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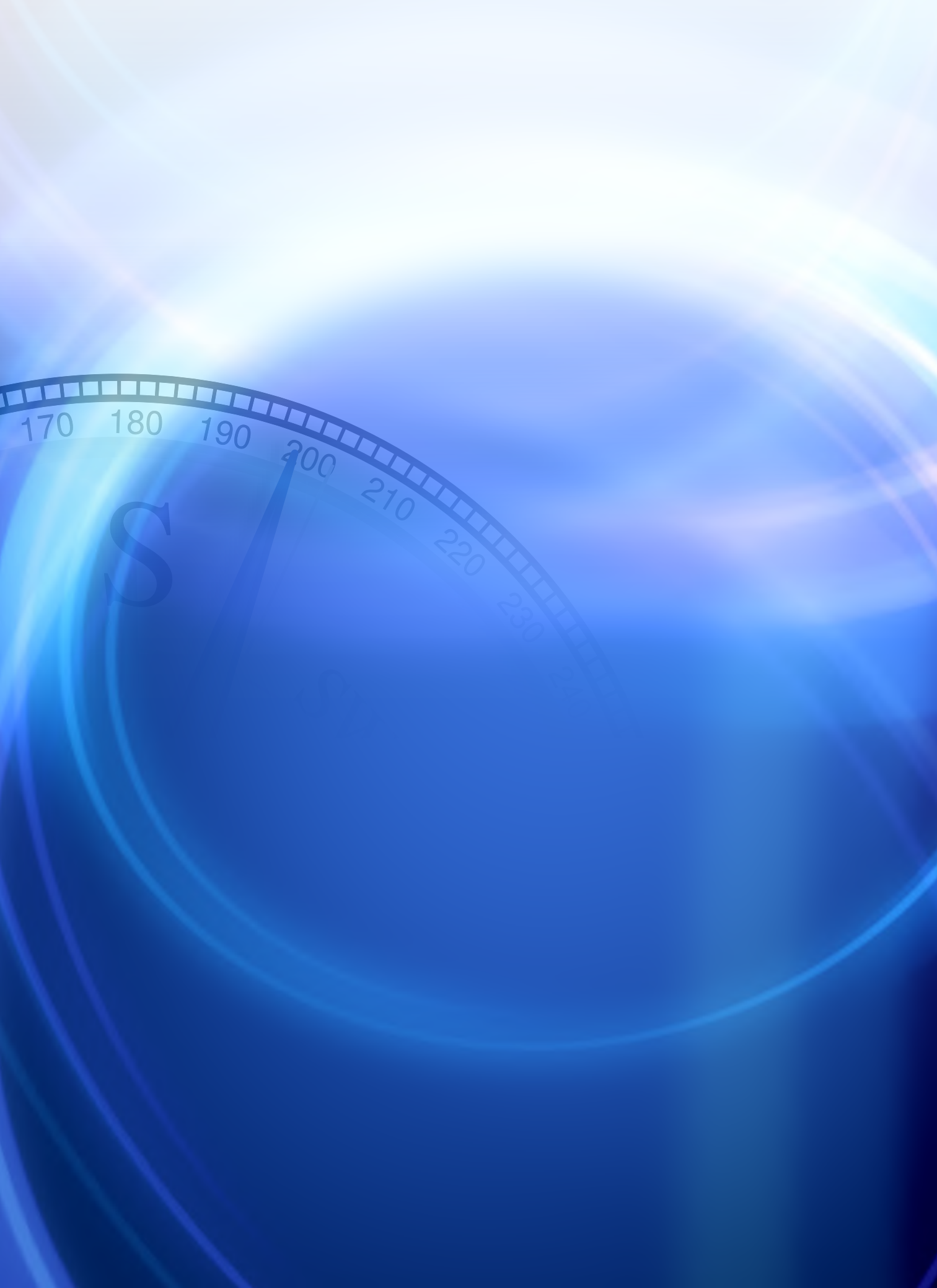
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EXPERIMENTAL STUDY

ORIGINAL ARTICLES

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Experimental Study

Comparing the Effects of Sevoflurane and Desflurane on Intracranial Pressure in Patients Undergoing Laparoscopic Cholecystectomy Via Ultrasonographic Measurement of the Optic Nerve Sheath Diameter

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Keywords: Desflurane; laparoscopic cholecystectomy; optic nerve sheath; sevofluran.

ABSTRACT

Objective: Anesthetics have various effects on intracranial pressure (ICP). We aimed to compare the effects of sevoflurane and desflurane on intracranial pressure during laparoscopic cholecystectomy.

Methods: After obtaining ethical approval and patients' informed consent, 69 patients scheduled for laparoscopic cholecystectomy were randomized into Group-S and Group-D. Demographic data, hemodynamics, and ultrasonographic optic nerve sheath diameter (ONSD) values were recorded. Patients were administered propofol, fentanyl, and rocuronium for induction of anesthesia. Anesthesia was maintained by administering sevoflurane in Group-S, desflurane in Group-D, and remifentanil infusion. The respiratory rate was adjusted, with end-tidal carbon dioxide ($ETCO_2$) values of 35–40 mmHg. The ONSD measurements, hemodynamics, and $ETCO_2$ levels were recorded at 5 minutes after induction (T1), 3 minutes after creating pneumoperitoneum and reverse Trendelenburg position (T2), 20 minutes of pneumoperitoneum (T3), and 5 minutes after terminating pneumoperitoneum (T4). All parameters were recorded by an anesthesiologist blinded to the groups.

Results: Patients had similar demographic data, intraoperative hemodynamic parameters, SpO_2, and end-tidal CO_2 levels. There was no difference between the groups in ONSD measured at T0, T1, T2, T3, and T4. Intragroup comparisons revealed that the ONSD was higher at all measurement times than the baseline in both groups.

Conclusion: Sevoflurane and desflurane had similar effects on ICP during laparoscopic cholecystectomy, and the intraoperative ICP was higher than the baseline in both groups.

INTRODUCTION

Organ systems are affected differently during anesthesia applications. Anesthetic agents cause perfusion and pressure changes in the central nervous system, which is their site of action. Inhalation anesthetics are known to slightly increase intracranial pressure (ICP) during anesthesia.[1] However, there are no reported adverse effects of these minimal intracranial pressure changes on postoperative neurological outcomes in healthy patients. Laparoscopic surgery is widely performed as an alternative to open surgery due to its advantages such as reduced bleeding, post-

operative pain, and length of hospital stay. However, pneumoperitoneum and the resulting intra-abdominal pressure (IAP) may cause many systemic physiological outcomes such as decreased venous return, hypercapnia due to CO_2 absorption through the peritoneal surface, and respiratory acidosis. Studies with animal models have reported the use of CO_2 pneumoperitoneum to be associated with ICP. Increases in intracranial pressure can decrease cerebral perfusion pressure, leading to cerebral ischemia. Therefore, anesthetic agents that would minimize fluctuations in intracranial pressure should be chosen in procedures known to increase intracranial pressure, such as laparoscopic surgeries.[2] There is a scarcity of research comparing the effects of inhalation anesthetics on intracranial pressure in humans.

Measurement of the optic nerve sheath diameter (ONSD) with ultrasound is a simple, reliable, and non-invasive technique for ICP assessment, which has been shown to detect compliance with the degree of ICP, and the increase in ICP in clinical settings.[3]

We aimed to compare the effects of sevoflurane and desflurane—commonly used agents in general anesthesia practice—on intracranial pressure during laparoscopic cholecystectomy via measuring the optic nerve sheath diameter with ultrasound.

MATERIALS AND METHODS

This study was carried out between 15.03.2019 and 15.03.2020. After ethical committee approval (2019/28) and obtaining informed consent forms from the patients, this prospective, randomized, double-blind study was carried out in accordance with the Helsinki Declaration. We randomized 69 ASA 1-3 risk group patients who were scheduled for laparoscopic cholecystectomy into Group S and Group D using the sealed envelope method. The patients were not provided any information about their group. Those with a history of increased intracranial pressure or with any condition that might cause an increase in intracranial pressure (ischemic cerebrovascular event, intracranial hemorrhage, brain tumor), those with eyeball diseases, glaucoma patients, those with a history of cataract surgery, and those <18 years of age were excluded from the study. Routine monitoring, which includes electrocardiography, non-invasive blood pressure, pulse oximetry, and the bispectral index, was performed, and the levels were recorded, followed by the optic nerve sheath diameter measurement on the right and left eyelids before induction (T0). Measurements were made 3 mm beneath the point where the optic nerve enters the globe by a USG (My Lab30 Gold, Esaote, Genova, Italy) 12 MHz linear probe placed transversely on the closed eyelid and at an angle of around 15 degrees. The measurements were repeated twice in both eyes, and the average was recorded. The patients were not premedicated, and 2 – 2.5 mg/kg propofol and 2 mcg/kg fentanyl were administered for anesthesia induction with a BIS value of <60, and 0.6 mg/kg rocuronium for muscle relaxation. After intubation, the patients were ventilated with volumes of 6–8 ml/min according to their ideal body weight. The respiratory rate was adjusted to 10–14/min, with the patient's end-tidal carbon dioxide values between 35–40 mmHg. Using a mixture of 40% oxygen and 60% air, anesthesia was maintained by administering 1-2% sevoflurane in Group S, 4-6% desflurane in Group D, and 0.05-0.5 mcg/kg remifentanil infusion, with a BIS value of 40–60. The vaporizers were adjusted according to randomization by a specialist who was not involved in the study follow-up, and the top of the vaporizers was covered with gauzes to block the view of the measurer. The pneumoperitoneum pressure was maintained at 12 mmHg during the surgery. The mean blood pressure, heart rate, peripheral oxygen saturation, end-tidal carbon dioxide level, and optic nerve sheath diameter were recorded at 5 minutes after induction (T1), 3 minutes after creating pneumoperitoneum and placing the patient in the reverse Trendelenburg position (T2), 20 minutes of pneumoperitoneum (T3), and 5 minutes after terminating pneumoperitoneum and placing the patient in the supine position. In addition, the average of the right and left optic nerve diameters was recorded. After the gallbladder was removed, 1 g paracetamol and 1 mg/kg tramadol were intravenously administered for postoperative analgesia, and 4 mg ondansetron for postoperative nausea prophylaxis. Following the completion of the skin sutures, the inhalation anesthetic was discontinued, and 0.02 mg/kg atropine and 0.05 mg/kg neostigmine were intravenously administered to reverse the neuromuscular blockade. Patients with a BIS value of >85 and adequate spontaneous ventilation were extubated. All perioperative parameters were recorded by an anesthesiologist who was not involved in patient follow-up and blinded to the inhalation anesthetic used.

The findings of the study were assessed using IBM SPSS Statistics 22 (IBM SPSS, Türkiye) for statistical analyses. The normality of the parameters was tested by the Shapiro-Wilk test. The assessment of the study data included descriptive statistical methods (mean, standard deviation, frequency) as well as the Student's t-test to compare normally distributed parameters between two groups, and the Mann-Whitney U test to compare non-normally distributed parameters between two groups for the comparison of quantitative data. A repeated-measures analysis of variance was used for within-group comparisons of normally distributed parameters, and the Bonferroni test was used to reveal the period causing the difference. The Friedman test was used for within-group comparisons of non-normally distributed parameters. The Fisher-Freeman-Halton's test and Yates's correction for Continuity were used to compare qualitative data. A p-value of <0.05 was considered statistically significant.

A study using sevoflurane found the ONSD measured at 3 minutes after the creation of pneumoperitoneum to be 4.9±0.4 mm.[4] Assuming that the ONSD in anesthesia with sevoflurane was 10% different from that in anesthesia

with desflurane, the mean difference between sevoflurane and desflurane was 0.49 mm. Accordingly, the number of samples was calculated to be at least 25 patients for each group, at 90% power, and a p level of <0.05. Considering the losses during follow-up, a total of 69 patients were included in the study.

RESULTS

A total of 69 patients were included in the study. Three patients were excluded due to desaturation in one patient and deteriorated hemodynamic parameters in two patients. The data were assessed for 66 patients, with 33 per

Table 1. Demographic data

	Group S Mean ± SD	Group D Mean ± SD	
Age (years)	47.94±11.93	49.45±11.47	[1]0.604
BMI (kg/m^2)	29.73±5.52	29.34±5.23	[1]0.770
	n (%)	n (%)	
Sex			
Male	8 (22.9%)	6 (19.4%)	[2]0.964
Female	27 (77.1%)	25 (80.6%)	
ASA			
1	29 (82.9%)	22 (71%)	[3]0.162
2	6 (17.1%)	6 (19.4%)	
3	0 (0%)	3 (9.7%)	

[1]Student t test, [2]Continuity (yates) correction, [3]Fisher freeman halton test. BMI: Body Mass Index.

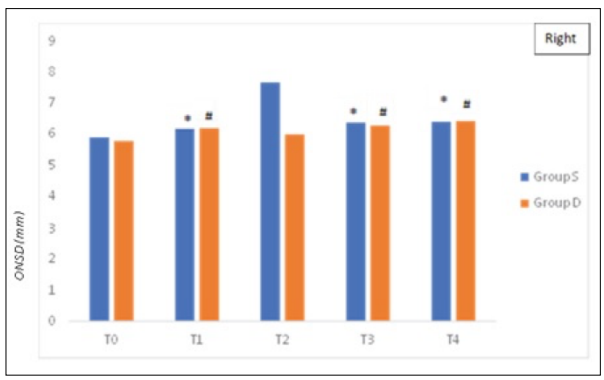

Figure 1. Right Optic Nerve Sheath Diameter Measurements. *Student t test, Bonferroni test, *p<0.05 indicates significant difference compared with the baseline measurements for Group S; #p<0.05 indicates significant difference compared with the baseline measurements for Group D.*

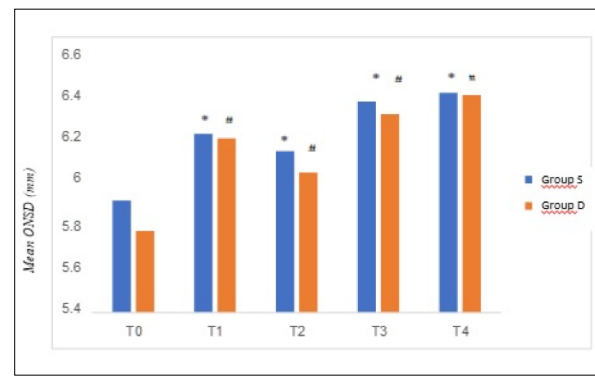

Figure 3. Mean Optic Nerve Sheath Diameter Measurements. *Student t test, Bonferroni test, *p<0.05 indicates significant difference compared with the baseline measurements for Group S; #p<0.05 indicates significant difference compared with the baseline measurements for Group D.*

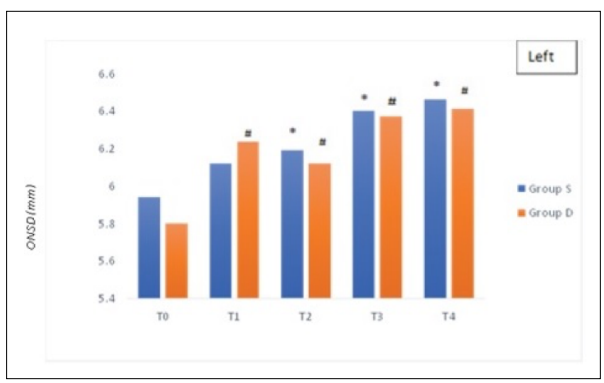

Figure 2. Left Optic Nerve Sheath Diameter Measurements. *Student t test, Bonferroni test, *p<0.05 indicates significant difference compared with the baseline measurements for Group S; #p<0.05 indicates significant difference compared with the baseline measurements for Group D.*

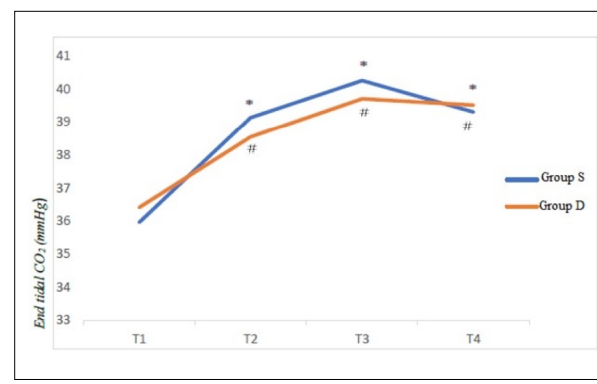

Figure 4. End-tidal Carbon Dioxide Levels. *Student t test, Bonferroni test, *p<0.05 indicates significant difference compared with the baseline measurements for Group S; #p<0.05 indicates significant difference compared with the baseline measurements for Group D.*

group. The demographic data of the study patients were similar (Table 1).

Right, left, and mean ONSD values were similar in both groups at all measurement times. The within-group comparison revealed that the mean ONSD was higher than the baseline value at all measurements (Figure 1-2-3).

The mean blood pressure (MBP) was similar. In Group S, the MBP was lower than the baseline value after intubation and at 5 minutes after terminating pneumoperitoneum (T4) (p=0.000; p=0.006). In Group D, the MBP was lower than the baseline value at all measurement times (p=0.000; p=0.003; p=0.000; p=0.000).

The mean heart rate was similar in both groups. There was no difference in the $ETCO_2$ levels between the two groups of patients, but the $ETCO_2$ levels in both groups were higher at all measurement times compared to the first measurements (Figure 4).

DISCUSSION

It is known that inhalation anesthetics, which are frequently used agents during anesthesia applications, have vasodilator effects. These effects become evident with increasing concentrations, and general anesthesia significantly increases cerebral blood flow, and thus may result in increased intracranial pressure.[5] Sujata et al.[2] compared the effects of propofol and sevoflurane on intracranial pressure during laparoscopic pelvic surgeries by measuring the ONSD and reported that the highest mean ONSD was significantly lower in the propofol group than in the sevoflurane group. Limited studies are exploring the effects of two inhalation agents on intracranial pressure. Fraga et al.[6] reported no difference in the effects of desflurane and isoflurane on intracranial pressure in normocapnic patients. Sponheim et al.[7] investigated the effects of isoflurane, desflurane, and sevoflurane on intracranial pressure in children with a suspected increase in intracranial pressure, showing that isoflurane and sevoflurane did not increase ICP from the baseline value, while desflurane caused an ICP higher than the baseline value. Holmström et al.[1] also demonstrated a greater effect of desflurane on ICP than sevoflurane. Our study assessed the effects of sevoflurane and desflurane on intracranial pressure during laparoscopic cholecystectomy by measuring optic nerve sheath diameter in patients without intracranial disease and established that the two inhalation agents had similar effects on intracranial pressure at all measurement times.

Laparoscopic surgery, which is preferred to conventional open surgery, has advantages such as being minimally invasive, reduced bleeding, and early discharge.[8] However, laparoscopic surgery requires the creation of pneumoperitoneum with CO_2 in the abdomen to achieve a better view of the surgical site. This may cause some hemodynamic, respiratory, and cerebrovascular side effects. The study by Kamine et al.[9] measured intracranial pressure with a ventricular catheter and reported an increase in ICP during laparoscopy. The study by Min et al.[8] with pediatric patients assessed intracranial pressure by ultrasonographic measurement of ONSD in cases undergoing elective laparoscopic surgery and found an increased ONSD to be correlated with pneumoperitoneum. In our study, ONSD was higher than baseline values during pneumoperitoneum. The study by Sahay et al.[10] showed that the mean optic nerve sheath diameter was higher at 5 minutes after desufflation than the baseline value. Our study also observed that the increase continued at the measurements after the pneumoperitoneum was created, and the values after desufflation were higher than the baseline value.

