin, PIV: Pan-immune-inflammation value, PLR: Platelet-to-lymphocyte ratio, r: Spearman correlation coefficient, RDW: Red cell distribution width, SII: Systemic immune-inflammation index

Discussion

To diagnose sarcoidosis, it is necessary to confirm the presence of granulomas in the lung or other tissues using invasive techniques such as biopsy or bronchoalveolar lavage. Once granulomas are detected, it is also crucial to exclude other diseases that share similar clinical or histopathological features to establish a diagnosis [13]. However, despite such meticulous efforts, the diagnosis can only be described as "near-conclusive" [6]. These challenges in sarcoidosis diagnosis (and ultimately management) could potentially be resolved by incorporating specific biomarkers into clinical practice for both diagnostic and prognostic purposes. Unfortunately, universally accepted biomarkers are not yet available to help diagnose or evaluate sarcoidosis [11].

In this study, we investigated the relationship of various biomarkers, including PIV and SII, with the diagnosis and clinical features of sarcoidosis. We found that patients with sarcoidosis had a lower absolute lymphocyte count, and higher RDW, ESR, and PLR than the control group. A significant weak positive correlation was found between PIV and disease stage, as well as between MPV and the presence of erythema nodosum. We also identified other correlations between sarcoidosis-related features and the examined parameters, but they were too weak to be notable.

It is increasingly evident that specific inflammatory pathways play a crucial role in the progression and outcomes of various diseases [33–35]. Immune system overactivation is believed to be a key factor in the pathogenesis of sarcoidosis. As the role of inflammation in pathogenesis becomes clearer, identifying potential biomarkers for managing sarcoidosis becomes even more important [10]. Numerous serum, bronchoalveolar lavage fluid, and radiological parameters have been studied as diagnostic and prognostic markers in sarcoidosis. However, Kraaijvanger et al. [4] reported a common limitation of these serum biomarkers, namely their low sensitivity and specificity for diagnosis. In our study, we observed that SII and PIV had no diagnostic role in sarcoidosis. Patients with sarcoidosis exhibited lower lymphocyte levels and significantly higher RDW, ESR, and PLR levels than healthy individuals. However, RDW and PLR performed poorly in distinguishing between patients with sarcoidosis and controls. Some studies have reported a higher incidence of leukopenia and lymphopenia in patients with sarcoidosis [36,37]. Additionally, other studies have demonstrated significantly higher levels of RDW [38,39], PLR [40,41], NLR [12,42], MPV [24,42], CRP [13,43] and ESR [43] in patients with sarcoidosis compared to healthy subjects. A review published in 2019 identified soluble interleukin-2 receptors, CRP, serum amyloid A, and chitotriosidase as the most effective markers for confirming sarcoidosis (highest sensitivity), while angiotensin-converting enzyme (ACE), gammaglobulins, and lysozyme exhibited the highest specificity values for ruling out sarcoidosis [13].

Kobak et al. [9] proposed that adipokines might play a significant role in granuloma formation in sarcoidosis by stimulating the Th1 response and activating various inflammatory cells. In their study, they investigated serum adipokines and their potential associations with disease activity or clinical phenotype in patients with sarcoidosis. They found that serum adiponectin levels, an anti-inflammatory protein, were higher in patients with sarcoidosis than healthy subjects, while serum leptin levels were similar to controls. The authors emphasized the potential role of adiponectin in the benign nature, self-limitation, and certain clinical features of sarcoidosis. Although sarcoidosis is generally benign and self-limiting, with spontaneous remission occurring at times, approximately one-third of patients develop chronic inflammation, pulmonary fibrosis, or irreversible damage to other organs [4,12,44]. Therefore, a comprehensive understanding of the pathogenesis of sarcoidosis and the role of immune responses is crucial [10]. Clarifying the relationship between the immune system and the pathogenesis of sarcoidosis would not only contribute significantly to diagnosing sarcoidosis and predicting prognosis but also aid in the development of new treatment strategies. Despite significant changes reported in the levels of several biomarkers in patients with sarcoidosis compared to healthy subjects, a specific marker exclusive to sarcoidosis has yet to be identified. Our data on SII and PIV also yielded similar results, suggesting that these indexes do not have a diagnostic role. Nevertheless, further comprehensive studies are needed to support the results of this study.