The study by Yashwashi et al.[11] reported that intracranial pressure increased with increasing pneumoperitoneum pressures during laparoscopic cholecystectomy. In our study, the pressure of pneumoperitoneum was fixed at 12 mmHg, and an increased ONSD was detected during the surgery performed at this pressure. Our findings suggest that the use of high pneumoperitoneum pressures, especially in patients with high intracranial pressure, may result in adverse neurological conditions.

In addition to the pressure effect of the pneumoperitoneum during laparoscopic surgery, the gas used for insufflation may also change intracranial pressure. The study comparing pneumoperitoneum with CO_2, helium, and nitrous oxide in pigs observed that the intracranial pressure increased significantly in pneumoperitoneum with CO_2 compared to other gases. This was attributed to an increase in $PaCO_2$, a decrease in pH values, and an increase in cerebral perfusion.[12] When intracranial pressures were compared during hyperventilation and hypoventilation after pneumoperitoneum with CO_2 in pigs, hypoventilation was found to cause an increase in intracranial pressure.[13] In our study, end-tidal CO_2 values were similar in both groups and were statistically higher than baseline values. In both groups, there was an increase in ONSD at the measurement times when carbon dioxide was higher than the baseline measurement. It was concluded that this finding supported the relationship between CO_2 and intracranial pressure reported in previous studies.

The extraventricular drainage system is considered the gold standard for the measurement of ICP. However, it has side effects such as brain damage, infection, and hemorrhage. With noninvasive CT and MRI, it is not possible to make simultaneous and repeated measurements during surgery. The ultrasonographic measurement of ONSD has been found correlated with increased intracranial pressure and produced reliable results in previous studies.[14] Also, it has become important as it enables instant monitoring.[15-17] Our study used the ultrasonographic measurement of the ONSD to evaluate ICP during the operation.

A study on the hemodynamic effects of inhalation anesthetics reported that when 1 MAC sevoflurane and desflurane were used, desflurane exhibited more potent vasodilator properties and reduced blood pressure more.[18] A study with patients undergoing bariatric surgery showed that the effects of sevoflurane and desflurane on hemodynamic parameters were similar when the inhalation agent concentration was titrated by maintaining BIS

levels between 40 and 60.[19] A study on intracranial surgeries found similar effects of sevoflurane and desflurane on blood pressure, while the heart rate was lower in the desflurane group.[20] Our study performed volatile agent titration to maintain the bispectral index in the range of 40-60 and found the heart rate and mean blood pressure to be similar between groups throughout the operation.

The limitation of our study was that the patients included in the study had no intracranial diseases. If patients with intracranial diseases were included, the effect of sevoflurane and desflurane on ICP might be different.

Conclusion

Sevoflurane and desflurane have similar effects on intracranial pressure and hemodynamic parameters during laparoscopic cholecystectomy. Laparoscopic cholecystectomy causes an increase in intracranial pressure. We believe that this should not be ignored in risk-group patients, and negative outcomes should be prevented by taking necessary precautions.

Ethics Committee Approval

This study approved by the University of Health Sciences Fatih Sultan Mehmet Health Application and Research Center Ethics Committee (Date: 14.03.2019, Decision No: FSMEAH-KAEK 2019/28).

Informed Consent

Informed consents were obtained from all patients.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.Ö.İ., S.A., D.E.A.; Design: S.A., M.Ö.İ., C.K.; Supervision: D.E.A., Ö.D.; Materials: M.Ö.İ., S.A., D.E.A.; Data: M.Ö.İ., S.A., Ö.D.; Analysis: S.A., C.K.; Literature search: M.Ö.İ., S.A.; Writing: M.Ö.İ., S.A.; Critical revision: D.E.A., Ö.D., C.K.

Conflict of Interest

None declared.

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Laparoskopik Kolesistektomi Geçiren Hastalarda Sevofluran ve Desfluranın İntrakraniyal Basınca Etkisinin Ultrasonografik Optik Sinir Kılıf Çapı Ölçümü İle Karşılaştırılması

Amaç: Anestezik ajanların intrakraniyal basınca (İKB) farklı etkileri mevcuttur. Çalışmamızda laparoskopik kolesistektomi operasyonlarında sevofluran ve desfluranın intrakraniyal basınca etkilerini karşılaştırmayı hedefledik.

Gereç ve Yöntem: Etik kurul onayı ve hastalardan bilgilendirilmiş onam alındıktan sonra laparoskopik kolesistektomi planlanan 69 hasta, Grup-S ve Grup-D olarak randomize edildi.Demografik ve hemodinamik veriler ile ultrasonografik optik sinir kılıfı çapı (OSKÇ) değerleri kaydedildi. İndüksiyon için propofol, fentanil ve rokuronyum kullanıldı. Grup-S'ye sevofluran, Grup-D'ye desfluran uygulandı; remifentanil infüzyonu yapıldı. OSKÇ ölçümleri ve hemodinamik veriler indüksiyondan 5 dk sonra (T1), pnömoperitonyum oluşturulduktan ve ters Trendelenburg pozisyonundan 3 dk sonra (T2), pnömoperitonyumdan 20 dk sonra (T3) ve pnömoperitonyum sonlandırıldıktan 5 dk sonra (T4) kaydedildi. Tüm parametreler gruplara kör bir anestezist tarafından takip edildi.

Bulgular: Hastaların demografik verileri, intraoperatif hemodinamik parametreleri, SpO2 ve ETCO2 düzeyleri benzerdi. T0, T1, T2, T3 ve T4'te ölçülen OSKÇ'de gruplar arasında fark yoktu.Grup içi karşılaştırmalarda, OSKÇ'nın tüm ölçüm zamanlarında her iki grupta da başlangıca göre daha yüksek olduğu görüldü.

Sonuç: Sevofluran ve desfluranın laparoskopik kolesistektomi sırasında İKB üzerine etkileri benzerdir; laparoskopik cerrahi esnasında her iki ajan ile intraoperatif İKB bazale göre yüksek seyretmektedir.

Anahtar Sözcükler: Desfluran; laparospik kolesistektomi; optik sinir kılıf çapı; sevofluran.

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Original Article

The Impact of the COVID-19 Pandemic on Lung Cancer Diagnosis

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Keywords: COVID-19, lung cancer, pandemic.

ABSTRACT

Objective: During the COVID-19 pandemic, a decrease in hospital admissions has been observed due to fear of exposure to the infectious agent. This situation has raised concerns about a decrease in presentations and delays in diagnosis among patients with symptoms and suspicion of lung cancer. Additionally, it is argued that the increase in the number of thoracic computed tomography scans due to COVID-19 infection supports the view that lung cancer is being detected in early stages. In this study, we aimed to investigate the impact of the pandemic on the diagnosis of lung cancer.

Methods: Patients diagnosed with lung cancer in our hospital between 2019-2021 were evaluated retrospectively. The sex, age, TNM classifications, stages, pathological diagnoses and treatments of the patients were recorded and the one-year periods before and after the start of pandemic were compared.

Results: 348 patients with lung cancers were included in the study. It was observed that 292 of these patients were diagnosed with non-small cell lung cancer, and 56 patients were diagnosed with small cell lung cancer. 182 patients were detected at the 1A-3A stages of non-small cel lung cancer, relatively early stages, while 110 were detected at the 3B-4B stages at diagnosis. The rate of early-stage non-small cell lung cancer diagnosis was 70.3% before the pandemic and 56.1% after the start of pandemic, with a statistically significant difference (p=0.013). It was found that the rate of those who underwent curative surgery in the non-small cell lung cancer group after the start of pandemic decreased (83/164, 50.6%) when the patient groups were compared in terms of treatment before the pandemic (80/128, %62.5) (p=0.034).

Conclusion: Our findings indicate that lung cancer diagnoses may have been delayed due to the restrictions during the pandemic and the anxiety of contracting the disease, or due to the increased burden on health care system.

INTRODUCTION

Lung cancer threatens public health and leads to significant mortality and morbidity, particularly with increased smoking. The incidence of lung cancer is 30-35% per year in men and 13-14% per year in women worldwide. Research reports that the incidence of lung cancer rises at a rate of 0.5% per year worldwide.[1] Due to the high growth rate and early metastasis, nearly two-thirds of cases present with extensive disease at diagnosis. Despite a positive initial response to chemotherapy and radiation, it is associated with worse long-term survival rates compared to other cancer types.[2,3]

Since the COVID-19 outbreak, there has been a significant fall in hospital admissions because of a fear of exposure by patients other than those with suspected infection to the infectious agent. Besides, there have been many restrictions around the world.[4] This suggests that there may have been some delays in diagnosis and treatment among patients with suspected and treated lung cancer. Moreover, the presence of similar symptoms in lung cancer and COVID-19 pneumonia can be complicated in the differential diagnosis. It also brings to mind the idea of diagnosing lung cancer at an early stage with the increase in the number of thorax computed tomography performed due to the same symptoms. We aimed to investigate the impact of the pandemic on lung cancer diagnosis and treatment in this study.

MATERIALS AND METHODS

We analyzed the files of 362 patients diagnosed with lung cancer in our hospital from March 15th, 2019 to December 31st, 2019, and from March 15th, 2020 to December 31st, 2020, retrospectively. Patients 18 years or older, with histologically or cytologically proven diagnosis of lung cancer [non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC)], were included in the study (Figure 1). Age, sex, tumor histological subtype, TNM classification, stage, and treatments of all patients (chemotherapy, radiotherapy, curative surgery) were recorded. Recurrent lung cancer and patients who did not receive any treatment (treatment denied or out of follow-up) were excluded. Patients were divided into two groups: before the pandemic and after the start of the pandemic. All data before and after the start of the pandemic were compared. The Local Ethics Committee approved the study protocol, number 2022/514/232/8, dated 26.08.2022.

Statistical Analyses

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) version 17 software. Descriptive data are expressed as number, mean, standard deviation, minimum-maximum values, and percentages. The chi-square test ($\chi 2$) was used to compare categorical values. Statistical significance level was taken as $p<0.05$.

RESULTS

A total of 362 patients were included in the study. Fourteen patients were excluded from the study because four patients denied treatment, five patients were out of follow-up, and five patients had recurrent lung cancer. Three hundred forty-eight patients with lung cancers, consisting of 259 (74.4%) males and 89 (25.6%) females, were included in the study. The mean age of all patients was 63.8±9.1 years. Demographic characteristics of patients are shown in Table 1. It was determined that 292 (83.9%) patients were diagnosed with NSCLC and 56 (16.1%) patients were diagnosed with SCLC. The most common subgroups in NSCLC were identified as adenocarcinoma (n=132, 37.9%) and squamous cell carcinoma (n=103, 29.6%). One hundred eighty-two patients were detected at the 1A-3A stages of NSCLC (90 patients before the pandemic, 92 patients after the start of the pandemic), relatively early stages, while 110 were detected at the 3B-4B stages (38 patients before the pandemic, 72 patients after the start of the pandemic) at diagnosis. Of all SCLC cases, only three patients were determined to have a limited stage (two patients before the pandemic, one patient after the start of the pandemic) and the remaining 53 patients were determined to have an extensive stage (31 patients before the pandemic, 22 patients after the start of the pandemic). When analyzed according to the years, the number of patients diagnosed in the year before the pandemic was 151 (43.4%), while 197 (56.6%) patients were diagnosed with lung cancer in the year after the start of the pandemic (NSCLC and SCLC). The flowchart is shown in Figure 1. The rate of early-stage NSCLC diagnosis was 70.3% (90/128) before the pandemic and 56.1% (92/164) after the start of the pandemic, with a statistically significant difference (p=0.013). It was found that the rate of those who underwent curative surgery in the NSCLC group after the start of the pandemic (83/164, 50.6%) decreased when the patient groups were compared in terms of treatment before the pandemic (80/128, 62.5%) (p=0.034) (Table 2). No significant difference was found in the SCLC group in terms of stage and curative surgery.

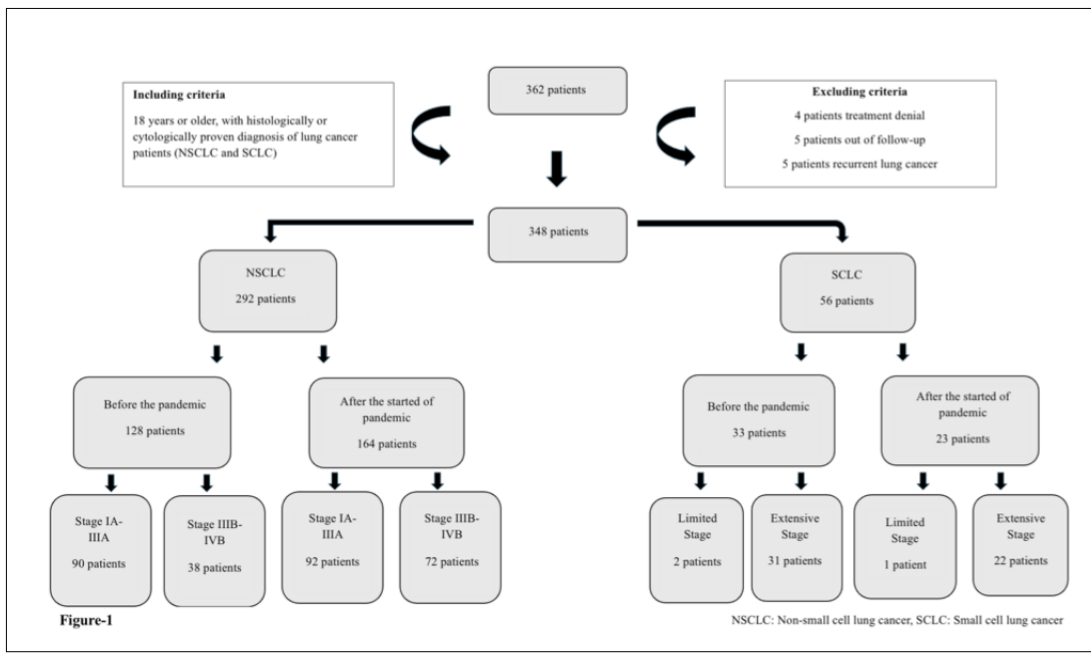

Figure 1. Patients 18 years or older, with histologically or cytologically proven diagnosis of lung cancer [non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC)].

Table 1. Demographic characteristic of patient

	Before the pandemic	After the start of pandemic	Total
Age	63.7±9.6	63.9±8.6	63.8±9.1
Patient (%)	151 (%43.4)	197 (56.6%)	348 (100%)
Gender			
Female n (%)	39 (25.8%)	50 (25.4%)	89 (25.6%)
Male n (%)	112 (74.2%)	147 (74.6%)	259 (74.4%)

Table 2. Comparison of non-small cell lung cancer stage and curative surgery before and after the start of the pandemic

	Before the pandemic	After the start of pandemic	p value
Stage 1A-3A (n, %)	90 (70.3%)	92 (56.1%)	p=0.013*
Curative surgery (n, %)	80 (62.5%)	83 (50.6%)	p=0.034*

*p value<0.05: Statistically significance

DISCUSSION

We retrospectively investigated 348 newly diagnosed lung cancer cases in March-December 2019 and March-December 2020. Accordingly, 151 patients were diagnosed in the year before the pandemic and 197 in the year after the start of the pandemic. We found that the rate of early-stage NSCLC diagnosis after the start of the pandemic was statistically significantly lower than before the start of the pandemic. Cantini et al.[5] retrospectively scanned cases from 25 Italian Oncology Clinics in March-December 2019 and March-December 2020. Similar to our study, they found that 72% of the patients diagnosed after the start of the pandemic were at Stage 4, statistically significantly higher than those diagnosed before the start of the pandemic. Conversely, in other literature, it was found that there was no statistically significant difference between the years in terms of cancer stages at diagnosis.[6]

In addition, it was found that the rate of those who underwent curative surgery in the NSCLC group decreased after the start of the pandemic when the patient groups were compared in terms of treatment. In the literature similar to our study, the number of patients who underwent surgery decreased after the start of the pandemic, but conversely, it was not statistically significant.[6]

The Netherlands Cancer Registry reported nearly a 30% decrease in all newly diagnosed cancers. This rate has been reported at a similar rate in newly diagnosed lung cancers.[7] Similarly, cases diagnosed with lung cancer from May to October in 2018, 2019, and 2020 were retrospectively compared. The authors reported that 124 (86.1%) cases were newly diagnosed with lung cancer in 2018, 132 (85.7%) in 2019, and 96 (85%) in 2020.[6] Patt et al.[8] retrospectively analyzed and compared cancer cases from the USA in March-July 2019 and March-July 2020. The authors found a significant decrease in the number of cancer screenings, biopsies, surgeries, and outpatient admissions. Furthermore, during April, when the pandemic had the highest impact, the rates of screenings for breast cancer, colon cancer, prostate cancer, and lung cancer were 85%, 75%, 74%, and 56%, respectively. Similarly, the impact of COVID-19 on cancer screenings was retrospectively evaluated, comparing low-dose CT scans for lung cancer before and after the start of the pandemic, and the authors highlighted that both the number of new patients participating in the screening program and the number of patients in the screening program decreased after the start of the pandemic.[9] In cross-sectional studies, it was observed that the rate of new diagnoses decreased by 46% in six common cancers, including esophageal and lung cancer, in the United States between January 2018 and April 2020.[10]

Our work has potential limitations as a retrospective and single-center study. In addition, neoadjuvant or adjuvant chemotherapy types of patients receiving chemotherapy were not recorded.

Conclusion

We compared the diagnoses of lung cancer stages one year before and after March 2020, when the COVID-19 pandemic was first declared in Turkey. Relatively more cases were diagnosed at a more advanced stage after the start of the pandemic, and relatively fewer patients had the opportunity for curative surgery during the pandemic. Our findings indicate that some lung cancer diagnoses may have been delayed due to the restrictions during the pandemic and the anxiety of contracting the disease, or due to the increased burden on the health care system.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 26.08.2022, Decision No: 2022/514/232/8).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.F.E.A., S.Ş.C., A.F., S.B.S., N.G.K. N.B.Ö., R.D.; Design: S.F.E.A., S.Ş.C., A.F., S.B.S., N.G.K. N.B.Ö., R.D.; Supervision: S.F.E.A., S.Ş.C., A.F., S.B.S., N.G.K. N.B.Ö., R.D.; Materials: S.F.E.A., N.B.Ö., S.Ş.C., R.D.; Data: S.F.E.A., S.Ş.C., A.F., R.D.; Analysis: S.F.E.A., S.Ş.C., A.F., R.D.; Literature search: S.F.E.A., S.Ş.C., R.D.; Writing: S.F.E.A., S.Ş.C., R.D.; Critical revision: S.F.E.A., S.Ş.C.

Conflict of Interest

None declared.

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COVID-19 Pandemisinin Akciğer Kanseri Tanısı Üzerindeki Etkisi

Amaç: COVID-19 pandemisinde bulaşıcı ajana maruz kalma korkusu ile hastane başvurularında azalma görülmüştür. Bu durumun, akciğer kanseri semptomları ve şüphesi olan hastaların başvurularında azalma ve tanıda gecikmeler olabileceğini düşündürmüştür. Bunun yanı sıra COVID-19 enfeksiyonu sebebiyle çekilen toraks bilgisayarlı tomografi sayısı arttığından akciğer kanserinin erken evrelerde yakalandığı görüşü de savunulmaktadır. Biz bu çalışmada pandeminin akciğer kanseri tanısı üzerine etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Hastanemizde 2019-2021 yılları arasında akciğer kanseri teşhisi konmuş hastalar retrospektif olarak değerlendirildi. Hastaların cinsiyeti, yaşı, TNM sınıflandırmaları, evreleri, patolojik teşhisleri ve tedavileri kaydedildi ve pandemi öncesi ve sonrası bir yıllık dönemler karşılaştırıldı.

Bulgular: Çalışmaya 348 akciğer kanseri tanısı konulan hasta dahil edildi. Bu hastaların 292'sine küçük hücreli dışı akciğer kanseri tanısı, 56 hastaya ise küçük hücreli akciğer kanseri tanısı konulduğu görüldü. Küçük hücreli dışı akciğer kanserlerinin nispeten erken evre olan Evre 1A-3A evresinde 182 hasta tespit edilirken, 110 hasta ise 3B-4B evresinde tespit edildi. Pandemi öncesi dönemde erken evre küçük hücre dışı akciğer kanseri teşhisi oranı %70.3 iken, pandemi başlangıcından sonraki dönemde %56.1 olarak bulundu ve bu iki grup arasında istatistiksel olarak anlamlı bir fark tespit edildi (p=0.013). Küçük hücreli dışı akciğer kanseri grubunda pandemi başlangıcından sonraki dönemde küratif cerrahi geçirenlerin oranı (83/164, %50.6), pandemi öncesi döneme (80/128, %62.5) göre karşılaştırıldığında istatistiksel olarak anlamlı olarak azalmış olduğu görüldü (p=0.034).

Sonuç: Bulgularımız, pandemi sırasındaki kısıtlamalar, hastalığa yakalanma kaygısı ve sağlık sistemindeki artan yük nedeniyle akciğer kanseri teşhisinin gecikmiş olabileceğini göstermektedir.

Anahtar Sözcükler: Akciğer kanseri; COVID-19; pandemic.

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Original Article

The Clinical Significance of Fibrinogen-Like Protein 2 (FGL-2) Levels in Nonalcoholic Steatohepatitis

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Keywords: FGL-2 levels; nonalcoholic steatohepatitis.

ABSTRACT

Objective: Non-alcoholic steatohepatitis (NASH) is one of the most common metabolic diseases of the liver. In patients with NASH, progression to cirrhosis can be observed in approximately 25% over a decade following diagnosis, and it is considered the most frequent cause of cryptogenic cirrhosis. Fibrinogen-like protein-2 (FGL-2) is a sub-member of the fibrinogen superfamily secreted by regulatory T cells. It inhibits the maturation of dendritic cells and induces apoptosis in B cells, playing a role in innate and adaptive immunity regulation. Recent studies have shown high serum FGL-2 levels are a poor prognostic indicator in patients with viral hepatitis.

Methods: The study included 30 NASH patients diagnosed by biopsy and a control group of 21 healthy individuals. Serum FGL-2 levels of individuals in both groups were compared. The relationship between the clinicopathological features of individuals in both groups and FGL-2 levels was also examined.

Results: Serum FGL-2 levels in NASH patients were found to be 47±12 ng/ml, while in the control group, it was 37±10 ng/ml. Statistical evaluation was performed using the Mann-Whitney U test. A significant difference was found between patients classified by biopsy as simple steatosis, borderline NASH, definite NASH, and the control group (p=0.002). A significant difference was also observed when evaluating these four groups among themselves (Kruskal-Wallis test, p=0.012).

Conclusion: Our study identified higher serum FGL-2 levels in patients diagnosed with NASH, consistent with steatohepatitis observed in biopsies. Elevated FGL-2 levels may indicate hepatic damage at the microinflammation level. Estimating disease severity, non-invasive monitoring and control of disease progression, selecting patients for aggressive treatment approaches, and intensifying monitoring intervals for cirrhosis and HCC could be crucial. However, more comprehensive studies on this topic are needed.

INTRODUCTION

Fatty liver disease is categorized into alcoholic and non-alcoholic fatty liver disease (NAFLD). NAFLD is a broad spectrum of disorders characterized by predominant macrovesicular steatosis in individuals without significant alcohol consumption.[1-4] NAFLD encompasses two distinct conditions: simple fatty liver without inflammation and fibrosis and non-alcoholic steatohepatitis (NASH) with steatosis and necroinflammatory activity.[5] Simple fatty liver disease presents a benign clinical course without chronic hepatitis or progression to fibrosis. In contrast, many NASH patients exhibit established chronic liver damage and even cirrhosis at diagnosis.[4-7] Liver biopsy remains the sole method for diagnostic differentiation between the two.[2,6] However, liver biopsy is invasive, may require hospitalization, can be painful, carries a risk of complications, is costly, and can be burdensome for both the patient and physician due to its potential for false negatives and the need for repeated procedures.

Fibrinogen-like protein 2 (FGL-2), also known as fibroleukin, was initially cloned from cytotoxic T lymphocytes. Due to its 36% similarity with fibrinogen beta and alpha chains, it is classified as a member of the fibrinogen superfamily.[8] FGL-2 primarily exists as a membrane-associated protein on the surface of macrophages and endothelial cells. This protein possesses prothrombinase activity, facilitating the conversion of prothrombin to thrombin.[9] Secreted by Treg cells, FGL-2 inhibits dendritic cell (DC) maturation and function and induces B cell apoptosis, thereby modulating immunoregulatory effects

[10-13] Animal studies have shown that serum FGL-2 levels increase in viral hepatitis and correlate with liver damage. [14,15] Reports suggest a relationship between serum FGL-2 levels and the extent and fibrosis of chronic hepatitis C.[16] In this study, we aimed to determine the predictive value of fibrinogen-like protein 2 (FGL-2) levels in forecasting the degree of hepatosteatitis in NAFLD.

MATERIALS AND METHODS

Patient Population

Our study included 30 patients monitored for Non-Alcoholic Fatty Liver Disease (NAFLD) and a healthy control group of 21 individuals. Inclusion criteria for the patients were: 1- No history of alcohol consumption (>20 mg/day) or substance addiction. 2- Negative ELISA results for HBsAg, anti-HCV, and anti-HIV. 3- Absence of conditions like hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, biliary obstruction, alpha-1 antitrypsin deficiency, and malignancy. 4- Absence of thrombotic diseases and non-use of anticoagulants.

Liver biopsies were performed on NAFLD patients. Concurrently, hematological, biochemical, waist, and hip circumference measurements were recorded. Patients were staged post-liver biopsy according to the Kleiner classification. Steatosis was semi-quantitatively scored based on its degree: <%5=0, %5-33=1, %33-66=2, >66=3. Lobular inflammation was scored as Stage 0: no affected lobules, Stage 1: <2 foci/x 200 magnification, Stage 2: 2-4 foci/x200 magnification, Stage 3: >4 foci/x200 magnification. Fibrosis was graded as follows: Stage 1: perisinusoidal or periportal, 1A: mild, zone 3, 1B: moderate, zone 3 and perisinusoidal fibrosis, 1C: portal and periportal fibrosis, Stage 2: perisinusoidal, portal, and periportal fibrosis, Stage 3: bridging fibrosis, Stage 4: Cirrhosis. NASH scores were obtained by summing the values of steatosis (0-3), lobular inflammation (0-3), and ballooning degeneration (0-2), resulting in scores ranging from 0-8. Scores of 0-2 were considered simple steatosis, 3-4 as borderline NASH, and > four as definite NASH.

The study was conducted in accordance with the Helsinki Declaration. All patients were informed about the study and provided written consent.

Statistical Analysis

Depending on the data distribution, the Mann-Whitney U and Independent Samples t-test were used to compare two independent groups. Distribution and variance analyses were performed for independent groups with more than two categories. ANOVA was used for groups with normal distribution and variances, and the Kruskal-Wallis test for those without. The correlation between continuous variables was calculated using the Pearson correlation coefficient. The Pearson Chi-Square and Fisher's exact tests were employed for categorical variables. The predictive value of FGL-2 levels in identifying NAFLD patients was assessed using ROC analysis. Means and standard deviations are provided. A significance level of $P<0.05$ was adopted. Statistical calculations were performed using SPSS 17.0 software.

RESULTS

The clinical and laboratory characteristics of the cases in our study are described in Table 1. There were no significant differences between the groups regarding age, gender, Hg, Htc, and Plt values. However, significant differences were observed for AST, ALT, HOMA IR, BMI, waist circumference, and serum FGL-2 levels. ($p<0.001$, <0.001, =0.001, =0.003, =0.0035, and =0.012, respectively). The histopathological features of the patients who underwent liver biopsy are presented in Table 2.

Serum FGL-2 levels were found to be 47±12 ng/ml in patients with biopsy-proven NAFLD, compared to 37±10 ng/ml in the control group. Upon evaluation using the Mann-Whitney U test, a significant difference was observed between the groups. (p=0.002, Figure 1) Comparisons within

Table 1. Demographic and characteristic features of the patients

Groups	Simple steatozis (n=7)	Borderline NASH (n=11)	NASH (n=12)	Control (n=21)	p
Age	47±14	45±15	45±12	37±10	NS
Gender (F/M)	5/2	6/5	5/7	13/8	NS
Hgb	14.3±1.4	14.1±1.6	13.7±1.2	13.9±1.3	NS
WBC	7787±2247	7654±3152	7670±1842	7392±1649	NS
Plt (x10^3)	236±63	258± 48	269±111	279±48	NS
AST	48±27	43±18	40±15	21±7	<0.001
ALT	62±42	52±24	46±17	25±13	<0.001
HOMA-IR	2.9±1.8	2.6±1.8	3.2±2.0	0.95±0.53	0.001
BMI	30±3	32±12	29±17	24±3	0.003
Waist circumference (cm)	99±22	99±12	104±17	86±12	0.035
FGL-2 (ng/ml)	43.6±12.3	46.1±9.7	51.2±13.5	37.6±19.3	0.012

Table 2. Histopathological findings in NAFLD patients

Steatoz	**n (%)**
0	1 (3.3)
1	15 (50)
2	9 (30)
3	5 (16.7)
NASH score	
1	1 (3.3)
2	4 (13.3)
3	2 (6.7)
4	6 (20)
5	5 (16.7)
6	5 (16.7)
7	6 (20)
8	1 (3.3)
Fibrozis Stage	
0	4 (13.3)
1	18 (60)
2	5 (16.7)
3	2 (6.6)
4	1 (3.3)

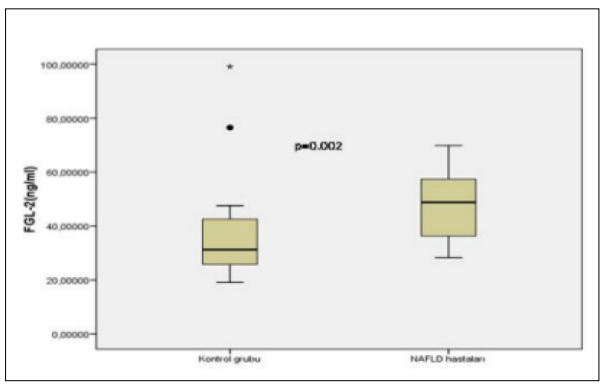

Figure 1. Mean FGL-2 (ng/ml) levels in NAFLD patients and the Control group.

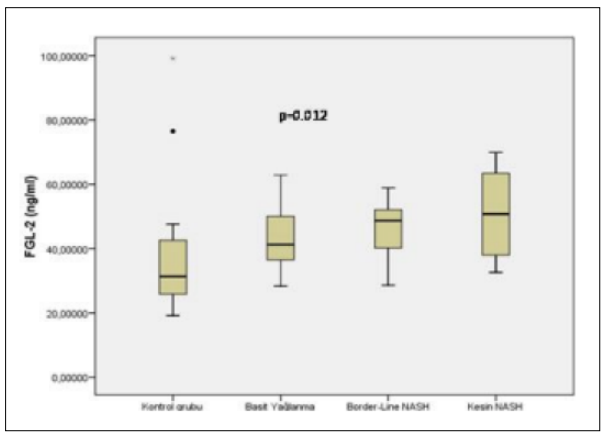

Figure 2. Mean FGL-2 (ng/ml) levels in subgroups of NAFLD patients and the Control group.

the four groups using the Kruskal-Wallis test also revealed significant differences. (p=0.012, Figure 2)

In the ROC analysis to evaluate the efficacy of patients' serum FGL-2 levels in predicting NAFLD, the AUC was determined to be 0.759, with p=0.002. It was observed that when FGL-2 levels were at 41 ng/ml, NAFLD patients could be predicted with a sensitivity of 67% and a specificity of 72%.

In the correlation analysis conducted on the patients, it was determined that FGL-2 was correlated with waist circumference (r=0.52, p=0.001), BMI (r=0.44, p=0.003), TG (r=0.37, p=0.016), and HOMA-IR (r=0.37, p=0.016).

DISCUSSION

The significance of FGL-2 in indicating chronic liver damage associated with viral hepatitis has been demonstrated in animal and human studies, particularly in patients with chronic hepatitis C.[17-22] In a study conducted by Foerster et al.,[22] it was observed that patients with chronic hepatitis C who had elevated serum FGL-2 levels exhibited more pronounced necroinflammatory activity and fibrosis. However, this study reported no association between serum FGL-2 levels and alcoholic-related chronic liver disease patients. In our cross-sectional case-control study, we compared the waist circumference, BMI, TG, HOMA-IR, and serum FGL-2 levels of patients diagnosed with NAFLD through biopsy to a control group. We aimed to elucidate the relationship between biopsy, FGL-2 levels, and the aforementioned metabolic parameters. In our study, where we aimed to determine the severity of NAFLD without a biopsy but solely based on FGL-2 measurements, we found that FGL-2 levels in NAFLD patients were significantly higher than in the control group. We also observed that FGL-2 levels correlated with waist circumference, BMI, TG, and HOMA-IR, independent of histological parameters.

In a study similar to ours, which comprehensively addressed the relationship between NASH and FGL-2, Çolak et al.[23] identified a significant difference between the NAFLD (borderline NASH + definite NASH) group and the control group in terms of FGL-2 levels. They determined that steatosis and the simple steatosis group did not correlate with FGL-2. Our study did not find a correlation between the degree of steatosis and FGL-2. (r=0.24, p=0.2) Additionally, when comparing the simple steatosis group with the control group, we did not find a significant difference in FGL-2 levels. (p=0.14) When the Borderline + Definite NASH group was collectively evaluated and compared with the control group, a significant difference was observed between the groups. (p=0.001) These findings suggest that FGL-2 levels may correlate with inflammation, like the previously demonstrated relationship with necroinflammation in chronic HCV rather than fibrosis.

The study conducted by Çolak and colleagues demonstrated that the predictive value of FGL-2 levels in forecasting NAFLD was high. Similarly, in our research,

we found that FGL-2 levels were effective in predicting NAFLD. (AUC=0.759, p=0.002)

Discussing the limitations of our study

Given the cross-sectional nature of our study, a long-term follow-up is necessary to discuss the relationship between histopathological findings and inflammation definitively. Moreover, our inability to show a correlation between transaminases and FGL-2 levels requires explanation. This situation might lead to an optimistic interpretation that FGL-2 levels could reflect the microinflammation level while suggesting that other confounding factors, such as medication, might not have been thoroughly evaluated.

When patients were divided into subgroups, the number of patients appeared marginal for a robust statistical analysis. A larger patient group is necessary for a reliable evaluation. The fact that all patients in our study group are of Turkish origin and belong to the same ethnic group could pose a disadvantage. Lastly, a noticeable deficiency is a lack of staining for FGL-2 in biopsy samples and the unexamined relationship between disease activity in the same preparation.

Conclusion

FGL-2 levels in NASH patients may reflect the balancing role of regulatory T cells and could indicate hepatic damage at the microinflammation level. Estimating disease severity, observing disease progression without biopsy, selecting patients for aggressive treatment approaches, and tightening follow-up intervals for cirrhosis and HCC could be significant. Moreover, we wish to emphasize in our study that FGL-2 could predict metabolic problems and potentially be a target in preventing metabolic liver diseases. For FGL-2 to become a non-invasive prognostic marker that obviates the need for a biopsy, comprehensive and long-term follow-up studies are needed in this field, along with standard measurements in both tissue and serum and transitioning to a cost-effective structure.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: D.I.; Design: D.I.; Supervision: D.I.; Fundings: D.I.; Materials: D.I.; Data: D.I.; Analysis: D.I.; Literature search: D.I.; Writing: D.I.; Critical revision: D.I.

Conflict of Interest

None declared.

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Nonalkolik Steatohepatitte Fibrinojen-Like Protein-2 (FGL-2) Düzeyinin Klinik Önemi

Amaç: Non-alkolik steatohepatit(NASH) karaciğerin en sık görülen metabolik hastalıklarından biridir. NASH hastalarında tanıdan sonraki on yıllık dönemde yaklaşık %25 oranında siroza gidiş izlenebilmektedir ve kriptojenik sirozun en sık nedeni olarak kabul edilmektedir. Fibrinojen like protein -2 (FGL-2), regülatuar T hücrelerince sekrete edilen fibrinojen süperfamilyasının bir alt üyesidir. Dendritik hücrelerin maturasyonunu engeller ve B hücrelerinin apoptozunu indükleyerek hem doğuştan hem de adaptif immunitenin regulasyonunda görev alır. Yüksek serum FGL-2 düzenin viral hepatitli hastalarda kötü prognostik gösterge olduğu yakın dönem çalışmalarda gösterilmiştir.

Gereç ve Yöntem: Çalışmaya biyopsi ile tanı konulan 30 NASH hastası ve kontrol koluna da 21 sağlıklı vaka dahil edildi. Her iki gruba dahil olan bireylerin serum FGL-2 düzeyleri karşılaştırıldı. Yine her iki gruba dahil edilen bireylerin klinikopatolojik özellikleri ile FGL-2 düzeyleri arasındaki ilişki incelendi.

Bulgular: Serum FGL-2 düzeyleri NASH hastalarında 47±12 ng/ml iken kontrol grubunda 37±10 ng/ml saptandı. İstatistiksel değerlendirme Mann-Whitney U testi ile yapıldı. Biyopsiyle basit yağlanma, border-line NASH, kesin NASH olarak sınıfladığımız hastalar ile kontrol grubu arasında anlamlı fark saptandı (p=0.002). Bu dört grubu kendi arasında değerlendirdiğimizde de aralarında anlamlı fark gördük (Kruskal – Wallis test, p=0.012).

Sonuç: Çalışmamızda NASH tanılı hastalarda biyopsideki steatohepatit ile uyumlu şekilde serum FGL-2 düzeylerini daha yüksek tespit ettik. Yüksek FGL-2 düzeyleri hepatik hasarı mikroinflamasyon düzeyinde iken gösterebilir. Hastalık şiddetinin tahmini, hastalık seyrinin biyopsisiz izlemi ve kontrolü, tedavi açısından agresif yaklaşılacak hastaların seçimi, siroz ve HCC takip aralıklarının sıklaştırılması açısından önemli olabilir. Yine de bu konuda yapılacak daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: FGL-2 düzeyi; nonalkolik steatohepatit; prognostik önem.

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Original Article

Relationship Between Blood Tests, CURB-65 Score and Prognosis in Pneumonia Patients

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Keywords: CRP albumin ratio; CURB-65 score; pneumonia; neutrophil lymphocyte ratio.

ABSTRACT

Objective: One of the most frequently used scoring systems routinely to determine whether pneumonia patients need inpatient treatment is the CURB-65 score. Recently, studies conducted with simple, cheap, and rapid blood tests such as hemogram and biochemistry parameters, which every clinician can easily interpret, have gained popularity. This study examined the relationship between blood tests requested in the emergency department (ED) and pneumonia severity and prognosis.

Methods: The study examined the files of patients who came to the ED with complaints of fever, cough, phlegm and fatigue between January 1 and December 31, 2017. Pneumonia severity according to thorax tomography and CURB-65 score at admission were evaluated. The patient's vital signs, hemogram, biochemistry and blood gas parameters were examined. It was compared with the ward they were admitted to and their 30-day prognosis.

Results: The files of 117 patients were examined. The age of the patients was significantly higher in the group with severe pneumonia than mild and moderate pneumonia groups. In the group with moderate and severe pneumonia, comorbidities were significantly higher than the mild pneumonia group. The rate of intensive care admission and ex in the group with severe pneumonia was significantly higher than in mild and moderate pneumonia groups. In the ex-group, the CURB-65 score, neutrophil-lymphocyte ratio (NLR), C-Reactive Protein (CRP)/Albumin and pneumonia severity were significantly higher than the other group.