The formation of granulomas in the affected organs of patients with sarcoidosis is considered a significant complication. Typically, granulomas are localized in the lungs, mediastinal and peripheral lymph nodes, skin, eyes, and liver, while vital organs such as the heart and central nervous system are rarely affected [44]. The etiopathogenesis of granulomas remains unknown [10]. Due to the variable manifestations of sarcoidosis, our current understanding does not allow for predicting the extent, progression, and response to therapy in patients [4,11].

In our study, we observed a weak positive correlation between PIV and the lung stage of sarcoidosis, as well as between MPV and erythema nodosum. Several studies in patients with sarcoidosis have reported significant associations between lymphopenia and severe visceral involvement [45], extrathoracic disease [46], higher disease activity [47], worse prognosis [36,37], more severe disease [37], sarcoid uveitis [37], and sarcoid myelitis [48]. One study found a correlation between serum adiponectin levels and arthralgia and ankle swelling [9]. Another study showed a higher frequency of high NLR in patients with extrapulmonary involvement [42]. Bekir et al. [25] demonstrated that lymphocyte count was significantly lower in the chronic group upon admission, while NLR was significantly higher in the chronic group compared to the remitting sarcoidosis group, suggesting a possible association between lymphocyte count, NLR levels, and prognosis. A review reported that tumor necrosis factor alpha and chemokine ligand 18 might help identify patients at high risk of developing pulmonary fibrosis or progressive disease [13]. In a different study, an NLR level greater than 35 was associated with pulmonary hypertension in patients with sarcoidosis [49]. Karataş et al. [38] found that stage II patients had significantly higher RDW compared to those with stage I disease, suggesting that serial RDW levels might be useful in predicting disease progression [50]. While serum ACE levels have been found to be elevated in 30–80% of sarcoidosis patients, their sensitivity for diagnosis ranges from 22% to 86%, and their specificity ranges from 54% to 95% [13]. Despite this

poor predictive performance, another study reported that elevated serum ACE levels before treatment were significantly associated with improved lung function after 6 months of methotrexate treatment [51]. Despite the wealth of research on prognostic markers, there is a lack of high-performance predictors associated with the severity, stage, extent, treatment response, and prognosis of sarcoidosis. Further studies are necessary to identify inflammatory markers that can be utilized in patients with sarcoidosis, even if they can only be applied to select patients.

Limitations

This study represents the first investigation into the relationship between SII and PIV and the diagnosis, severity, and extent of sarcoidosis. However, it is important to consider several limitations when interpreting the findings. First, the study had a retrospective, single-center design and a relatively small sample size, which can be attributed to the rarity of the disease. Consequently, it is challenging to generalize the results to broader populations. Additionally, the study only assessed patient parameters at the time of diagnosis without evaluating longitudinal changes in these variables. As a result, the study did not explore the association between these parameters and treatment response, prognosis, or mortality, nor did it provide information on follow-up times and disease duration. While efforts were made to exclude potential influencing factors, some patient data may have been omitted or not recorded, introducing potential bias. Nonetheless, this limitation applies to all studies examining these inflammatory parameters, and our exclusion of recent infections and comorbidities would have minimized the number of confounding variables. Finally, the study did not consider recent medication information; however, given the exclusion criteria, this particular limitation is likely to have had a minimal impact on the results.

Conclusions

In summary, the study findings indicated that PIV and SII values in patients with sarcoidosis did not significantly differ from those of healthy individuals. Only a weak positive correlation was observed between PIV and lung stage, as well as between MPV and erythema nodosum. The study also revealed that low lymphocyte counts and high RDW, PLR, and ESR were associated with sarcoidosis diagnosis. Although the predictive performance of these parameters was limited, they are readily available and cost-effective, suggesting potential value for clinicians in terms of diagnosis, prognosis, or management. Further comprehensive studies are necessary to better understand the roles of SII, PIV, and other markers in sarcoidosis diagnosis and determination of its extent.