Conclusion: NLR and CRP/Albumin ratios may be as effective as CURB-65 scoring in predicting 30-day mortality, and ED burden can be reduced with simple blood tests.

INTRODUCTION

Pneumonia is the leading cause of hospitalisation worldwide.[1] It causes the death of more than 4 million people every year.[2] Cough, sputum production, and chest pain may be seen in most patients. Still, findings such as increased oxygen demand, dyspnea, and impaired consciousness can be guiding in predicting the severity of pneumonia, and these rapidly developing symptoms may lead to emergency department admission.

Clinical findings are guiding for diagnosing pneumonia in the emergency department. Routine blood tests and lung imaging are usually ordered. Various scores can be used to estimate disease severity and prognosis, but this may be difficult to predict in patients with mild symptoms. In addition, different symptoms may develop in people with comorbidities and older age, and the clinician may move away from diagnosing pneumonia.

C-reactive protein (CRP) is an acute-phase protein synthesised in hepatocytes in response to pro-inflammatory cytokines during infectious processes.[3] The albumin concentration is negatively associated with the systemic inflammatory response due to increased catabolism and downregulation of hepatic synthesis by the cytokine tumour necrosis factor-alpha (TNF-α).[4] There is data in studies on hypoalbuminemia, which is associated with inflammation and nutritional status that negatively affects survival.[5] Also, in the literature, data show that the neutrophil-to-lymphocyte ratio (NLR) increases the severity of infection, and as this ratio increases, the risk of 30-day mortality increases.[6] Infectious processes can progress rapidly, like pneumonia. Such tests can speed diagnosis and reduce emergency room crowding.

One of the most frequently used scoring systems routinely to determine whether pneumonia patients need inpatient treatment is the CURB-65 score. It is a practical calcula-

tion method combining the patients' state of consciousness, examination findings, and tests. It may be difficult to predict the severity of pneumonia, the unit to be followed, and its prognosis in the emergency department. For this reason, we are investigating whether the tests taken and the scoring systems used effectively predict prognosis. Recently, studies conducted with simple, cheap, and rapid blood tests such as hemogram and biochemistry parameters, which every clinician can easily interpret, have gained popularity. This study examined the relationship between blood tests requested in the emergency department and pneumonia severity and prognosis.

MATERIALS AND METHODS

This study was approved by the Local Ethics Committee of the University (595/19.12.2017). The study examined the files of patients who came to the Emergency Department with complaints of fever, cough, phlegm, and fatigue between January 1 and December 31, 2017. Among these patients, patients over 18 who requested pulmonologist consultation and were diagnosed with pneumonia were included. Patients who had symptoms but were not diagnosed with pneumonia, who were diagnosed with pneumonia by chest radiography, who had an atypical image on thorax computer tomography (CT), or who did not have a pneumonic area were excluded from the study. CT images were classified according to the reports in the archive system. According to the Japanese Respiratory Society guideline, patients with symptoms of infection in less than ⅓ of both lungs are classified as mild, patients with infection in ⅓ or more of the lungs are classified as moderate, and patients with infection in ⅔ or more of the lungs are classified as severe.

Pneumonia severity at admission was evaluated according to the CURB-65 score. The patient's vital signs, hemogram, biochemistry, and blood gas parameters were examined. It was compared with the ward they were admitted to and their 30-day prognosis.

Statistical Method

Mean, standard deviation, median, lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov Test. ANOVA (Tukey Test), Kruskal-Wallis, and Mann-Whitney U tests were used to analyse quantitative independent data. Paired sam-

Table 1. Demographic characteristics of the patients

	Min-Max	Median	Mean±SD/n-%
Age	20.0-97.0	72	68.8±17.3
Gender			
Female			59-50.4%
Male			58-49.6%
Comorbidities			
(-)			64-54.7%
(+)			53-45.3%
Lung disease			15-12.8%
Cardiovascular			22-18.8%
Hypertension			19-16.2%
Neurological			11-9.4%
Endocrine			14-12.0%
Others			15-12.8%
Pneumonia severity			
Mild			77-65.8%
Moderate			24-20.5%
Severe			16-13.7%
Result in ED			
Discharged			77-65.8%
Transfer to service			24-20.5%
Transfer to ICU			15-12.8%
Exitus			1-0.9%
30-day results in the inpatient service			
Discharged			24-61.5%
Exitus			15-38.5%

SD: Standard Deviation; Others: HIV, Breast cancer, Hyperthyroidism, Benign Prostate Hyperplasia, Ulcerative Colitis, Psychiatric Disease; ED: Emergency Department; ICU: Intensive Care Unit.

ple T-test and Wilcoxon test were used to analyse dependent quantitative data. The Chi-Square Test was used to study qualitative independent data, and the Fischer Test was used when the conditions were not met. The effect level and cut-off were investigated with the ROC curve. The SPSS 28.0 program was used in the analyses.

RESULTS

When the files of 117 patients who met the study criteria were examined, the average age was 68.8±17.3, and 50.4% were female. 45.3% had comorbidities. Mild pneumonia was detected at the highest rate (65.8%), and most of them (65.8%) were discharged (Table 1).

In the group with severe pneumonia, the age of the patients was significantly ($p<0.05$) higher than in the groups with mild and moderate pneumonia severity. In the group with moderate and severe pneumonia severity, the presence of comorbidities was significantly ($p<0.05$) higher than in the group with mild pneumonia severity. The rate of cardiovascular disease and hypertension (HT) in the group with moderate and severe pneumonia severity was significantly ($p<0.05$) higher than in the group with mild pneumonia severity. In the group with severe pneumonia, mean arterial pressure, temperature, pulse, respiratory rate, and pneumonia severity were significantly ($p<0.05$) higher than in the groups with mild and moderate pneumonia (Table 2).

Table 2. Relationship between patients' comorbidities, examination, and pneumonia severity

	Pneumonia severity Mean±SD/n-%			
	Mild	**[1]Moderate**	**[2]Severe**	**p**
Age	65.5±18.5	70.0±11.2	83.3±10.0	0.000[K]
Gender				
Female	37-48.1%	10-41.7%	12-75%	0.092[x2]
Male	40-51.9%	14-58.3%	4-25%	
Comorbidities				
(-)	57-74%	2-8.3%	5-31.3%	0.000[x2]
(+)	20[1,2]-26%	22-91.7%	11-68.7%	
MAP	94.4±10.3	94.6±15.7	85.2±15.7	0.016[K]
Pulse	78.0±10.2	88.7±15.1	103.4±17.6	0.000[A]
Respiratory rate	17.5±2.4	22.1±4.5	31.6±6.5	0.000[K]
Temperature	37.3±0.6	37.9±0.8	37.9±0.3	0.000[K]

K: Kruskal-Wallis (Mann-Whitney U test); X^2: Chi-square test (Fischer test); A: ANOVA. [1]The difference with moderate group $p<0.05$; [2]The difference with severe group $p<0.05$. MAP: Mean arterial pressure.

Table 3. Relationship between patients' blood test and pneumonia severity

	Pneumonia severity Mean±SD/n-%			
	Mild	**Moderate**	**Severe**	**p**
Leukocyte ($x10^3$)	11.4±4.5	14.0±7.8	16.8±10.8	0.088[K]
Platelet ($x10^3$)	256.5±97.1	249.7±125.5	228.2±117.9	0.624[A]
Neutrophil ($x10^3$)	8.4±4.1	11.2±7.2	14.1±9.8	0.021[K]
Lymphocyte ($x10^3$)	2.04±1.24	1.60±1.11	1.70±1.68	0.018[K]
Creatinine	0.92±0.32	1.35±0.67	1.55±1.35	0.014[K]
AST	26.8±14.5	59.2±78.3	41.0±25.0	0.001[K]
ALT	21.4±21.0	40.8±49.3	22.8±19.4	0.007[K]
CRP/Albumin	20.4±24.5	60.9±53.6	50.2±34.3	0.000[K]
pH	7.40±0.04	7.42±0.05	7.36±0.14	0.055[K]
pCO_2	41.4±5.0	35.9±8.3	45.1±17.3	0.006[K]
SO_2	94.3±2.9	87.7±4.2	77.7±5.3	0.000[K]
Lactate	1.36±0.40	1.67±0.86	2.48±1.06	0.000[K]
HCO_3	25.0±1.9	23.2±3.6	24.5±6.5	0.012[K]

K: Kruskal-Wallis (Mann-Whitney U test); A: ANOVA; AST: Aspartate transaminase; ALT: Alanine transaminase.

The neutrophil count in the group with severe pneumonia was significantly ($p<0.05$) higher than in the groups with mild and moderate pneumonia severity. Aspartate aminotransferase (AST) in the group with moderate and severe pneumonia severity was significantly higher ($p<0.05$) than in the group with mild pneumonia severity. The CRP in the group with moderate and severe pneumonia severity was especially ($p<0.05$) higher than in the group with mild pneumonia severity. The CRP/Albumin in the group with moderate and severe pneumonia severity was significantly ($p<0.05$) higher than in the group with mild pneumonia severity. The lactate in the group with severe pneumonia was significantly ($p<0.05$) higher than in the groups with mild and moderate pneumonia severity (Table 3).

The discharge rate from the emergency department in the group with mild pneumonia severity was significantly ($p<0.05$) higher than in the groups with moderate and severe pneumonia severity. The rate of intensive care admission and death in the group with severe pneumonia was significantly ($p<0.05$) higher than in the groups with mild and moderate pneumonia severity (Table 4).

The CURB-65 score, NLR, CRP/Albumin, and pneumonia severity in the ex-group were significantly ($p<0.05$) higher than in the survivor group (Table 5).

The significant effectiveness of CRP/Albumin [area under the curve 0.736 (0.630-0.843)] was observed in distinguishing patients with mild and moderate-severe pneumonia. The significance of the CRP/Albumin 27 cut-off [area under the curve 0.740 (0.641-0.838)] was observed in distinguishing patients with mild pneumonia severity and moderate-severe pneumonia severity (Figure 1).

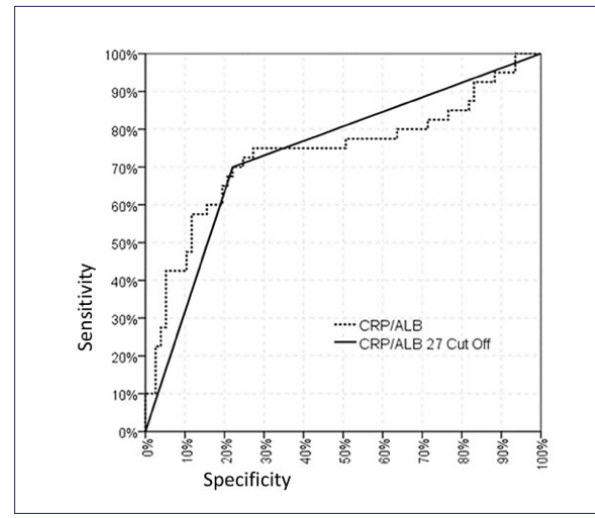

Figure 1. ROC analysis of CRP/Albumin ratio with pneumonia severity.

Table 4. Relationship between pneumonia severity and prognosis

	Pneumonia severity n-%			
	[1]Mild	[2]Moderate	[3]Severe	p
Result in the hospital				
Discharged	77[2,3]-100.0%	0-0%	0-0%	
Transfer to service	0-0%	24[1,3]-100%	0-0%	0.000[X²]
Transfer to ICU	0-0%	0-%0	15[1,2]-93.8%	
Exitus	0-0%	3[1]-12.5%	13[1,2]-81.3%	

[1]The difference with mild group $p<0.05$; [2]The difference with moderate group $p<0.05$; [3]The difference with severe group $p<0.05$; X^2: Chi-square test (Fischer test).

Table 5. Results predicting prognosis in ex and surviving groups

	Ex group Mean±SD/n-%	Survivor group Mean±SD/n-%	p
CURB-65 score	3.3±1.0	1.3±0.9	0.000[m]
NLR	12.3±7.9	6.3±5.4	0.001[m]
CRP/Albumin	74.0±49.6	26.3±31.1	0.000[m]
Pneumonia Severity			
Mild	0-0.0%	77-76.2%	0.000[X²]
Moderate	3-18.8%	21-20.8%	
Severe	13-81.3%	3-3.0%	

[m]: Mann-Whitney U test; X^2: Chi-square test (Fischer test).

DISCUSSION

This study determined that NLR and CRP/Albumin ratios could be as effective as CURB-65 scoring in predicting 30-day mortality. Considering that immunity decreases as we age, this may explain the high average age of the patients with severe pneumonia in this study.

Pneumonia severity is directly related to the rate of infected tissue detected in the lung. NLR has been the subject of many studies because it is a value that can be easily calculated with simple tests in each patient. It is already known that neutrophils increase first during infection, but studies have discovered that the increased neutrophil subset suppresses lymphocytes.[7] Therefore, it can be said that the infection burden or mortality rate of patients with high NLR rates has increased. In the study, this may be why the NLR value in the ex-group is higher than in the other group. The NLR value can be used in patients with chronic infections and frequent emergency visits because it is low-cost.[8]

A study by Li Jian et al.[9] showed that the NLR value increases with age, even in the healthy population. In this case, it can be predicted that the NLR level of the elderly group, which is a sensitive population, may change significantly even in a mild infection. Especially in the elderly population, the NLR value can be an alternative to scoring systems such as CURB-65 and can guide the service where the patient will be followed.

In studies, the presence of additional diseases increases the possibility of dying from pneumonia.[10] Similar findings were found in this study. Most of the patients had comorbidities, and pneumonia was severe. Consistent with the literature, the highest rates were cardiovascular diseases and hypertension.[11] Considering that comorbidities are more common in older age, it can be said that pneumonia has a fatal course in this age group.[12]

A study conducted by Ruot et al.[13] in rats found that the rate of albumin synthesis increased during infection, but its plasma concentration was low. They stated that the most important factor causing this may be the limited protein source due to nutrition during infection. This result may explain the high leukocyte, neutrophil, and CRP values and low albumin values in the moderate and severe pneumonia patient group.

Therefore, the CRP-albumin ratio in the mortal patient group was significantly higher than the other group. Additionally, in this group, vital signs liver and kidney function tests were observed to deteriorate more significantly than in the other group. Multiple organ failure develops due to intense infection, thus increasing mortality.

As a result, pneumonia can be fatal in elderly patients. Although many factors affect mortality, they can be predicted with simple tests.

Limitations

The main limitation of this study is that it is a retrospective study. The cause of infection in the development of pneumonia is not specified. Since the classification was planned radiologically, the outcome of the patient's hospitalisation may have varied depending on the factor. In addition, the duration of hospital stay and the type of treatment (such as steroids or the use of appropriate antibiotics according to culture results) were not examined. In this case, it is unclear whether patients additionally develop hospital-acquired pneumonia.

Ethics Committee Approval

This study approved by the Health Sciences University Haseki Research and Training Hospital Ethics Committee (Date: 19.12.2017, Decision No: 595).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: I.D., O.T.; Design: O.G.; Supervision: .O.S.; Fundings: I.D., O.T.; Materials: I.D., O.T., O.S.; Data: I.D., O.T., O.S.; Analysis: O.G.; Literature search: O.G.; Writing: I.D., O.G.; Critical revision: I.D.

Conflict of Interest

None declared.

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Pnömoni Hastalarında Kan Testleri, CURB-65 Skoru ve Prognoz Arasındaki İlişki

Amaç: Pnömoni hastalarının yatarak tedavi ihtiyacı olup olmadığını tespit etmek için rutinde en sık kullanılan skorlama sistemlerinden biri CURB-65 skorudur. Son dönemde her klinisyenin rahatça yorum yapabileceği hemogram ve biyokimya parametreleri gibi basit, ucuz ve hızlı kan testleri ile yapılan çalışmalar popülerlik kazanmıştır. Bu çalışmada, acil serviste istenen kan testleri ile pnömoni şiddeti ve prognoz arasındaki ilişki incelendi.

Gereç ve Yöntem: Çalışmada; 1 Ocak-31 Aralık 2017 tarihinde acil servise ateş, öksürük, balgam, halsizlik şikayeti ile gelen hastaların dosyaları incelendi. Toraks tomografisine göre pnömoni şiddeti ve başvuru anındaki CURB-65 skoru değerlendirildi. Hastaların vital bulguları, hemogram, biyokimya ve kan gazı parametreleri incelendi. Hastaların yattığı servis ve 30 günlük prognozu ile kıyaslandı.

Bulgular: 117 hastanın dosyası incelendi. Hastaların yaşı, pnömoni şiddeti ağır olan grupta, pnömoni şiddeti hafif ve orta olan gruplardan anlamlı olarak daha yüksekti ($p<0.05$). Pnömoni şiddeti orta ve ağır olan grupta, ek hastalık varlığı, pnömoni şiddeti hafif olan gruptan anlamlı olarak daha yüksekti ($p<0.05$). Pnömoni şiddeti ağır olan grupta yoğun bakım yatış ve ölüm oranı, pnömoni şiddeti hafif ve orta olan gruplardan anlamlı olarak daha yüksekti ($p<0.05$). Hayatını kaybeden hastaların grubunda CURB-65 skoru, nötrofil-lenfosit oranı (NLR), C-Reaktif Protein (CRP)/Albumin değeri ve pnömoni şiddeti diğer gruptan anlamlı olarak daha yüksekti ($p<0.05$).

Sonuç: NLR ve CRP/Albumin oranları, 30 günlük mortaliteyi öngörmede CURB-65 skorlaması kadar etkili olabilir, basit kan testleri ile acil servis kalabalıklığı azaltılabilir.

Anahtar Sözcükler: CRP albümin oranı; CURB-65 Skoru; nötrofil lenfosit oranı; pnömoni.

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Original Article

Comparison of Obstetric Outcomes in Patients with Intrahepatic Cholestasis of Pregnancy Between Pregnancies Following *In Vitro* Fertilization and Spontaneous Conception: Four-Year Experience in a Tertiary Care Hospital

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Keywords: Intrahepatic cholestasis of pregnancy; in-vitro fertilization; perinatal management; perinatal outcomes; total fasting bile acids.

ABSTRACT

Objective: Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-specific liver disease, associated with a 4 to 10-fold increased risk of stillbirth if appropriate interventions are not taken. The aim of the study was to compare the obstetric outcomes of singleton pregnancies with ICP in which pregnancies were achieved spontaneously and by *in vitro* fertilization (IVF).

Methods: Women who gave birth between January 2018 and September 2022 were evaluated retrospectively. After applying the inclusion criteria, a total of 91 patients with ICP were eligible, consisting of spontaneously conceived (group 1, n=74) and IVF-conceived (group 2, n=17) pregnancies. The participants in group 2 were classified into two subgroups: fresh embryo transfer (n=9) and frozen embryo transfer (n=8), depending on the method of embryo transfer.

Results: Perinatal outcomes and demographic characteristics, with the exception of age, gravidity, and parity, were similar. While age was significantly higher in group 2 [32 (27-35) vs. 27 (24-31), p=0.017], gravidity and parity were significantly higher in group 1 [2 (1-3) vs. 1 (1-2), p=0.021 and 0 (0-1) vs. 0 (0-0), p=0.009]. Aspartate (AST) and alanine (ALT) transaminase levels, fasting total bile acid (FTBA) level, and treatment dose of ursodeoxycholic acid were significantly higher in the frozen embryo transfer group than in the fresh embryo transfer group [126 (83-242) vs. 32 (31-43), p=0.001; 200±123.9 vs. 51±39.4, 0.001; 44±20.4 vs. 15±5.0, p=0.001, and 100 (750-1250) vs. 750 (750-750), p=0.004].