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Case report

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Radiological approach to multinodular and vacuolating neuronal tumor: Two case report

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Abstract

Multinodular and vacuolating neuronal tumors (MVNT) are indolent, low-grade, superficial neuronal tumors of the cerebrum that consist only of neuronal cells in adults. They were first reported in 2013 by Huse et al. and defined by the World Health Organization in 2016. MVNT is characterized by vacuolated tumor nodules with glial and/or neuronal differentiation histopathologically. MVNT is most commonly located in the temporal lobe. Radiologically, it has a subcortical, soap-bubble morphology, sometimes extending to the cortex, and is almost as hyperintense as cerebrospinal fluid on T2-weighted images. Its signal is not suppressed on the FLAIR sequence, and there is no diffusion restriction on diffusion-weighted images. Usually, there is no enhancement after gadolinium injections, but a few reports show weak enhancement in the literature. In the first case, we present a 22-year-old female with MVNT who underwent MRI for a complaint of dizziness which was detected incidentally. MRI showed a clustered multinodular lesion in the left superior frontal gyrus that was hyperintense on T2-weighted/FLAIR series and isointense with gray matter on T1-weighted images. There was no diffusion restriction or contrast enhancement on MRI. In the second case, a 51-year-old female with complaints of numbness and pain in her left arm had an MRI that showed a lesion in the right cerebral hemisphere at the temporoparietal junction. The lesion did not cause edema or mass effect and was distributed in the cortical-subcortical area. The lesion was hyperintense in T2-weighted and FLAIR series and consisted of many millimetric nodular components in close intensity with gray matter in the T1-weighted series. No contrast enhancement was detected. Knowing the characteristic imaging findings of MVNT is important in avoiding aggressive diagnosis and treatment approaches in asymptomatic cases. In conclusion, MVNT is a newly identified tumor that appears hyperintense on the FLAIR sequence and should not be operated on.

Keywords: magnetic resonance imaging, multinodular, neuronal, tumor, vacuolating

Introduction

A multinodular and vacuolating neuronal tumor (MVNT) is a low-grade cerebral neuronal tumor defined as a "unique cytoarchitectural pattern of gangliocytoma" with an "uncertain class assignment" according to the 2016 World Health Organization (WHO) classification of central nervous system tumors [1-4]. It is unclear whether MVNT is a dysplastic or neoplastic cerebral lesion [2,3]. A cluster of nodular lesions is located within the superficial subcortical white matter and deep cortical ribbon [1,2]. MVNT can be unifocal, multifocal, bilateral or diffuse [5], asymptomatic, and detected incidentally. Sometimes, epileptic seizures can occur as symptoms. MVNT is typically stable with or without excision on follow-up, and recurrence is rare, even following incomplete resection [4,6-8]. It has been referred to as a "don't touch lesion" and "leave me alone lesion" by Nunes et al. [2] and De Wandeler et al. [9], respectively.

The diagnosis of MVNT is based on magnetic resonance imaging (MRI). Computed tomography (CT) may not detect small lesions. However, it can be seen as low-attenuation, non-calcified and non-enhanced lesions in subcortical white matter on CT [10]. MRI provides a more detailed examination than CT. On MRI, MVNT appears as a multinodular clustered lesion that hyperintense on T2-weighted images/fluid-attenuated inversion recovery (FLAIR) and iso-

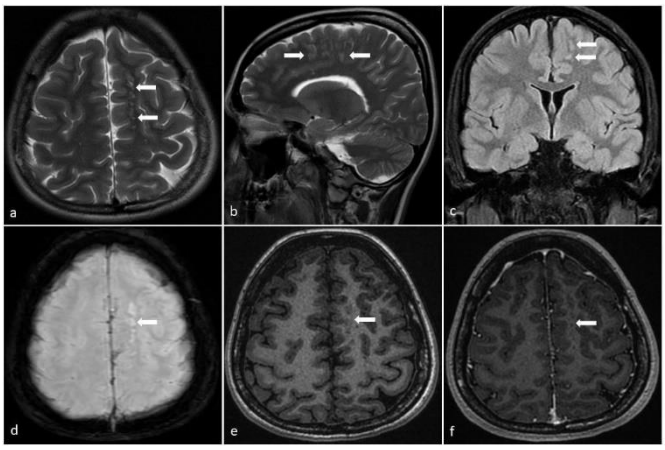
hypointense on T1-weighted images in the subcortical white matter without peripheral edema. There is usually no enhancement after gadolinium injections, but a few reports show weak enhancement in the literature [1,6]. MVNTs lacked IDH mutations (like infiltrating gliomas), and BRAF mutations (like ganglion cell tumors) in all cases reported [6-8]. MEK1 mutation has been reported in only one MVNT case [1,5]. HuC/HuD neuronal antigens were detected in tumor cells by nuclear immunolabeling in all cases [6]. We present our experience in two cases below.

Case presentation

Patient 1

The first case involved a 22-year-old female patient who underwent a 1.5T contrast-enhanced brain MRI due to dizziness that had been ongoing for three months. The MRI revealed a lesion approximately 4×3×1 cm in size, consisting of millimetric nodular components that did not cause edema or mass effect in the left superior frontal gyrus and distributed in the subcortical area. The multinodular clustering lesion was hyperintense on T2-weighted (Figure 1a, b)/ FLAIR (Figure 1c) and eSWAN (Figure 1d) series, similar to the intensity of gray matter on T1-weighted (Figure 1e) series, and did not enhance (Figure 1f) after gadolinium injections. The lesion did not have diffusion restriction on diffusion-weighted images. The lesion's appearance and stability in the follow-up MRI examination performed 16 months later support the diagnosis of MVNT. The patient was excluded from our follow-up after the last control MRI examination. Because the MR images used in the study did not contain any identifying information about the patient and because of the study's retrospective nature, informed consent was not obtained from the patients.

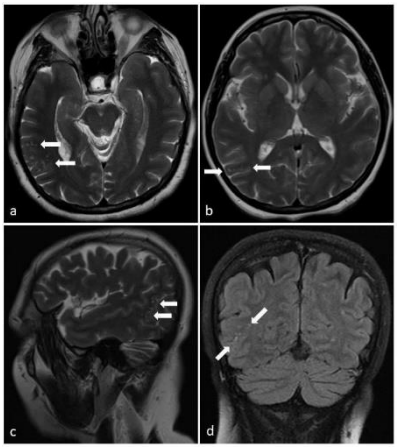
Figure 1: MR images of a 22-year-old female patient with dizziness. (a) Axial T2-weighted, (b) sagittal T2-weighted, (c) coronal FLAIR, and (d) eSWAN images shows hyperintense lesion; (e) axial T1-weighted images show the same intensity with grey matter, (f) and images taken after gadolinium injection show non-enhanced clustering multinodular lesion located in subcortical area of the left superior frontal gyrus.



Patient 2

In the second case, a 51-year-old female patient underwent a 1.5T contrast-enhanced brain MRI due to complaints of numbness and pain in her left arm. The MRI revealed a mass lesion consistent with an extra-axially located meningioma in the right frontal region. Incidentally, multinodular millimetric lesions distributed approximately 3.5×2×1.5 cm in the cortical-subcortical area were noted in the right cerebral hemisphere at the temporoparietal junction on MRI examination. The lesions did not cause edema or mass effect. The lesion was hyperintense on the T2-weighted (Figure 2a-c) and FLAIR (Figure 2d) series, isointense with the grey matter on the T1-weighted series, and did not enhance after contrast administration. The appearance of the lesion was compatible with MVNT based on the previous MRI examination. There was no difference in the appearance of the MVNT lesion in the first-year follow-up MRI examination of the patient who underwent surgery for meningioma. Informed consent was not obtained from the patients because the MR images used in the study did not contain any identifying information about the patient and because of the study's retrospective nature.

Figure 2: MR images of a 51-year-old female patient with complaints of numbness and pain in her left arm (a) and (b) axial T2-weighted, (c) sagittal T2-weighted, (d) coronal FLAIR images show a hyperintense multinodular lesion (arrows) located in subcortical area of the right temporoparietal area.



Discussion

MVNT typically occurs in the temporal lobe of elderly patients with seizures and has no common mutations [4]. It is usually discovered incidentally through MRI. The exact prevalence of MVNT may be unknown, as most lesions are not removed in asymptomatic individuals [2]. There have been a few "out of the ordinary" lesions; however, MTVN is defined in the literature as a non-enhanced, non-progressive cerebral lesion. Agarwal et al. [11] reported three cerebellar lesions. Huse et al. [6] reported 20% (2 out of 10 patients), and Alsufuyan et al. [5] reported 11% (2 out of 24 patients) contrast-enhancement lesions. Additionally, Alsufayan et al. [5] reported progression in 6.7% of lesions monitored by MRI, which goes against the literature.