Conclusion: Our results suggest that there is an association between high FTBA, ALT, and AST levels due to estrogen treatment in IVF pregnancies, especially when the frozen embryo transfer method was used.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most prevalent pregnancy-related liver disease, characterized by high serum bile acid concentrations and varying degrees of itching, ranging from mild to intolerable.[1,2] The disease usually occurs in late pregnancy and recovers dramatically within a week after birth. The disease occurs with varying frequency in different parts of the world, with the lowest incidence (0.8%) in the USA and the highest incidence (27.6%) among the Araucanos Indians in Chile.[3,4] Although the reasons for the large variation in incidence are not fully understood, the disease is thought to be influenced by geographical and regional differences, variations in genetic vulnerability of ethnic groups, and differences in environmental components, as it is more common in certain regions with intense winters.[5-7] On the other hand, the diagnosis may be overlooked, and the true incidence not determined, especially in cases where the symptoms occurred shortly before delivery and there was insufficient time for serum bile acids to rise.[8]

In addition to geographical, genetic, ethnic, and environmental risk factors, hormonal factors also appear to play an important role in the pathogenesis, as ICP occurs more frequently in conditions with increased estrogen production, such as twin pregnancies and pregnancies with ovarian hyperstimulation.[9-11] The rapid regression of the disease after the birth of the placenta, which is the main source of pregnancy hormones, again points to the effect of estrogen, while there is still no clear evidence for the effect of progesterone.[11] Recent research has identified ICP-specific mutations of genes such as the multidrug resistance protein 3 (Mrp3) gene, which encodes transport proteins involved in canalicular bile secretion.[12,13] The risk for the occurrence of cholestasis increases with age, parity, presence of underlying chronic liver disease, and family and personal history of ICP.[5,14-16] The exact trigger of ICP is unclear and the etiology is also multifactorial. It is therefore a diagnosis of exclusion, which is only made after dermatological diseases with pruritus, and liver and biliary tract diseases have been ruled out. Although there are no specific skin lesions characteristic of ICP, scratch marks, excoriations, and prurigo nodules caused by intense scratching may occur.

In recent years, due to various factors such as financial security, career priority, and lack of emotional and psychological preparation, women tend to postpone the decision to become pregnant until an older age when their reproductive capacity declines. Accordingly, the number of pregnancies conceived using assisted reproductive techniques, including IVF, and the associated complications are increasing. Therefore, the management of high-risk conditions such as ICP, which are more common in this pregnancy population, must be well understood.

As there are few studies comparing ICP in spontaneous and IVF pregnancies, we aimed to examine and compare such patients to investigate the possible association between exogenous estrogen exposure and the development of ICP or the severity of ICP in some IVF pregnancies.

MATERIALS AND METHODS

Study Design

We conducted a retrospective cohort study of singleton pregnancies with ICP between January 1, 2018, and September 1, 2022, in the perinatology clinic of a large tertiary referral hospital. After obtaining ethical approval (date: 24.10.2022, decision no.: 14/08), the data were collected by reviewing the medical records. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. As this was a retrospective study and not all participants could be contacted, it was not possible to obtain written informed consent. The Ethics Committee, therefore, waived informed consent for participation and publication.

Characteristics of Study Population

Pregnant women with multiple fetuses, congenital fetal malformations and genetic abnormalities, diseases such as choledocholithiasis and pancreatitis leading to extrahepatic biliary tract obstruction, liver diseases with damage to the liver parenchyma, hemolysis, elevated liver enzymes, low platelet syndrome, acute fatty liver of pregnancy, women taking medications that may alter liver function, and patients with missing data were excluded. Patients with a history of ICP were also not included in the study.

Imaging Methods, Laboratory Measurements and Definitions

Fetal biometry and other sonographic examinations were performed with the GE Voluson 730 Ultrasound System (General Electric Medical Systems, Milwaukee, WI, USA), using a 4-8 MHz transabdominal probe and a 5-9 MHz transvaginal probe when more detail was required. Gestational age was calculated from the first day of the last menstrual period (LMP) and confirmed by sonographic dating. If the two calculations differed by ≤7 days, the calculation based on LMP was used.

Blood samples for biochemical parameters and viral serology were collected in tubes containing a separating gel and analyzed in a Roche Cobas e801 chemiluminescence immunoassay analyzer (Roche Diagnostics International Limited, Rotkreuz, Switzerland). For the determination of fasting total bile acids (FTBA) in serum, blood samples of at least 2 mL were collected in tubes containing a separating gel and analyzed using an enzymatic method (3alpha-hydroxysteroid dehydrogenase) after 8 hours of fasting. After excluding other pruritic disorders and hepatobiliary diseases in the differential diagnosis, ICP was diagnosed by the presence of generalized pruritus, predominantly on the palms and soles, without specific skin lesions typical of dermatological diseases, together with elevated serum FTBA levels (>10 μmol/L).[17] After confirmation of the diagnosis, all patients were treated perorally with a dose of

10-15 mg/kg/day of ursodeoxycholic acid. The total dose was divided into two or three doses per day with peroral capsules containing 250 mg ursodeoxycholic acid. After the initiation of treatment, regular follow-up examinations were carried out to assess fetal well-being. To evaluate the treatment, aspartate transaminase (AST), alanine transaminase (ALT), and FTBA were retested, and the intensity of pruritus was questioned.

Data Collection

Demographic data, including body mass index (BMI), age, gravidity, parity, miscarriage, and sonographic fetal biometry, gestational age at diagnosis; laboratory measurements, including FTBA levels, anti-hepatitis C antibody, and hepatitis B surface antigen, and antenatal, perinatal, and neonatal characteristics were obtained from the hospital database and patient records.

Statistical Analysis

Statistical analyses were carried out with R Statistical Software Version 2021.09.4+403.pro3 (R Foundation for Statistical Computing, Vienna, Austria). Variables were analyzed using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to investigate whether they were normally distributed or not. Levene's test was applied in order to assess the variance homogeneity. Descriptive analyses for normally distributed variables were presented using standard deviations and mean values. These parameters were compared between the groups using the t-test for independent samples. Descriptive analyses for the non-normally distributed numerical data were presented using medians, first and third quartiles. These parameters were compared between the groups using Mann-Whitney U-tests. Descriptive analyses for the categorical variables were performed using percentage and frequency. The chi-square test or Fisher's exact test (when the assumptions of the chi-square test did not hold due to low expected cell counts) were used to analyze the correspondences between categorical variables. The correlation coefficients and their significance were calculated using the Pearson test if the parameters had a normal distribution. When analyzing associations between non-normally distributed parameters, the Spearman test was used to calculate the correlation coefficients and their significance. A p-value of less than 0.05 was considered a statistically significant result.

RESULTS

In the period of almost 4 years covered by the study, there were 38,127 births, of which 116 (3.3%) were diagnosed with ICP. After applying inclusion criteria, a total of 91 patients with ICP were eligible, consisting of spontaneously conceived (Group 1, n=74) and IVF-conceived (Group 2, n=17) pregnancies. Group 2 was divided into two groups: fresh embryo transfer (n=9) and frozen embryo transfer (n=8), depending on the embryo transfer method used (Figure 1). Demographic characteristics such as BMI, number of previous miscarriages, gestational age at diagnosis (GAD), number of patients complaining of pruritus, laboratory tests such as AST, ALT, FTBA, the minimum dose of ursodeoxycholic acid (UDCA) to relieve symptoms, and birth characteristics such as delivery mode, gestational age at birth, birthweight, neonatal gender, appearance, pulse, grimace, activity, respiration scores at the first and fifth minute (APGAR 1 and 5) did not differ between the two groups, while age was significantly higher in Group 2 [32 (27-35) vs. 27 (24-31), p=0.017] and gravidity and parity were significantly higher in Group 1 [2 (1-3) vs. 1 (1-2), p=0.021 and 0 (0-1) vs. 0 (0-0), p=0.009] (Table 1).

A comparison of the clinical features of the participants

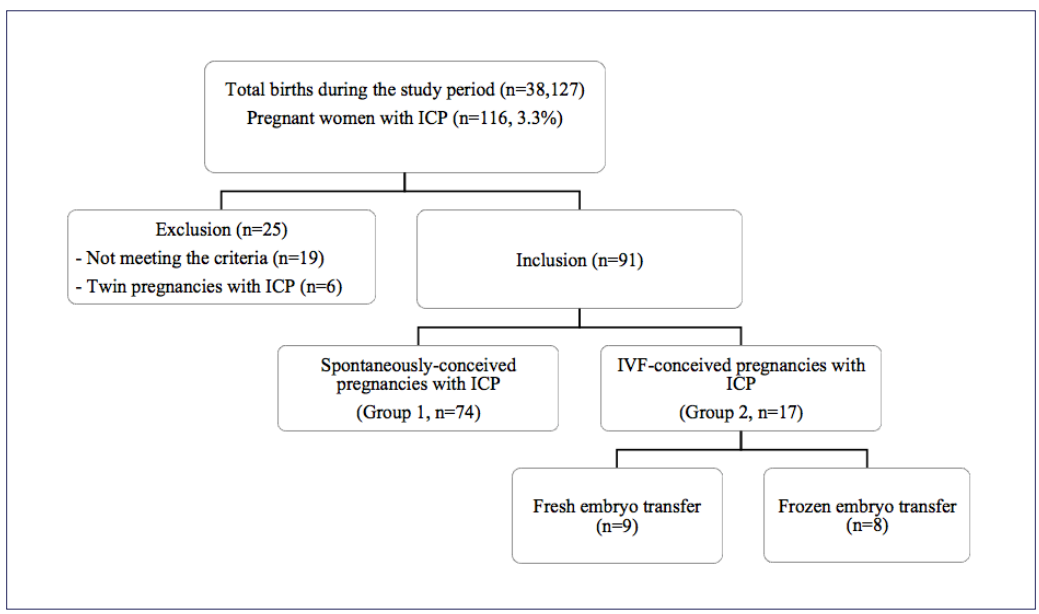

Figure 1. Flow chart of the study.

Table 1. Comparison of demographic and birth characteristics of women with ICP by type of fertilization

Variable	Group 1 (n=74)	Group 2 (n=17)	Total (n=91)	p
Age (years)	27 (24-31)	32 (27-35)	28 (24-32)	**0.017**
BMI (kg/m^2)	27 (24-30)	25 (21-27)	26 (23-30)	0.067
Gravida (number)	2 (1-3)	1 (1-2)	1 (1-3)	**0.021**
Parity (number)	0 (0-1)	0 (0-0)	0 (0-1)	**0.009**
Miscarriage (number)	0 (0-1)	0 (0-0)	0 (0-0)	0.435
Gestational age at diagnosis (weeks)	34 (32-35)	34 (32-35)	34 (32-35)	0.758
AST level at diagnosis (IU/L)	67 (41-101)	45 (32-126)	59 (38-103)	0.661
ALT level at diagnosis (IU/L)	80 (47-164)	81 (31-194)	81 (44-167)	0.831
Fasting total bile acids (μmol/L)	16 (11-32)	20 (13-45)	16 (11-35)	0.341
Patients with pruritus (number)	55 (74.3)	16 (94.1)	71 (78.0)	0.106
Ursodeoxycholic acid (mg/day)	750 (750-750)	750 (750-1000)	750 (750-750)	0.249
Mode of Delivery				
Vaginal (number)	31 (41.9)	6 (35.3)	37 (40.7)	0.821
Cesarean (number)	43 (58.1)	11 (64.7)	48 (59.3)	
Gestational age at birth (weeks)	37 (36-37)	37 (36-37)	37 (36-37)	0.888
Birthweight (grams)	2917 (2658-3297)	2870 (2745-3579)	2910 (2680-3360)	0.222
Neonatal gender				
Male (number)	34 (45.9)	7 (41.2)	41 (45.1)	0.724
Female (number)	40 (54.1)	10 (58.8)	50 (54.9)	
APGAR 1 (scores)	9 (9-9)	9 (9-9)	9 (9-9)	0.847
APGAR 5 (scores)	10 (10-10)	10 (10-10)	10 (10-10)	0.593

ALT: Alanine aminotransferase; APGAR: Appearance, pulse, grimace, activity and respiration; AST: Aspartate transaminase; BMI: Body-mass index; GAD: Gestational age at diagnosis; ICP: Intrahepatic cholestasis of pregnancy; IU/L: International units per liter; IVF: *In-vitro* fertilization; Kg/m^2: Kilograms per square meter; μmol/L: Micromole per liter. Data are presented as median (quartile 1-quartile) or number (percentage) where applicable. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

with ICP in whom the pregnancy was conceived by IVF is shown in Table 2. AST, ALT, FTBA, and the treatment dose of UDCA were significantly higher in the frozen embryo transfer group than in the fresh embryo transfer group [126 (83-242) vs. 32 (31-43), p=0.001; 200±123.9 vs. 51±39.4, p=0.001; 44±20.4 vs. 15±5.0, p=0.001, and 1000 (750-1250) vs. 750 (750-750), p=0.004, respectively].

In all pregnant women diagnosed with ICP, there was a statistically significant positive correlation between FTBA and AST (r=0.388, p<0.001), ALT (r=0.343, p=0.002), and treatment dose of UDCA (r=0.262, p=0.024), while gestational age at diagnosis showed a negative correlation with FTBA (r=-0.262, p=0.036). There were lack of correlations found between age and FTBA both in Group 2 and in overall pregnancies with ICP (p<0.05). In IVF pregnancies with ICP, there was a statistically significant positive correlation between FTBA and AST (r=0.692, p=0.004) and treatment dose of UDCA (r=0.646, p=0.005), while there was no correlation between FTBA and AST and GAD (Table 3).

Symptoms and/or laboratory findings associated with ICP resolved in all patients within one week of delivery. There were no maternal deaths or near misses, while only one stillbirth occurred in Group 1. Ten patients developed preeclampsia [7 (9.5%) in Group 1 and 2 (11.8%) in Group 2].

DISCUSSION

Intrahepatic cholestasis of pregnancy is a serious condition associated with perinatal morbidity and mortality and carries a 4 to 10-fold increased risk of stillbirth if appropriate interventions are not taken.[3] The pathophysiology of stillbirth in women with ICP is not clearly understood, but it is assumed that elevated maternal serum FTBA levels, which are cardiotoxic to the fetus, are responsible.[18] To date, there is no universally accepted method for the diagnosis, management, and treatment of ICP. On the other hand, there is only a consensus that total bile acid levels are closely related to perinatal outcome. The risk of fetal death increases in particular with FTBA values of 100 μmol/L and above. On this basis, the decision on the timing of delivery is made depending on the initial FTBA values. At our clinic, we follow the recommendations of the Royal College of Obstetricians and Gynecologists' guideline for women with ICP, which recommends a planned delivery at 40, 38 to 39, and 35 to 36 weeks' gestation for peak bile acid levels <40 μmol/L, 40-99 μmol/L, and ≥100 μmol/L respectively.[19] On the other hand, the rate of induced preterm births in women with ICP has increased due to fetal and/or maternal concerns. In addition, rates of spontaneous preterm birth have also increased for various reasons, including the effect of increased bile acids inducing the expression of myometrial oxytocin receptors.[2]

Table 2. Comparison of ICP pregnancies conceived by IVP according to the embryo transfer method used

Variable	Fresh Embryo Transfer (n=9)	Frozen Embryo Transfer (n=8)	p
Age (years)	32±4.1	29±4.6	0.198
BMI (kg/m^2)	26.9±5.51	22.4±2.50	0.051
Gravida (number)	1 (1-2)	1 (1-1)	0.277
Parity (number)	0 (0-1)	0 (0-0)	0.481
Miscarriage (number)	0 (0-1)	0 (0-0)	0.743
Gestational age at diagnosis (weeks)	34±2	34±1	0.960
AST level at diagnosis (IU/L)	32 (31-43)	126 (83-242)	**0.001**
ALT level at diagnosis (IU/L)	51±39.4	200±123.9	**0.004**
Fasting total bile acids (μmol/L)	15±5.0	44±20.4	**0.001**
Patients with pruritus (number)	8 (88.9)	8 (100)	1.000
Ursodeoxycholic acid (mg/day)	750 (750-750)	1000 (750-1250)	**0.004**
Mode of Delivery			
Vaginal (number)	2 (22.2)	4 (50.0)	
Cesarean (number)	7 (77.8)	4 (50.0)	0.335
Gestational age at birth (weeks)	35 (35-37)	37 (36-37)	0.963
Birthweight (grams)	3036±461.9	3251±501.9	0.373
Neonatal gender			
Male (number)	5 (55.6)	2 (24.5)	
Female (number)	4 (44.4)	6 (75.1)	0.335
APGAR 1 (scores)	9 (7-9)	9 (9-9)	0.481
APGAR 5 (scores)	10 (9-10)	10 (10-10)	0.481

ALT: Alanine aminotransferase; APGAR: Appearance, pulse, grimace, activity and respiration; AST: Aspartate transaminase; BMI: Body-mass index; ICP: Intrahepatic cholestasis of pregnancy; IU/L: International units per liter; IVF: In-vitro fertilization; Kg/m^2: Kilograms per square meter; μmol/L: Micromole per liter. Data are presented as median (quartile 1-quartile 3), mean±standard deviation or number (percentage) where applicable. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

Table 3. Correlation of FTBA levels with various parameters in women with ICP

	All pregnancies with ICP					IVF-conceived pregnancies with ICP				
	Age	AST	ALT	UDCA	GAD	Age	AST	ALT	UDCA	GAD
FTBA										
r	-0.140	0.388	0.343	0.262	-0.235	0.050	0.692	0.426	0.646	-0.306
p	0.215	**<0.001**	**0.002**	**0.024**	**0.036**	0.850	**0.004**	0.088	**0.005**	0.233

ALT: Alanine aminotransferase; AST: Aspartate transaminase; FTBA: Fasting total bile acid; GAD: Gestational age at diagnosis; ICP: Intrahepatic cholestasis of pregnancy; IVF: *In-vitro* fertilization; UDCA: Ursodeoxycholic acid. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

Luteal phase support with exogenous progesterone, gonadotropin-releasing hormone agonists, or human chorionic gonadotropin is a known intervention for almost all IVF cycles, whereas exogenous estrogen support is not initiated in all IVF cycles. Since estrogen exposure plays an important role in the pathogenesis of ICP and estrogen support to prepare the endometrium for implantation is a common treatment application, we conducted this study comparing spontaneously conceived and IVF-conceived women with ICP, taking into account whether fresh or frozen embryo transfer methods were used. As far as we know, this study is the first to compare women with ICP conceived by IVF according to the type of embryo transfer. According to the results of our study, although FTBA and transaminase levels did not differ by fertilization method, when patients in the IVF group were compared by embryo transfer method, FTBA and transaminase levels were significantly higher in the frozen ET group than in the fresh ET group. Therefore, the severity of ICP appears to be closely related to the effect of exogenous estrogen on the liver, which is used during the endometrial preparation period for implantation and sometimes even up to 12 weeks of pregnancy in patients undergoing frozen embryo transfer.

In a study by Bolukbas et al.[20] although the number of

women with a history of ICP, a strong risk factor for recurrence of ICP, was significantly higher in the spontaneous pregnancy group, serum FTBA levels were significantly higher in the IVF pregnancy group. In our study, however, we did not find a similar result but observed a significant difference in FTBA values depending on the embryo transfer method in the IVF group. Serum FTBA levels were significantly higher in the frozen embryo transfer group, as were AST and ALT levels. In addition, FTBA levels were inversely correlated with gestational age at diagnosis. On the other hand, it is noteworthy in the study by Bolukbas et al.[20] that there were multiple pregnancies in both groups, but the rate of multiple pregnancies was significantly higher in the IVF group. A study by Batsry et al.[16] which investigated the perinatal outcomes of ICP in twin pregnancies versus singleton pregnancies, also found that FTBA levels were significantly higher in twin pregnancies. In another study comparing spontaneous twin pregnancies with ICP with IVF twin pregnancies with ICP, there was also no significant difference in FTBA levels.[21] Therefore, significantly high FTBA serum levels are more likely associated with consecutive multiple pregnancies rather than with IVF itself. In the study by Bolukbas et al.[20] in addition to the high number of multifetal pregnancies, the hormone treatments used in the IVF cycles also explain the high FTBA values in the IVF pregnancy group. We believe that the results of our study will be more accurate as there were no multiple pregnancies in the study groups. On the other hand, in the same study, there were no differences between the groups in terms of family history of ICP. In our study, maternal and perinatal outcomes were similar in both groups and no difference was found between the spontaneous and IVF pregnancy groups in terms of preterm birth. In the study by Bolukbas et al.[20] the rates of spontaneous preterm birth were higher in the IVF group, which is closely related to the high number of multifetal pregnancies in the same group.

Our study has limitations, mainly because of its retrospective nature and relatively small sample size. Besides, it was not possible to collect data on the duration and dosage of estrogen exposure in all patients who underwent frozen embryo transfer. However, as multiple pregnancies, which are an important risk factor for ICP, were not included, the effect of estrogen treatment on ICP could be analyzed more precisely. Despite the retrospective nature of the study, the study was conducted in a large tertiary referral hospital where the same algorithms for diagnosis, treatment, and follow-up were applied, which was a major strength.

Conclusion

In conclusion, our results show that there is an association between high FTBA, ALT, and AST levels due to estrogen treatment in IVF pregnancies, especially when the frozen embryo transfer method was used. This is a comprehensive investigation that can serve as a basis for future research. If the results are supported by multicenter, prospective, randomized controlled studies, they can serve as a guideline for the clinical use of estrogen in such pregnancies.

Ethics Committee Approval

This study approved by the Ankara Etlik Zübeyde Hanım Maternity Training And Research Hospital Ethics Committee (Date: 24.10.2022, Decision No: 14/08).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.L.D., A.K.Ö.; Design: E.M., P.Y., S.Ö.; Supervision: E.M., P.Y., Y.E.Ü.; Materials: Y.A., Ö.K., F.B.F.; Data: E.M., S.Ö., F.B.F.; Analysis: P.Y., M.L.D., A.K.Ö., S.T.S.; Literature search: M.L.D., P.Y., S.T.S., A.K.Ö; Writing: M.L.D.; Critical revision: E.M., P.Y., Y.E.Ü.

Conflict of Interest

None declared.

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In Vitro Fertilizasyon ve Spontan Gebelikler Arasından İntrahepatik Gebelik Kolestazı Gelişen Hastaların Obstetrik Sonuçlarının Karşılaştırılması: Üçüncü Basamak Bir Hastanede Dört Yıllık Deneyim

Amaç: Gebeliğin intrahepatik kolestaz (GİK), uygun müdahaleler yapılmazsa ölü doğum riskinin 4 ila 10 kat artmasıyla ilişkili, gebeliğe özgü en yaygın karaciğer hastalığıdır. Çalışmanın amacı, spontan ve *in vitro* fertilizasyon (IVF) ile elde edilen gebelikler arasında GİK gelişen tekil gebeliklerin obstetrik sonuçlarını karşılaştırmaktır.

Gereç ve Yöntem: Ocak 2018 ile Eylül 2022 tarihleri arasında doğum yapan kadınlar geriye dönük olarak değerlendirildi. Dahil etme kriterleri uygulandıktan sonra, spontan olarak gebe kalan (grup 1, n=74) ve IVF ile gebe kalan (grup 2, n=17) toplam 91 GİK'li hasta çalışmaya uygun bulundu. Grup 2'deki hastalar embriyo transfer yöntemine göre taze embriyo transferi (n=9) ve dondurulmuş embriyo transferi (n=8) olmak üzere iki alt gruba ayrıldı.

Bulgular: Yaş, gravidite ve parite dışındaki perinatal sonuçlar ve demografik özellikler benzerdi. Grup 2'de yaş anlamlı derecede yüksek iken [32 (27-35) vs. 27 (24-31), p=0,017], gravidite ve parite grup 1'de anlamlı olarak yüksekti [2 (1-3) vs. 1 (1-2), p=0.021 and 0 (0-1) vs. 0 (0-0), p=0.009]. Aspartat (AST) ve alanin (ALT) transaminaz seviyeleri, total açlık safra asit (TASA) düzeyleri ve ursodeoksikolik asit tedavi dozu, dondurulmuş embriyo transfer grubunda taze embriyo transfer grubuna göre anlamlı derecede yüksekti [126 (83-242)'ya karşı 32 (31-43), p=0.001; 200±123.9'a karşı 51±39.4, 0.001; 44±20.4'e karşı 15±5.0, p=0.001, and 100 (750-1250)'e karşı 750 (750-750), p=0.004].

Sonuç: Sonuçlarımız, özellikle donmuş embriyo transfer yönteminin kullanıldığı IVF gebeliklerinde östrojen tedavisine bağlı olarak yüksek TASA, ALT ve AST düzeyleri arasında bir ilişki olduğunu göstermektedir. Eksojen östrojenin etkisini netleştirmek için geniş örneklemli prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Gebeliğin intrahepatik kolestazı; perinatal sonuçlar; perinatal yönetim; total açlık safra asidi; tüp bebek.

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Original Article

The Effects of Obesity on Cognitive Functions in Adolescents

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Keywords: Adolescent; cognitive functions; obesity.

ABSTRACT

Objective: Obesity continues to be an important problem in childhood as well as in adults worldwide. It is known that obesity experienced in childhood has effects on emotional development besides physical effects. In this study, it was aimed to investigate the effects of obesity on cognitive functions in adolescents, which is the most important step of the transition to adulthood.

Methods: Obese and non-obese adolescents with no other known health problems were included in the study. In order to evaluate cognitive functions in obese patients and the control group, tests evaluating auditory and visual memory and attention were applied.

Results: As a result of the assessments made, a statistically significant difference was found in terms of visual memory scores and verbal fluency total and sub-dimension total mean scores. No statistically significant difference in terms of WISC-R verbal, performance, and total score means applied to the participants was found.

Conclusion: In our study, it was observed that obesity may adversely affect cognitive functions in childhood in some areas. It may be necessary to determine the factors that negatively affect cognitive functions in obese children and to take supportive interventions and measures.

INTRODUCTION

Nutrition is among the most vital aspects of lifelong habits that significantly affect the holistic health of a person. Nutrition is an important social phenomenon for emotional satisfaction as well as physical development.[1] However, socio-economic and cultural conditions of the social or familial structure, genetic structure, food production and consumption methods, cognitive and behavioral characteristics play an important role in child nutrition. Nowadays, childhood malnutrition and obesity are among the most common chronic health problems of childhood. In the report published by WHO, in 2016, overweight or obesity impacted nearly 340 million children between the ages of 5 and 19. Less than 1% of children between the ages of 5 and 19 were obese in 1975; by 2016, this number had increased to more than 124 million. Obesity affects all developed and developing countries.[2] It is known that childhood obesity, which is difficult to detect in childhood, is due to genetic and environmental factors. In studies, it was determined that the fat ratio in children was similar to the fat ratio of their families, and the probability of the children of obese people being obese was 2-3 times higher than that of non-obese children. A family's diet, eating habits, socio-economic level, and education level are among the other factors affecting obesity.[1-3]

There are two important reasons for childhood obesity

due to its effects on physical and emotional development. The first reason is that childhood obesity can lead to many metabolic and chronic diseases. Secondly, the psychological problems that have the potential to arise due to social reasons, especially the bullying that these children are exposed to by their peers, cause them to experience problems of lack of self-confidence and adaptation to the environment in the future.[4] There are studies showing that childhood obesity has negative effects on school success.[5] Poor school performance appears to occur, in part, as a result of reduced cognitive abilities. In addition, it is stated that excessive fat deposition accompanies learning and memory problems.[6] In another study on this subject, it was found that overweight/obese male students had lower reading skills and math scores compared to normal-weight students; however, there was no difference in reading skills and math scores of obese female students compared to normal-weight female students.[7]

This study focused on examining the impact of obesity on cognitive functions in adolescents, a critical phase that represents the most significant step towards adulthood.

MATERIALS AND METHODS

The study was conducted as a single-center, prospective study with voluntary participants, whose parents provided written consent. Those with genetic and metabolic diseases, mental retardation and pre-existing cognitive dysfunction, comorbid chronic disease, attention deficit hyperactivity disorder, learning disability, tic disorder, and autism that may affect neuropsychological test performance, diagnosed by a child psychiatrist with a DSM-5-based semi-structured interview, were excluded from the study. The volunteer group included in the study was clas-

Table 1. Comparison of socio-demographic and the characteristics of the time they started reading and writing among voluntary participant groups

	Volunteer Participant Socio-Demographical and the Time to Start Reading-Writing Distribution					
	Study (case) Group (n=35)		Control Group (n=34)			
	Number (n)	Percentage* (%)	Number (n)	Percentage* (%)	X^2	p**
Gender						
Female	16	45.7	14	41.2	0.1	0.7
Male	19	54.3	20	58.8		
Mother's educational status						
Middle school or lower	24	68.6	18	52.9	1.8	0.18
High school and above	11	31.4	16	47.1		
Father's educational status						
Middle school or lower	22	62.9	18	52.9	0.7	0.4
High school and above	13	37.1	16	47.1		
Mother's employment status						
Unemployed	25	71.4	22	64.7	0.4	0.55
Employed	10	28.6	12	35.3		
Income status						
***Hunger level and lower	3	8.6	15	44.1		
***Between hunger and poverty level	23	65.7	15	44.1	11.6	<0.01
***Poverty level and above	9	25.7	4	11.8		
Parent relationship						
Together	35	100	24	70.6	12	<0.01
Separate	-	-	10	29.4		
Kinship status						
None	24	68.6	30	88.2	3.9	0.048
Yes	11	31.4	4	11.8		
Family type						
Nuclear family	5	14.3	34	100	51.6	<0.01
Extended family	30	85.7	-	-		
Literacy						
1st year 1st semester	16	45.7	32	94.1	19.1	<0.01
1st year 2nd semester	19	54.3	2	5.9		

*Column Percentage, **Chi-Square test, ***According to TUIK December 2018 data, Hunger Limit: 1.941 TL, Poverty Limit 6.323 TL.

Table 2. Distribution of physical characteristics of the participants

Distribution of physical characteristics	Case (n=35)	Control (n=34)	t	p*
Height (cm) [min-max]	138-180	139-182	0.8	0.45
(median)	160.4	163.6		
Mean±SD	160.5±10.2	160.2±11.1		
Body Weight (kg) [min-max]	47.2-115.2	34.2-95.5	-6.1	<0.01
(median)	77.7	55.5		
Mean±SD	81.6±18.6	56.3±17.2		
BMI (kg/m^2)[min-max]	23-40.7	13-29.5	-9.3	<0.01
(median)	30.4	21.3		
Mean±SD	31.3 ± 4.8	21.9±3.5		
BMI Z Score(SD)[min-max]	1.62-3.73	0.92-2.63	-6.7	<0.01
(median)	2.53	1.73		
Mean±SD	2.55±0.56	1.67±0.41		
Waist circumference (cm)[min-max]	78-130	41-83	-14.1	<0.01
(median)	101.2	61.3		
Mean±SD	102.4±12.8	65.1±11.2		
Heart Peak Pulse(/minute)[minmax]	68-98	65-86	0.8	0.45
(median)	80	75		
Mean±SD	80±8	160.2±11.1		

*Represents the student's t-test.

sified into two categories: the study and control groups. The study group comprised 35 adolescents, consisting of 16 girls and 19 boys, aged between 10 and 16 years. These individuals were being monitored at the pediatric endocrinology outpatient clinic with a diagnosis of obesity. There were 34 adolescents in the control group, 14 girls and 20 boys, who applied to the general pediatric outpatient clinic between the same dates, in the same age group, and were randomly selected, without any diagnosed disease. National percentile curves were used as BMI percentile curves.[8] Children with a percentile value of >95 were considered obese. Demographic data of all children included in the study and their families, physical examination findings, diet-exercise status, oral glucose tolerance tests (OGTT), fasting blood glucose, insulin, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) values were recorded.

The following tests were applied to obese patients and control groups to evaluate cognitive functions:

1. Wechsler Intelligence Scale for Children—Revised (WISC-R); to determine the intelligence levels of children and to evaluate the problems they experience in certain areas,

2. Benton visual memory test; to assess visual memory,

3. Stroop Test; to assess the ability to suppress a habitual behavior pattern and perform an unusual behavior, focused attention, and information processing speed,

4. Trailing; to assess attention speed, motor speed, visual scanning, mental flexibility, endurance, response inhibition, and proneness to interference,

5. Auditory Verbal Learning Test (AVLT); to assess attention, verbal fluency, and verbal learning.

RESULTS

The data gathered in the study were analyzed using the statistical software package SPSS 23 (Statistical Package for the Social Sciences – IBM®). Descriptive statistics were utilized, providing numbers and percentages for categorical variables and mean and standard deviation for numerical variables. For numerical variables, an ANOVA Test was used when the assumption of normal distribution was provided in multiple independent group comparisons, and the Kruskal-Wallis Test was used when the Wilcoxon Test was not suitable. Chi-square test and T-test statistics were used for categorical variables. To establish the statistical significance level, significance was considered at a 95% confidence interval, and $p<0.05$ was considered as indicating significance.

Socio-Demographic and Literacy Time Analysis

Of the obese cases participating in the study, 45.7% were girls, and the mean age was 13.0±1.7 years, while 41.2% of the control group were girls, and the mean age was 12.2±1.7 years (Table 1). When comparing the ages of first walking, pronouncing the first word, producing the first sentence, and receiving toilet training, no statistically significant difference was discovered between the groups in terms of motor mental development ($p>0.05$). Other-

Table 3. Study and control group comparative results of WISC-R, STROOP test, visual memory test, verbal fluency test, trail making test, AVLT test

Assessment tools and subscales		Study (Case) Group (n=35)	Control Group (n=34)	p
WISC-R	WISC-R Verbal [min-max]	69-115	70-127	0.59
	Mean±SD	94±12	96±15	
	WISC-R Performance [min-max]	70-123	86-128	0.06
	Mean±SD	99±14	105±12	
	WISC-R Total [min-max]	73-121	75-128	0.13
	Mean±SD	96±13	100±13	
STROOP TEST	Stroop Total Time [min-max]	72-213	66-180	0.03
	Mean±SD	121 ± 44	102±26	
	Stroop Total Error [min-max]	0-26	0-5	0.68
	Mean±SD	1.8±4.6	2.2±1.6	
VISUAL MEMORY TEST	Visual Memory Test [min-max]	9-15	3-14	<0.01
	Mean±SD	12.7±1.5	7.9±2.9	
VERBAL FLUENCY TEST	Verbal Fluency Total [min-max]	12-60	14-50	0.79
	Mean±SD	28.4±12.7	27.7±9.8	
TRAIL MAKING	Trail A time [min-max]	29-105	16-94	0.79
	Mean±SD	49.5±14.2	48.4±19.9	
	Trail A error [min-max]	0-1	0-1	0.71
	Mean±SD	0.1±0.4	0.2±0.4	
	Trail B time [min-max]	76-288	35-300	0.02
	Mean±SD	153±49	124±56	
	Trail B error [min-max]	0-9	0-5	0.57
	Mean±SD	1.6±2.3	1.4±1.7	
AVLT	AVLT List Total [min-max]	28-67	28-59	0.1
	Mean±SD	43±9	47±9	
	AVLT-LR [min-max]	1-15	5-14	<0.01
	Mean±SD	7.8±3.3	10.2±2.4	
	AVLT Recognition [min-max]	8-28	11-15	<0.01
	Mean±SD	17.9±5.5	14.1±1.4	
	AVLT False Recognition [min-max]	0-2	0-2	0.03
	Mean±SD	0.7±0.6	1.1±0.8	

wise, the living together of the parents, parents being related, and having an extended family type were found to be considerably more than the study group's control group ($p<0.05$).

Analysis of Physical Characteristics

Information on the average body weight, BMI, BMI Z score, waist circumference, and the number of heartbeats of the participants are given in Table 2. Obese adolescents were found to have substantially higher mean body weight, BMI, BMI Z score, waist circumference, and heart rate values than those in the control group ($p<0.01$). However, there was no significant difference in height between the groups ($p>0.05$).

Analysis of Results Obtained from Assessment Tools

The Stroop test is an easy-to-apply assessment tool that is commonly used in the control of frontal functions. Interference sensitivity and inability to suppress inappropriate automatic responses can be evaluated more specifically in this test. The Stroop Test assesses perceptual setup, the ability to change in line with changing demands and under the influence of a disturbance, the ability to suppress a habitual behaviour pattern and perform an unusual behaviour, focused attention, and information processing speed. This test is regarded as the most selective test for inappropriate stimulus inhibition and is sensitive to damage to the left frontal lobe, particularly the orbitofrontal cortex.[9]

Table 3 displays the comparison between groups of the Stroop test administered as part of the study. As a result, obese teenagers had substantially higher Stroop 1-2-3 and Stroop total time means than those in the control group ($p<0.05$). However, there was no appreciable difference in the means of the Stroop total errors across the groups ($p>0.05$).

Trail Making Tests assess the attention speed, motor speed, visual scanning, mental flexibility, persistence, re-

sponse inhibition, and proneness to interference.[10] The analysis revealed a statistically significant difference only in terms of Trail B times in the trailing tests, as shown in Table 3 ($p<0.05$). The average duration of Trail B in the case group was found to be significantly longer than that of the control group.

Auditory Verbal Learning Test (AVLT) is a neuropsychological memory test used to assess verbal memory, verbal learning, backward and forward interference, instant recall, delayed recall, and recognition processes.[11] No statistically significant difference was discovered in terms of the AVLT total, AVLT List 1, AVLT List 5, and AVLT Perseverance scores as a consequence of the test used to compare the two groups within the parameters of the study ($p>0.05$). The study revealed that AVLT long-term delayed recall (AVLT-LR) and false recognition mean scores were significantly higher in the control group, while AVLT recognition mean scores were significantly lower in the case group ($p<0.05$), as presented in Table 3.

Studies show that abstract shapes are encoded in the right prefrontal cortex, and words are encoded in the left prefrontal cortex.[12] The tests employed in this study aimed to assess the verbal and visual memory learning, spontaneous recall, and recognition abilities of the participants. After conducting the assessments (Table 3), regarding scores for visual memory, a statistically significant difference was found ($p<0.01$). In the study group, the mean scores of the visual memory test were significantly higher than those of the control group. Additionally, a statistically significant difference was observed in terms of verbal fluency total and sub-dimension total mean scores ($p<0.05$). The subjects' mean WISC-R verbal, performance, and total score values did not show any statistically significant differences ($p>0.05$).

Analysis of WISC-R Scores by Biochemical and Lifestyle Characteristics

The comparison of WISC-R scores by some biochemical and lifestyle characteristics in the obese adolescent group is given in Table 4. Accordingly, the WISC-R score of those with fasting blood glucose below 100 mg/dl is significantly higher than that of those with 100 mg/dl and above ($p<0.01$). In the study, there were no statistically significant differences observed among obese cases concerning fasting insulin, HOMA-IR levels, exercise and diet status, and WISC-R scores ($p>0.05$).

Analysis of Correlation of WISC-R Scores with Other Test Scores

The correlation of age and WISC-R scores with other test scores in adolescents is given in Table 5. Accordingly, the study did not find any statistically significant correlation between age and WISC-R scores in adolescents ($p>0.05$). However, a statistically significant but weak correlation was found between age and AVLT false recognition (negatively), verbal fluency, and visual memory scores in adolescents ($p<0.05$). In the study, a statistically significant yet weak correlation was observed between WISC-R scores and Stroop total time, AVLT list total, AVLT-LR, Trail A, Trail B, and Verbal Fluency total scores in adolescents ($p<0.05$).