Although the most common clinical presentation was seizure episodes, Nunes et al. [2] observed seizures in only 19% of patients in their study. In the study by Alsufayan et al. [5], which involved 24 patients, 50% had a headache, 25% had visual symptoms, 20-25% had seizures, 17% had paresthesia, and 17% had cognitive difficulties. Gökçe [1] also reported that one of the patients had epilepsy and the other had a headache in his study of two cases. In Huse et al.'s [6] study, 70% of the lesions were found in the temporal lobe, whereas in Alsufayan et al.'s study [5], 50% of the lesions were found in the frontal lobe, 23% in the parietal lobe, 10% in the occipital lobe, 6% in the temporal lobe, and 6% in the frontotemporal lobes. Our cases were located in the frontal and temporoparietal areas.

It is unclear whether MVNTs are dysplastic or neoplastic. Histologically, MVNTs consist of multinodular tissue with a vacuolated stroma populated by the irregular proliferation of neuronal cells of uncertain phenotype containing ganglion-like cells [7]. Secondary features, such as perivascular lymphocytic infiltrate, Rosenthal fibers, eosinophilic granular bodies, and

microcalcifications commonly found in ganglion cell tumors, are entirely absent in MVNTs [12]. On the other hand, they have shown negativity or mild positivity for neuronal markers such as neurofilament proteins, neuronal nuclear antigen, and synaptophysin, which are related to mature neurons [1,6-8,10].

Thom et al. [4] also found that these lesions were more similar to dysplastic lesions than to true neoplasms in their study. MVNTs have some overlapping imaging findings with dysembryoplastic neuroepithelial tumors (DNETs), malformations of cortical development such as focal cortical dysplasia (FCD), and enlarged Virchow-Robin perivascular spaces (VRPVS). All of these should be considered in the differential diagnosis of MVNTs [1,2,10].

Dysembryoplastic neuroepithelial tumor (DNET) should be the first tumor to consider in the differential diagnosis of MVNT based on radiologic examinations [1]. Some studies have reported that at least 3 out of 12 MVNT cases were diagnosed with DNET radiologically [6,8]. DNET is a cortical, well-demarcated, wedge-shaped, lobulated contour lesion with low-isointense and a bright frame on T2/FLAIR images on MRI [1,5,7,13]. Calcification and hemosiderin staining can be seen on CT images in DNET, unlike MVNT. The absence of cortical involvement and predominance of deep white matter help distinguish MVNT from DNET [5]. However, histological analyses can differentiate between MVNTs and DNETs. MVNTs lack the "specific glioneuronal element" that is a signature finding in classic DNETs. Moreover, the combination of prominent vacuolation, lesion cells of indeterminate lineage, and multinodular coarse stroma that characterizes MVNTs is not seen in DNET [7,13]. Malformations of cortical development (MCD), such as nodular heterotopia or FCD type 2, may also be confused with MVNT [5,7]. Nodular heterotopia is characterized by the presence of mature gray matter in the white matter. Unlike MVNT, there are NeuN-positive mature neurons in nodular heterotopia [7,14]. FCD type 2 has a high T2 signal in the deep cortex, similar to MVNT. It is usually associated with a radial glial band (transmantle sign) extending towards the ventricle and having abnormal cortical thickness. MVNT can also resemble FCD when they extend towards the ventricle. However, MVNT shows a bubble-like extension rather than a band-like one [5]. Virchow-Robin perivascular spaces (VRPVS) may also have similar imaging features to MVNT. Although VRPVS may have the same location as MVNT, they are generally longer along the long axis of the vessel [2,5]. In some cases, a few cystic changes may be present in VRPVS, which may be confusing [5]. However, MVNT is typically seen as cerebrospinal fluid-like a signal on all series on MRI, while MVNTs are bright on FLAIR [2,5].

The major limitation of this case is the lack of pathological evidence, and it is based only on MRI. Fortunately, the MRI findings are almost pathognomonic [3]. In this case, the characteristic MRI findings of the lesion, such as the absence of structural or size changes on follow-up examinations, support that it is MVNT.