DISCUSSION

In this study, which looked at how obesity affects cognitive abilities in adolescence—the most crucial stage of the transition to adulthood—a significant link between the groups' mean WISC-R verbal, performance, and total scores was found. The WISC-R test is an individually administered intelligence test approved for children aged

Table 4. Comparison of WISC-R scores by some biochemical and lifestyle characteristics in the obese group

Total WISC-R Score	n	Med/DA	Z	p*
Fasting Blood Glucose				
<100 mg/dl	25	103/41	-2.9	<0.01
≥100 mg/dl	10	85/34		
Fasting Insulin Level				
<15 uU/mL	10	96/34	-0.1	0.94
≥15 uU/mL	25	97/48		
HOMA-IR Level				
<3.16	11	93/34	97/48	0.7
≥3.16	24	97/48		
Exercising Status				
None	29	97/48	-0.1	0.95
Yes	6	97/25		
Dieting status				
None	29	97/48	0.7	0.51
Yes	6	92/25		

Table 5. Correlation of age and WISC-R scores with other test scores in adolescents

	Age	WISC-R Total Score	Stroop Total Time	Stroop Total Error	AVLT List Total	AVLT- LR	AVLT Recognition	Trail B time	Verbal Fluency Total	Visual Memory
Age	1	-0.21	0.02	-0.05	0.19	0.06	-0.01	-0.15	0.29*	0.33**
WISC-R	-0.21	1	-.28*	0.04	.33**	0.24*	-0.1	-.35**	.24*	0.01
Stroop total time	0.02	-.28*	1	0.23	-0.23	-0.2	-0.28*	0.14	-0.39**	0.1
Stroop total error	-0.05	0.04	0.23	1	-0.03	0.02	0.06	-0.08	-0.2	-0.17
AVLT list total	0.19	0.33**	-0.23	-0.03	1	0.63**	0.23	-0.19	0.23	-0.1
AVLT-LR	0.06	0.24*	-0.2	0.02	0.63**	1	0.04	-0.21	0.07	-0.22
AVLT recognition	-0.01	-0.01	-0.28*	0.06	0.23	0.04	1	0.25*	-0.13	0.23
Trail B time	-0.15	-0.35**	0.14	-0.08	-0.19	-0.21	0.25*	1	-0.21	-0.1
Verbal fluency total	0.29*	0.24*	-0.39**	-0.2	0.23	0.07	-0.13	-0.21	1	0.26*
Visual memory	0.33**	0.01	0.1	-0.17	-0.09	-0.22	0.23	-0.1	0.26*	1

**p<0.05; ***p<0.01.

6-16. The validity and reliability of the WISC-R have been adapted for children and adolescents in Turkey.[13] When reviewing the literature, it is possible to encounter many studies reporting the relationship between obesity and cognitive functions and different results. It is observed that studies are generally conducted with high school students, university students, and adolescents.[14] However, there are many studies reporting the relationship between high body weight and low intelligence score, and cognitive function.[15,16] Some studies show that obesity can cause a decrease in IQ, while others emphasize that low IQ can cause obesity.[17]

In this study, it was discovered that the mean of Stroop 1-2-3 and Total Time in obese adolescents was significantly higher than those of the control group. The Stroop test, which was used in many studies before, was applied as a mental stressor.[18,19] In a related study by Cohen et al.[20] it was discovered that the obese group's overall Stroop test length was substantially longer than that of the control group. In the same study, attention/concentration assessments, working memory, and psychomotor/processing speed assessments showed significantly better results in the normal-weight group compared to the obese group.[20]

In the study, it was discovered that the case group's mean score on the visual memory test was much greater than that of the control group. In a study by Cohen et al.[20] unlike the findings of the study, visual memory performance has been reported to be higher in non-obese children, both in the forward and backward steps. In the Baltimore Cohort of Aging, obesity indices have been associated with poor performance in various cognitive fields, memory, and verbal fluency functions.[21] However, similar to the study in the Baltimore cohort, obesity was associated with better performance on attention tests and visual-spatial ability.[21] Electrophysiological studies in obese children revealed an association between impaired peripheral nerve conduction and insulin resistance, inspiring other studies showing that the visual and auditory pathways are also affected by hyperinsulinemia.[22] Regarding total verbal fluency and sub-dimension total score means, no statistically significant differences between the groups were found in this investigation. Similarly, in a study by Verdejo-Garcia et al.[23] the performance of overweight children on IQ, working memory, and verbal fluency assessments did not differ from controls, and its relationship with BMI was not reported. In some studies in the literature, it has been reported that poor performance levels in the Trail and Verbal Fluency tests are associated with high leptin levels.

In our study, we found a statistically significant relationship between the groups only concerning Trail B times, one of the trail-making tests. The study group's mean Trail B time was substantially longer than the control group's. The Trail Making Test (Parts A and B) provides information on visual scanning, processing speed, mental flexibility, and executive functions.[10] A shorter time to complete the test indicates better performance. Overweight has lower neuropsychological performance on tests of response inhibition, flexibility, and decision making. In a study, multivariate analyses have shown that BMI has a significant detrimental effect on flexibility performance and cognitive flexibility (as assessed by TMT) may be significantly reduced in overweight adolescents.[24] In the study conducted by Cohen et al.[20] it has been determined that normal-weight participants completed the Trail Making Test B-A in a shorter time than obese participants.

Regarding the study's AVLT total, AVLT List 1, AVLT List 5, and AVLT Perseveration scores, there were no statistically significant differences found between the groups. On the other hand, the study revealed that the mean AVLT-LR and recognition scores were significantly higher in the control group, whereas the mean AVLT false recognition scores were significantly lower in the case group. Similarly, Yesavage et al.[25] have found no significant relationship between AVLT and obesity in their study.

There were no statistically significant differences observed among obese cases concerning fasting insulin, HOMA-

IR levels, exercise and diet status, and WISC-R scores. In studies investigating dieting status, it is commonly reported that obese individuals have a higher propensity for dieting, and there is a statistically significant distinction between the groups.[26] The lack of difference between the groups in the study is believed to be attributable to the fact that obese individuals did not decide to lose weight. Previous studies have shown that diseases associated with insulin resistance, such as metabolic syndrome and type-II diabetes, are also associated with neurocognitive dysfunction, and it has been suggested that the effects of insulin resistance on the neurological system are probably due to abnormalities in insulin-dependent vascular reactivity.[27]

A statistically significant but weak correlation was noted between WISC-R and Stroop total time, AVLT list total, AVLT-LR, Trail A, Trail B, and Verbal Fluency total scores in adolescents in the study. In the literature reporting correlations between age and WISC-R and other assessments. In a study by Belsky et al.[17] it has been reported that age was positively associated with the completion time in TMT-B.

As a result, in this study investigating the effects of obesity on cognitive functions in adolescence, which is the most important step of the transition to adulthood, it was observed that obesity negatively affects cognitive functions in childhood. It is necessary to determine these factors that negatively affect cognitive functions in obese children and to take these factors into consideration in the follow-up of children as they get older, and supportive interventions and measures should be taken.

Ethics Committee Approval

This study approved by the Istanbul University Ethics Committee (Date: 04.10.2018, Decision No: 2018 / 1441).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.Ö., A.K.S.; Design: M.Ö., A.K.S.; Supervision: M.Ö., İ.Z.G.; Materials: A.K.S., A.K.; Data: A.K.S., İ.Z.G.; Analysis: M.Ö., A.K.S.; Literature search: M.Ö., A.K.S., A.K.; Writing: M.Ö., İ.Z.G., Y.Ç.; Critical revision: M.Ö., İ.Z.G., Y.Ç.

Conflict of Interest

The authors confirmed that there is no conflict of interest in this study and that no funding is given for this study.

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Ergenlerde Obezitenin Bilişsel İşlevler Üzerine Etkileri

Amaç: Obezite, dünya çapında yetişkinlerde olduğu kadar çocukluk çağında da önemli bir sorun olmaya devam etmektedir. Çocukluk çağında yaşanan obezitenin fiziksel etkilerinin yanı sıra duygusal gelişim üzerinde de etkileri olduğu bilinmektedir. Bu çalışmanın amacı, yetişkinliğe geçişin en önemli basamağı olan adölesanlarda obezitenin bilişsel işlevler üzerindeki etkilerini araştırmaktır.

Gereç ve Yöntem: Çalışmaya herhangi sağlık sorunu olmayan obez ve obez olmayan olarak sınıflandırılan ergenler dahil edildi. Obez ve obez olmayan grupta bilişsel işlevlerin değerlendirilmesi için işitsel ve görsel bellek ve dikkat testleri uygulandı.

Bulgular: Obez ve obez olmayan grup aarsında görsel bellek puanları ile sözel akıcılık toplam ve alt boyut toplam puan ortalamaları arasında istatistiksel olarak anlamlı farklar saptandı. Katılımcılara uygulanan WISC-R sözel, performans ve toplam puan ortalamaları açısından anlamlı bir fark bulunmadı.

Sonuç: Çalışmamdan elde edilen sonuçlar obezitenin bazı alanlarda çocukluk çağında bilişsel işlevleri olumsuz etkileyebileceğini ortaya koymaktadır. Bu nedenle, obez çocuklarda bilişsel işlevleri olumsuz etkileyen faktörleri, önleyici müdahaleleri ve önlemleri belirlemek için tahmin ve önleme temelli sistemlerin kullanılması gerekli olabilir.

Anahtar Sözcükler: Bilişsel fonksiyonlar; ergen; obezite.

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Original Article

How Do the Coping Styles of Anesthesiologists Differ from Other Physicians' According to Teamwork Levels?

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Keywords: Anesthesiology; coping styles; social support; teamwork; occupational health psychology.

ABSTRACT

Objective: Anesthesiologists are constant members of teamwork, especially in operating room and ICU. However, the relationship between teamwork (TW) and psychological state of anesthesiologist has not been adequately studied in the literature. This study aimed to compare the anesthesiologists with other medical branches in terms of coping strategies and perceived social support, considering the levels of teamwork reliance.

Methods: We conducted two online surveys. In the preliminary survey, we tested our prediction about the TW levels of anesthesiologists and other branches on medical faculty graduates (n=266). In the main survey with a new sample, we examined the relationship between social support and coping styles against stress in anesthesiology (high TW group, n=107) and dermatology (low TW group, n=91) residents.

Results: Preliminary survey showed that anesthesiology had high TW levels (Mean=4.03), as expected. Dermatology who had low TW levels (Mean=2.53) were selected for the comparison group of the main survey. The main survey indicated that dermatologists (Mdn=16) use the submissive coping approach more than anesthesiologists (Mdn=15; p=.007). There was no significant difference in perceived social support levels of the two groups.

Conclusion: We found a relationship between passive coping strategies that aim to protect from negative emotions caused by stressful events rather than solving the problem and low teamwork level. We think that teamwork may contribute to problem-solving processes by helping anesthesiologists to actively cope with stress.

INTRODUCTION

Teamwork in healthcare, which is defined as a dynamic process that requires coordination and articulation of all tasks and activities performed for caring for patients among groups of health professionals, is essential for the normal functioning of a health system and sharing the workload among health professionals.[1,2] The literature shows that the practice of teamwork can enhance physicians' work engagement, clinical performance, and job satisfaction.[3] These outcomes are also strongly linked to the psychological well-being of physicians, which, in turn, can impact the overall quality of care.[3,4] Considering the highly demanding, high-risk, and stressful characteristics of healthcare practices, teamwork can protect physicians' psychological health and well-being. However, these protective outcomes are most likely to be achieved when collaboration is effective.[3,5]

It is widely accepted that teamwork in healthcare is challenging.[6] Therefore, working in a team requires adopting skills that facilitate dealing with stressful situations that can increase distraction, cognitive load, negative emotions, and social impairment.[7] Researchers emphasize that adaptive stress coping strategies, which aim to actively change the problem that causes the stressful situation, can facilitate effective teamwork in healthcare through improving communication.[8,9] On the other hand, a high-demand work environment may lead to maladaptive coping, which aims to protect an individual from negative emotions caused by stressful events rather than solving the problem. This type of coping includes the use of emotion-focused/avoidance-based strategies, such as experiencing and expressing negative emotions, adopting unhealthy habits, and submissive withdrawal, and is strongly linked to anxiety and depression.[10]

Anesthesiologists are constant members of teamwork, especially in operating rooms and intensive care units (ICUs). It is well known that both the physical and emotional burden in these units can make anesthesiologists susceptible to excessive stress and burnout.[11,12] However, anesthesiologists are not among the health professionals reporting the highest level of stress.[12]

For instance, in a study conducted with health professionals working together in the operating room, it was found that anesthesiologists and anesthesiology residents experienced moderate levels of stress, which were relatively lower compared with other medical professionals' stress levels.[6] Another study objectively measured the acute stress levels of anesthesiologists by recording their heart rates during different stages of the anesthetic process and salivary cortisol concentration.[13] In line with Hull et al.'s [6] study, the authors detected a small but statistically insignificant change in heart rates at all three stages of the perioperative period, which were preoperative, intraoperative, and postoperative. However, the extent of the decrease in cortisol levels tended to change with years in practice, suggesting that experienced physicians are more likely to deal with stress successfully.

The researchers interpreted the differences in stress levels between anesthesiologists and members of other physicians by focusing on individual differences in stress reactance. However, these findings may also indicate that anesthesiologists seem to manage to deal with stress effectively despite the stressful and high-demanding working conditions in operating rooms and ICUs. Therefore, whether this difference is related to the implementation of stress management strategies distinct from those employed by other team members remains unclear. Considering the teamwork dynamics unique to operating rooms and ICUs, anesthesiologists may adopt more adaptive approaches to effectively deal with stress than professionals from other physicians.[11] To the best of our knowledge, however, there is a lack of research investigating the differences in coping skills of anesthesiologists and medical physicians from other specialties that are not heavily teamwork-dependent.

Besides stress coping styles, perceived social support is also one of the significant determinants of the psychological well-being of healthcare professionals. Social support in medical settings can reduce work-related stress and positively affect the health status of health workers.[14,15] This suggests social support as both an essential component and an outcome of successful teamwork in healthcare. Therefore, this study aimed to compare anesthesiologists with other medical physicians in terms of stress-coping strategies and perceived social support, considering the levels of teamwork reliance.

MATERIALS AND METHODS

Instruments

Demographic Information Sheet (DIS): DIS was used to obtain participants' sociodemographic information, including age, gender, and year of residency.

The Teamwork Assessment Form (TAF): This form was developed ad hoc to measure the perceived level of required teamwork for medical, surgical, and basic science divisions and subdivisions (n=43) on a 5-point Likert scale ranging from 1 to 5. Higher scores show a higher level of teamwork dependence for each division. The definition of teamwork given to the participants was as follows: "Teamwork refers to the members of a team working together, anticipating and meeting each other's needs, reassuring each other, and communicating effectively."[16] The Cronbach's alpha reliability for the Teamwork Assessment Form (TAF) in our study was 0.96.

The Brief Coping Style Inventory (BCSI): The BCSI originates from the Ways of Coping Questionnaire developed by Folkman and Lazarus and was adapted by Sahin and Durak for the Turkish population.[10,17] The scale measures the use of different stress coping strategies through 30 items and five subscales, which are helpless (8 items), optimistic (5 items), self-confident (7 items), submissive (6 items) styles, and seeking social support (4 items). Each item is rated on a 4-point Likert scale ranging from 0 to 3, and higher scores obtained from subscales show higher use of the relevant coping style. The scale's Cronbach's alpha reliability was found to be 0.89 in this study.

The Multidimensional Scale of Perceived Social Support (MSPSS): The scale was developed by Zimet et al.[18] to measure the level of perceived social support. The Turkish adaptation of MSPSS was performed by Eker, Arkar, and Yaldiz.[19] The 12 items are rated on a 7-point Likert scale ranging from 1 (very strongly disagree) to 7 (very strongly agree), and form three subscales: significant other, family, and friends. Also, a total scale score is calculated, and higher scores show higher levels of perceived social support. The Cronbach's alpha reliability of the scale was found to be 0.88 in the present study.

Study Design and Participants

The present research was a two-phase study consisting of a preliminary survey and the main study, which adopted a cross-sectional design. The data were collected between November and December 2019. In the preliminary survey study, the participants were asked to score the level of teamwork required in each medical division. After determining the highest- and lowest-scoring divisions, medical doctors were selected from those departments to conduct a comparison of the divisions that required the most and least teamwork.

The medical doctors working at different hospitals in Türkiye participated in both studies. The data were anonymously collected online using the Qualtrics Online Survey Tool (https://www.qualtrics.com). The questionnaire was distributed to the participants through social media, WhatsApp groups, and communication listservs. After the purpose of the study was explained, informed consent was obtained from each participant.

This study was conducted in accordance with the Declaration of Helsinki. Ethical board approval was obtained from Başkent University, Social Science and Humanities Scientific Research and Publication Ethics Committee (IRB Number: 62310886-604.01.01/17475). This study is open to public access in accordance with Open Science principles. The pre-registration link for the study is https://osf.io/r7qev/

Statistical Analyses

The data management and analysis were performed using the IBM SPSS version 22 statistical analysis software. Descriptive statistics are expressed as mean ± standard deviation. The between-group analyses were performed using the independent samples t-test for continuous variables and the Chi-square test for categorical variables. Shapiro-

Table 1. Teamwork scores of medical branches (Min=1, Max=5)

	Median	Mean	SD
Emergency Medicine	5	4.20	1.103
Anesthesiology and Reanimation	4	4.03	1.031
General Surgery	4	4.00	1.028
Cardiovascular and Thoracic Surgery	4	3.99	1.097
Neurosurgery	4	3.95	1.047
Orthopedics and Traumatology	4	3.89	.999
Chest Surgery	4	3.75	1.085
Pediatric Surgery	4	3.73	1.149
Cardiology	4	3.66	1.002
Obstetrics and Gynecology	4	3.62	1.151
Plastic Reconstructive and Aesthetic Surgery	4	3.58	1.154
Urology	4	3.55	1.024
Internal Medicine	4	3.54	1.102
Otorhinolaryngology	3	3.50	1.061
Pediatrics	4	3.48	1.147
Neurology	3	3.25	1.042
Infectious Diseases and Clinical Microbiology	3	3.22	1.129
Chest Diseases	3	3.19	1.033
Ophthalmology	3	3.12	1.096
Radiation Oncology	3	3.11	1.186
Radiology	3	3.10	1.246
Psychiatry	3	2.95	1.135
Medical Pathology	3	2.95	1.244
Physical Medicine and Rehabilitation	3	2.88	1.193
Child and Adolescent Psychiatry	3	2.82	1.154
Nuclear Medicine	3	2.76	1.199
Forensic Medicine	3	2.73	1.201
Public Health	2	2.62	1.268
Medical Genetics	2	2.59	1.173
Family Medicine	2	2.55	1.265
Dermatology	2	2.53	1.103
Sports Medicine	2	2.51	1.173
Medical Microbiology	2	2.48	1.127
Medical Biochemistry	2	2.29	1.093
Medical Education and Informatics	2	2.26	1.168
Medical Pharmacology	2	2.23	1.031
Biostatistics	2	2.20	1.123
Histology and Embryology	2	2.11	1.060
Medical Biology	2	2.11	1.041
Anatomy	2	2.08	1.058
Physiology	2	2.06	1.053
Biophysics	2	1.98	1.035
Medical History and Ethics	2	1.94	1.090

Wilk statistics were used to determine whether the data of continuous variables showed normal distribution. To compare the two groups, the independent samples t-test was used on mean scores having a normal distribution. The Mann-Whitney U test was performed for non-normally distributed variables. The correlations between the teamwork level and demographic variables were assessed using Spearman's rank-order correlation analysis. p-values less than 0.05 were considered statistically significant.

RESULTS

The research aimed to compare the perceived social support levels and stress coping styles of the medical doctors working in the departments requiring high and low teamwork.