Conclusion

MVNT is a newly defined entity often detected incidentally on MRI and is considered a "don't touch me lesion" with current knowledge. Understanding the characteristic imaging findings of MVNT is crucial to avoid aggressive diagnostic and treatment approaches in asymptomatic case.

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Case report

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A case of necrotizing fasciitis developing after cesarean section

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Abstract

Necrotizing fasciitis (NF) is a rare condition that is observed in obstetric and gynecological practices. It is a rapidly progressive and often fatal complication. Failure to obtain an early diagnosis and delay in initiating appropriate treatment can lead to significant morbidity and mortality. Our case was 25 years old, and she was in her first pregnancy. The patient had no systemic disease or history of previous surgery. Our patient's baby was delivered by cesarean section with an indication of emergency fetal distress. During the cesarean section, it was observed that the amniotic fluid contained very dark meconium. No complications occurred during the cesarean section. Our patient presented with complaints of severe pain, bullae, and hyperemia at the level of the incision line one week later. In her vital findings, fever was 39.3 ºC, blood pressure was 90/60 mmHg, and heart rate was 110 /min. In laboratory tests, white blood cell count was 25,280 /mm^3, C-reactive protein (CRP) was 431 mg/dL, and sedimentation was 100 mm/hour. On the ultrasonographic examination, air, significant edema, and thickening were observed in the incision line, skin, and subcutaneous tissues. On the computed tomography scan, thickening of the skin and subcutaneous tissues, fluid locations, and areas of air densities were observed over a wide area extending to the level of the thoracic 10th and 11th vertebrae superiorly and to the mons pubis inferiorly. Based on these findings, the patient was diagnosed with NF. After broad-spectrum antibiotic therapy and fluid-electrolyte support, extensive surgical debridement was performed under emergency conditions. Before applying the skin graft, vacuum-assisted wound closure was performed, and a very good response was obtained. The patient, whose pathology result was compatible with necrotizing fasciitis, was discharged on the 20th post-operative day. In this case, we aimed to present a case of NF after cesarean section.

Keywords: cesarean section, necrotizing fasciitis, wound infection, CRP

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

Conflict of Interest
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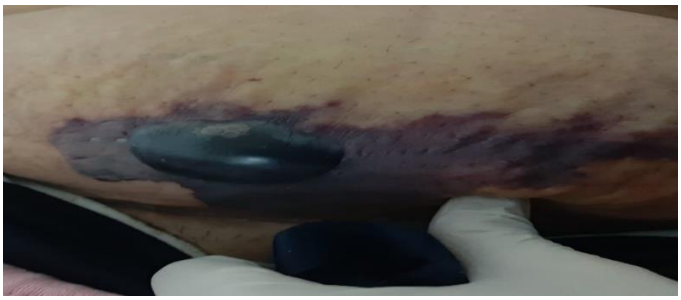
Introduction

Necrotizing fasciitis (NF) is a severe, life-threatening infection characterized by aggressive necrosis of the skin, subcutaneous tissues, and fascia. The main factors that reveal the course of the disease are the age of the patient, the extent of the infection area, the time of the first debridement, concomitant systemic diseases, including malnutrition, and the type of causative pathogen. The most common reason for delayed diagnosis in necrotizing fasciitis is the inconsistency between clinical findings, such as severe pain and tenderness, and the physical appearance of both the lesion and the patient [1]. Rapidly progressive necrosis in tissues often causes systemic sepsis, toxic shock syndrome, and multi-organ failure [2]. Therefore, early diagnosis and treatment of NF are very important. Informed consent was obtained from the patient before the study.

Case presentation

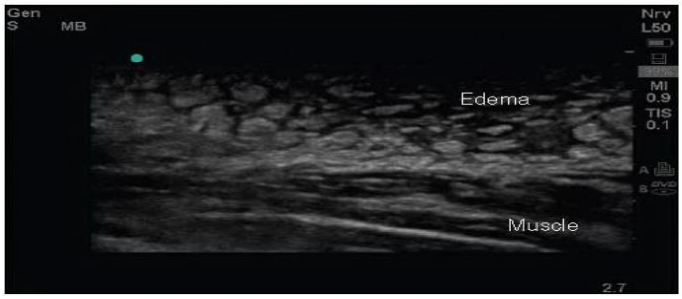
Our case was 25 years old and in her first pregnancy. The patient had no systemic disease and previous surgery history. Her body mass index (BMI) was 33, indicating she was obese. Our case presented to the delivery room of our hospital in labor at 42 weeks of gestation. Our patient, who was in active labor with a 4 cm opening, 60%–70% effacement, and active amniotic fluid discharge, was admitted to the delivery room for follow-up and treatment. An emergency cesarean section was performed because the patient had late decelerations based on the non-stress test (NST) follow-up, and the amniotic fluid contained dark meconium. No complications occurred during the cesarean section. The patient was discharged uneventfully at 48 h after the cesarean section. Low molecular weight heparin (LMWH) was started in the obese patient for venous thromboembolism prophylaxis. One week after discharge, the patient presented with the complaint of severe pain, bullae, and hyperemia at the incision line (Figure 1).

Figure 1: Wound image



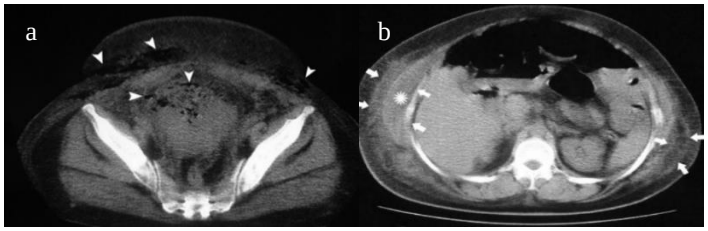
In her vital findings, temperature was 39.3 ºC, blood pressure was 90/60 mmHg, and heart rate was 110/min. In laboratory tests, the white blood cell was 25,280/mm^3, C-reactive protein (CRP) was 431 mg/dL, and sedimentation was 100 mm/hour. On the ultrasonographic examination, air, significant edema and thickening were observed in the incision line, skin, and subcutaneous tissues (Figure 2). Abdominal contrast-enhanced tomography (CT) was performed on the patient since the abdominal organs due to edema could not be seen clearly on the ultrasonography image

Figure 2: Ultrasound Image



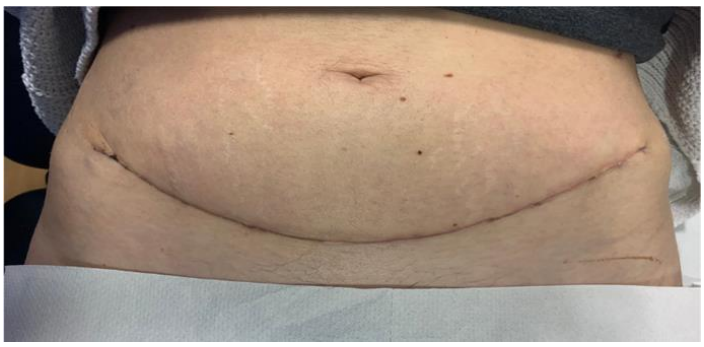
On the abdominal contrast-enhanced tomography (CT) scan, thickening, fluid loculations, and areas of air densities were observed in the skin and subcutaneous tissues in a large area extending to the level of the thoracic 10th and 11th vertebrae superiorly and to the mons pubis inferiorly (Figure 3a). On the computed tomography scan, air values (arrowheads) under the skin at the level of the incision line in the pelvic area and (Figure 3b) thickening (arrows) in the skin-subcutaneous tissues at the thoracic level, fluid loculations (stars) can be observed.

Figure 3: Pre-operative computed tomography (CT) image of the patient.



Based on these findings, the patient was prediagnosed with NF, and broad-spectrum ampicillin/sulbactam 4 x 1 g IV, gentamicin loading (2 mg/kg), maintenance (1.5 mg/kg), and clindamycin 3 x 900 mg intravenous (IV) antibiotic treatment were started. Extensive surgical debridement was performed under emergency conditions. The abdomen was not entered. A sample was taken for a culture antibiogram. Vacuum-assisted wound closure was performed after debridement. The VAC system (Kinetic Concept Ing. USA) was used as the vacuum-assisted system. Vacuum-assisted dressing was continued for one week. Vancomycin treatment was started in the patient who had *Enterococcus* sp. growth based on the culture antibiogram. CRP values showed a dramatic decrease at the follow-up visit. Fever and leukocytosis regressed. Open wound dressings were applied to the patient for 10 days, and she had a good response to vacuum-assisted dressing. Secondary suturing combined with a cutaneous flap shift operation was performed on the patient, who did not have any infected tissue at the wound site. A drain was placed under the skin as a precaution. The pathology result was consistent with NF. The patient was discharged on the 20th post-operative day after the subcutaneous drain was removed. No problems were encountered in the outpatient clinic visits by the patient.

Figure 4: Post-operative wound location



Discussion

Cesarean section is the most common operation in clinical gynecology practice. The frequency of NF after undergoing a cesarean section procedure is reported as 1.8/1000 in the literature [2]. The mortality and morbidity of infections of the subcutaneous soft tissues with a necrotizing course is quite high. Reported mortality rates range from 30% to 70%. It frequently leads to mortality due to multiorgan failure, respiratory failure, renal failure, and sepsis. NF is more common in elderly and immunocompromised patients. In addition, chronic diseases, IV drug use, varicella zoster, malnutrition, obesity, cancer, human immunodeficiency virus (HIV), and long-term use of nonsteroidal anti-inflammatory and immunosuppressive drugs are also counted among the predisposing factors [2]. NF initially begins as a localized infection, and later, it rapidly spreads along the fascial planes due to various factors and becomes gangrene. These risk factors include a disease affecting the immune system, old age,

diabetes, obesity, debility, alcohol/substance abuse, liver and kidney diseases, trauma, and/or surgery. Although the disease is common in people with risk factors, it can also occur in healthy people [3–5]. In our case, however, risks related to previous cesarean section and obesity were present. Early diagnosis and urgent extensive surgical debridement are very important in the treatment. Pain, erysipelas, and excessive edema are observed in the early stages of infection. The mild severity of the focal findings at first may lead to errors in the differential diagnosis. In this period, it is very important to diagnose and perform early surgical intervention. A delay in surgical treatment causes an increase in the mortality rate. Early debridement of necrotic subcutaneous tissue and fascia and leaving wounds open and providing drainage are life-saving. In addition, an effective antibiotic therapy is also important for causing a reduction in the risk of death [6,7]. Early diagnosis was made in our case, and emergency debridement was undertaken. In addition, the patient was immediately started on broad-spectrum antibiotics. Antibiotherapy was adjusted according to the culture results. Vacuum-assisted dressings were performed. In addition, the healing progress was followed very closely with open wound dressings. Diagnosis of NF is mostly based on clinical findings. The most defining clinical finding for NF is severe pain-tenderness, which is incompatible with the physical appearance of the lesion. Pain may precede infection. In the following days, edema, redness, and an increase in temperature are observed in the infected area. In untreated cases, thin-walled hemorrhagic bullae occur in this area within 3 to-5 days [8]. Although NF can be seen in any part of the body, the areas in which it is frequently observed are the extremities, abdominal wall, and perineum. In NF cases, the rate of spread of the infection can reach up to 2.5 cm/hour with minimal changes in the skin over it [1]. Radiological imaging has a very important role in the diagnosis of NF, which spreads rapidly and progresses with high mortality. In these cases, since the treatment involves emergency surgical debridement, imaging procedures should not delay surgical intervention and should provide a rapid and accurate diagnosis. In our case, an abdominal CT with contrast was performed because the abdominal organs due to edema could not be seen clearly with ultrasonography. Based on the CT, thickening of the skin and subcutaneous tissues in a wide area extending to the level of the thoracic 10^{th} and 11^{th} vertebrae superiorly and to the mons pubis inferiorly, fluid locations, and areas of air densities led us to a definite diagnosis. Also, emergency debridement prevented aggressive progression of the infection.

Conclusion

Early diagnosis and extensive surgical debridement of NF is the most effective treatment method for stopping the rapidly progressing infectious process. This treatment should be combined with intensive antibiotic therapy and other measures in cases with systemic clinical findings. Vacuum-assisted dressing accelerates wound healing and is a good treatment option for preparing the wound for surgery.

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