To achieve this aim, a preliminary survey was conducted to determine the physicians requiring the highest and lowest levels of teamwork and confirm if the anesthesiology and reanimation branch was regarded as highly dependent on teamwork. In total, 266 medical physicians from various hospitals in Türkiye participated in the study. Fifty-nine percent of the participants were women (156 female), and the mean age was 35.3 (SD=8.4) (range: 23-64) years. According to the preliminary survey results, the anesthesiology division had one of the highest teamwork requirement scores following emergency medicine, as expected. Dermatology and sports medicine were the physicians with the lowest teamwork scores after basic science divisions (see Table 1). We decided to include dermatology as the comparison group because the number of physicians in the field of dermatology is higher than in sports medicine in Türkiye.

After evaluating the preliminary study results, the main study data were collected from 198 resident physicians based in the anesthesiology and reanimation (n=107) and dermatology (n=91) departments. Seventy-six (71%) anesthesiology residents were female, and the mean age was 29.3 (SD=2.91) (range, 24-42) years. Seventy-one (66%) anesthesiology residents had 3 or more years of residency. Seventy-nine participants (75%) of dermatology residents were female, and the mean age was 29.2 (SD=3.59) (range, 24-45) years. Fifty-nine (65%) dermatology residents had 3 or more years of residency. The demographic characteristics of the participants are given in Table 2. The normality of distribution was violated for all mean scores assessed using Shapiro-Wilk's test (p<.001). Therefore, non-parametric analyses were performed.

Correlations Between Variables: Preliminary analyses showed the relationship to be non-linear with all variables as assessed using Shapiro-Wilk's test (p>.05). A Spearman's rank-order correlation was performed to evaluate the relationships between BCSI subscale scores and MSPSS total and subscale scores.

All results were in the expected direction (see Table 3). Age and the seeking social support subscale of MSPSS were not significantly correlated with any variable. All subscale scores and total scores of MSPSS were positively intercorrelated (p<.001).

Between-Group Comparisons: The sex and division-based between-group comparisons were performed using Mann-Whitney U tests to determine whether the Perceived Social Support Scale and Brief Coping Style Inventory scores and sub-scores were differentiated.

According to the results, distributions of family subscale scores of MSPSS were found significantly different between men (Mdn=24) and women (Mdn=25, U=3120, p=.041), using an exact sampling distribution for Mann-Whitney U test.[20] The two groups were not differentiated in terms of other MSPSS subscales. In terms of BCSI subscales, the

Table 2. Demographic variables, perceived social support scores, and types of coping styles of the participants

Demographic Variables	Anesthesiology (n=107)	Dermatology (n=91)	p
Age (year)	29 (24-42)	28 (24-45)	.386
Gender (Female/Male)	76/31	69/22	.520
Years of Residency (<2 years/ ≥ 2 years)	36/71	32/59	.881
Multidimensional Scale of Perceived Social Support (MSPSS)			
Family	24 (10-28)	25 (14-28)	.780
Friend	24 (5-28)	24 (10-28)	.648
Significant Other	23 (4-28)	24 (4-28)	.919
Total	69 (28-84)	70 (34-84)	.817
Brief Coping Style Inventory (BCSI)			
Self-confident	27 (13-35)	27 (14-35)	.152
Helpless	23 (9-38)	24 (13-37)	.673
Submissive	15 (9-25)	16 (9-23)	.007**
Optimistic	18 (7-25)	18 (5-23)	.199
Social Support Seeking	13 (9-20)	13(9-18)	.262

Non-parametric variables analyzed using the Mann-Whitney U test and presented as median (minimum-maximum). **p<.01.

Table 3. Spearman's rank-order correlations among variables

Variable	n	1	2	3	4	5	6	7	8	9	10
1. Age	198	-									
2. MSPSS	198	-0.02	-								
3. MSPSS-F	198	0.02	0.69	-							
4. MSPSS-FR	198	-0.08	0.72	0.46	-						
5. MSPSS-SO	198	-0.01	0.89	0.45	0.46	-					
6. BCSI-SC	198	0.07	0.20**	0.21**	0.20**	0.15*	-				
7. BCSI-H	198	-0.07	-0.12	-0.15*	-0.18*	-0.02	-0.56	-			
8. BCSI-S	198	-0.02	-0.05	-0.05	-0.06	-0.05	-0.32	0.41	-		
9. BCSI-O	198	0.03	0.15*	0.14*	0.19**	0.09	0.66	-0.58	-0.14*	-	
10. BCSI-SSS	197	0.13	-0.01	-0.00	-0.12	0.00	-0.04	0.14	-0.01	-0.03	-

Significant correlations in bold are at p<.001, **p<.01, *p<.05. Rho: Spearman's rho value. MSPSS: Multidimensional scale of perceived social support total score; MSPSS-F: Multidimensional scale of perceived social support from family; MSPSS-FR: Multidimensional scale of perceived social support from Friends; MSPSS-SO: Multidimensional scale of perceived social support from significant others; BCSI-SC: Brief Coping Style Inventory Self-confident; BCSI-H: Brief Coping Style Inventory Helpless; BCSI-S: Brief Coping Style Inventory Submissive; BCSI-O: Brief Coping Style Inventory Optimistic; BCSI-SSS: Brief Coping Style Inventory Seeking Social Support.

distributions of scores were not significantly different between male and female participants.

The division-based Mann-Whitney U tests for MSPSS total scores and subscale scores showed that distributions of MSPSS scores were not significantly different between dermatologists and anesthesiologists. The two groups were only differentiated regarding the submissive coping scores of BCSI. Anesthesiologists had significantly lower submissive coping scores (Mdn=15) than dermatologists (Mdn=16; U=3786, p=.007; see Table 2).

DISCUSSION

There is a growing body of literature on teamwork and its implications in healthcare. Most of these studies are on decision-making mechanisms, patient safety, and cost improvement in healthcare.[21] However, the relationship between teamwork and the psychological well-being of healthcare professionals has not been studied much. Previous studies showed that social support and coping styles were the two main buffer systems of depression and anxiety of individuals.[11,12] In our study, we aimed to discuss the association of different teamwork levels with stress coping styles and perceived social support.

To achieve this purpose, we investigated whether anesthesiologists used different stress-coping strategies and had different levels of perceived social support than those of other medical branch physicians who depended on teamwork less.

The preliminary survey confirmed that anesthesiologists were perceived as one of the highest teamwork-dependent physicians following emergency medicine compared with other physicians, as we predicted. To be able to compare the physicians based on their teamwork reliance, we included physicians from the dermatology department in the study because there was a similar number of physicians compared to anesthesiologists. Therefore, the main research was conducted with the residents of these two departments. In terms of gender-based comparisons, female physicians reported higher social support from their families than male physicians. This finding is in line with the literature showing that women are more likely to perceive themselves as supported by their families compared with men.[22]

The results of this study revealed that anesthesiologists were less likely to use a submissive approach to deal with stressful situations compared with dermatology residents. It is well-documented that higher stress levels impair cognitive processes, such as memory, attention, and decision-making, leading to serious adverse consequences, especially in healthcare.[23,24] Considering the anesthesiologists' ethical and legal responsibilities, developing autonomy as an acquired characteristic is essential for healthy decision-making processes.[25] Therefore, adopting a submissive coping approach may prevent them from fulfilling their professional responsibilities. This finding also supports Demir and Ataman's the study showing that emergency medicine physicians mostly use active/problem-oriented approaches in coping with stress during COVID-19.[26] Consistent with this finding, emergency medicine physicians were one of the highest teamwork-dependent groups, as were anesthesiologists in our preliminary study. Therefore, the use of active coping strategies by anesthesiology residents was an expected finding.

In terms of other coping strategies, these two groups were not differentiated. A possible explanation for this result may be related to the limited ways of coping addressed in this study. Stress management generally involves a combination of behavioral, cognitive, and emotional coping strategies, and there are both interpersonal and intrapersonal differences in the use of this combination.[10,17] Therefore, this study could have benefited from a more detailed examination of coping strategies.

However, we found a relationship between passive coping strategies and teamwork level as we expected. Passive coping strategies (i.e., helpless and submissive) are higher in dermatology residents, a low teamwork group, than in anesthesiology residents, a high teamwork group. One remarkable finding was that the use of passive coping strategies increased as the level of teamwork decreased. Avoiding actively confronting problems to indirectly reduce emotional tension or engaging in other behaviors are passive coping strategies.[27] People who use active coping strategies can have positive self-views and take a proactive, optimistic, and confident approach to managing stressful situations.[28] Anesthesiologists working in high-stress environments, such as operating rooms and ICUs, may be actively coping with stress more than dermatologists. It is consistent with the literature that dermatologists working in less stressful environments than anesthesiologists use passive coping strategies more.[29]

On the other hand, anesthesiologists and dermatologists did not report different levels of social support. The literature suggests that the link between stress response and social support depends on the sources of that support.[30] In this study, social support from family, friends, and significant others was addressed, and these sources may be linked to different outcomes compared with the support from supervisors, employees, and coworkers in healthcare.

Limitations

This study has some limitations. First, because the present study adopted a cross-sectional design, establishing causal relationships was not possible. Therefore, the findings only have correlational implications. Second, this study did not evaluate the stress levels of participants, which might have allowed testing mediational models on the role of different coping strategies in managing stress. Furthermore, objectively measured teamwork levels would have been beneficial to reach a more accurate classification to perform division-based comparisons. In this context, it is a matter of debate whether lower teamwork or lower stress levels led to passive coping strategies in dermatologists.

Conclusion and Future Implications

Adaptive stress coping strategies and high levels of perceived social support are central to psychological resilience and well-being in health settings. Therefore, health professionals should be actively supported in terms of improving coping skills and strengthening social ties. To be able to determine the specific areas that need to be supported most, similar studies should be performed in healthcare settings. Further research testing the mediational models to examine the possible direct and indirect pathways is also needed.

Anesthesiology and reanimation physicians work in a high-intensity and high-risk work environment and strongly depend on well-coordinated collaboration and good communication. Therefore, more research on the mutual relationships between mental health and teamwork functioning needs to be undertaken to develop interventions to improve anesthesiologists' psychological health and maintain successful teamwork.

Ethics Committee Approval

This study approved by the Baskent University Ethics Committee (Date: 15.04.2019, Decision No: 14739).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.T.; Design: M.T., P.O.P.; Supervision: P.O.P.; Fundings: M.T.; Materials: M.T.; Data: M.T., P.O.P.; Analysis: P.O.P.; Literature search: M.T.; Writing: M.T., P.O.P.; Critical revision: P.O.P.

Conflict of Interest

None declared.

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Takım Çalışması Düzeylerine Göre Anestezistlerin Başa Çıkma Tarzları Diğer Hekimlerden Nasıl Farklılaşıyor?

Amaç: Anestezi uzmanları, özellikle ameliyathane ve yoğun bakım ünitelerinde ekip çalışmasının daimi üyeleridir. Ancak ekip çalışmasına dayalı olma düzeyi ve anestezistlerin psikolojik durumu arasındaki ilişki literatürde yeterince çalışılmamıştır. Bu çalışmanın amacı ekip çalışmasına dayalı olma düzeylerini göz önünde bulundurarak, anestezi uzmanlarını baş etme stratejileri ve algılanan sosyal destek açısından diğer tıp branşları ile karşılaştırmaktır.

Gereç ve Yöntem: Çalışmanın amacı doğrultusunda iki çevrimiçi anket uygulaması gerçekleştirilmiştir. Ön çalışmada anestezistlerin ve diğer branşların EÇ düzeylerine ilişkin öngörüler tıp fakültesi mezunları (n=266) üzerinde test edilmiştir. Yeni bir örneklemle yapılan temel çalışmada ise anesteziyoloji (yüksek EÇ grubu, n=107) ve dermatoloji (düşük EÇ grubu, n=91) asistanlarında sosyal destek ve stresle başa çıkma tarzları arasındaki ilişkiyi incelenmiştir.

Bulgular: Ön çalışmada, beklendiği gibi, anesteziyolojinin yüksek EÇ düzeyine (Ort.=4.03) sahip olduğunu bulunmuştur. Düşük EÇ düzeyine (Ort.=2.53) sahip olan dermatoloji, ana çalışmanın karşılaştırma grubu olarak belirlenmiştir. Ana çalışma sonucunda dermatologların (Mdn=16) anestezistlere (Mdn=15; p=.007) kıyasla pasif başa çıkma stratejilerinden olan boyun eğici başa çıkma yaklaşımını daha fazla kullandığı bulunmuştur. İki grubun algılanan sosyal destek düzeyleri arasında anlamlı bir fark bulunmamıştır.

Sonuç: Araştırma sonucunda sorunu çözmek yerine stresli olayların neden olduğu olumsuz duygulardan korunmayı amaçlayan pasif başa çıkma stratejileri ile düşük ekip çalışması düzeyi arasında bir ilişki bulunmuştur. Ekip çalışmasının anestezistlerin stresle aktif olarak başa çıkmalarına yardımcı olarak problem çözme süreçlerine katkıda bulunabileceği düşünülmektedir.

Anahtar Sözcükler: Anesteziyoloji; başa çıkma tarzları; takım çalışması; sosyal destek; iş sağlığı psikolojisi.

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Original Article

Analysis of Association Between Health Care Workers' Perceived Stress and Burnout Levels During COVID-19 Pandemic in Neurosurgery Clinic

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Keywords: Burnout; covid-19; healthcare worker; perceived stress; stress.

ABSTRACT

Objective: COVID-19 disease has recently affected the whole world and caused drastic changes in people's lives with its emergence. Hospitals and healthcare personnel are among the most affected sides. Our study aimed to demonstrate the effects of the pandemic on healthcare workers regarding changes in their perceived stress and burnout levels.

Methods: 110 individuals, including physicians, nurses, and auxiliary personnel working in a neurosurgery clinic, were involved in the study. Demographic information form, Perceived Stress Scale-14 (PSS), and Maslach Burnout Index (MBI) were used during the data collection phase.

Results: No difference was found between PSS and MBI scales between females and males. Higher MBI points were seen in workers who desire to change their occupations. Married participants had higher MBI personal accomplishment scores than single participants. An increase in education level was associated with higher PSS scores. Participants who found their payments unsatisfactory had higher stress and burnout levels.

Conclusion: Findings of higher occupational burnout among physicians and nurses than auxiliary personnel have been consistent with previous research. A similar case is also present for lower perceived stress levels among married participants when compared to singles. This finding, which has also been demonstrated in other studies, can be explained by fewer responsibilities for singles.

INTRODUCTION

Starting in January 2019 in China and rapidly spreading to the world, COVID-19 has brought many problems and changes to attention and caused many changes in areas including economy, politics, health, and education. It causes people to experience both physical and mental problems. The latest and largest epidemic caused by coronaviruses started in December 2019 in Wuhan, the capital of the Hubei province of China.[1,2]

An increase in case numbers, especially due to the spread of COVID-19 disease, negatively affected levels of anxiety and stress, and there was an evident increase in these levels.[3]

In epidemics, healthcare workers are the ones who have the closest and most frequent contact with infected people. The psychological status of healthcare workers, especially those working in emergency departments and intensive care units, is most severely affected.[4,5] Studies show that 45% of physicians and 50% of nurses have experienced burnout syndrome.[6] Furthermore, in other studies, depression rates are higher in healthcare workers when compared to population levels.[7] In light of all these findings, our study aims to investigate changes in perceived stress and burnout levels in healthcare workers. Results of our study show that because of intense working hours due to the pandemic, the infectiousness of the disease, working in risky environments, frequent shifts, and an increased number of patients lead to higher stress and burnout levels.

MATERIALS AND METHODS

This cross-sectional study was done on 110 healthcare workers working in the Neurosurgery Clinic. Participants of the study were composed of 37 physicians, 37 nurses,

and 36 auxiliary and operating room personnel.

In the provided personal information form, age, sex, level of education, marital status, professional title, experience in occupation (years), willingly selected occupation, desire to change the occupation, satisfaction with payments, and duration of work were evaluated.

The 22-item Maslach Burnout Inventory, 14-item Perceived Stress Scale, and the demographic information form

Table 1. Sociodemographic Distribution of Study Cohort

Variable	Number (n)	Percentage (%)
Age		
18-29	39	35.5
30-39	40	36.4
40-59	28	25.5
60-65	3	2.7
Total	110	100.0
Sex		
Female	57	51.8
Male	53	48.2
Total	110	100.0
Education Level		
Primary School	3	2.7
Middle School	4	3.6
High School	21	19.1
University	39	35.5
Master's Degree / PhD	43	39.1
Total	110	100.0
Marital Status		
Married	65	59.1
Single	34	30.9
Divorced	11	10.0
Total	110	100.0
Professional Title		
Physician	37	33.6
Nurse	37	33.6
Other Healthcare Worker	36	32.7
Total	110	100.0
Duration of Work		
1-5	36	33.0
6-10	25	22.9
11-15	26	23.9
15 and higher	22	20.2
Total	109	100.0
Desire to Change the Occupation		
Yes	87	79.1
No	23	20.9
Total	110	100.0
Would change his/her profession if given the chance to		
Yes	77	70.0
No	33	30.0
Total	110	100.0
Satisfaction over Payments		
Satisfactory	11	10.0
Partially Satisfied	49	44.5
Unsatisfactory	50	45.5
Total	110	100.0

prepared by the researcher were applied to participants and the difference between scores between groups was analyzed.[8]

Maslach Burnout Inventory: Maslach Burnout Inventory (MBI) is an inventory to measure burnout degrees of individuals, which was developed in 1981 by Maslach and Jackson. The inventory consists of 22 items with five-level Likert types and has three sub-dimensions.[9]

MBI consists of three sub-dimensions: personal accomplishment, emotional exhaustion, and depersonalization. Sub-dimensions and items in the inventory are as follows:

1. Emotional Exhaustion: 1, 2, 3, 6, 8, 13, 14, 16, 18, 20 (0-36 points)

2. Depersonalization: 5, 10, 11, 15, 22 (0-20 points)

3. Personal Accomplishment: 4, 7, 9, 12, 17, 18, 19, 21 (0-32 points)

Higher points in emotional exhaustion and depersonalization mean increased burnout, and lower points in personal accomplishment mean decreased burnout levels. Items in the personal accomplishment sub-dimension are scored in reversed order. Inventory scores range from one to five.

Statistical Methods

To evaluate the findings of the study, the statistical analysis program SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp., Armonk, NY, USA) was used. All points derived from statistical analysis of continuous variables were evaluated for normality with descriptive and statistical methods. While evaluating study data, besides descriptive statistical methods (number, percent, mean, median, standard deviation, etc.), the T-test was used for comparisons of quantitative data between two groups, and analysis of variance (ANOVA) was used for more than two groups. Since MBI subdivisions were not homogeneously distributed, ANOVA was inapplicable. To test differences between groups, the Kruskal-Wallis Test was used.

Ethical Considerations

This study was conducted in accordance with the ethical principles outlined in the latest version of the Declaration of Helsinki. Ethical approval was obtained from the ethical committee of the hospital (No:160622223), and informed consent was obtained from all participants prior to their inclusion in the study.

RESULTS

The sociodemographic status of patients is summarized in Table 1. The mean of total points taken from the MBI personal accomplishment sub-dimension was higher for females when compared to males (Table 2). MBI emotional exhaustion points of those participants desiring to change their occupation were higher than those patients who do not desire to change their occupations. According to PSS means, the mean of individuals with master's degrees and Ph.D. (43.26) was highest, whereas the mean of individuals with primary and middle school education was lowest (38.71). When MBI emotional exhaustion points are taken into consideration, the mean of individuals with master's degrees and Ph.D. (20.09) was highest, whereas the mean of individuals with primary and middle school education was lowest (13.43). The mean MBI depersonalization total point was highest in individuals with master's degrees and Ph.D. (8.67), whereas it was lowest in individuals with high school education (4.57) (Table 3). The mean MBI personal accomplishment total point was found to be different between married and single individuals. The mean of married individuals was highest (20.14), whereas the mean of singles was lowest (16.12) (Table 4). According to PSS points, the mean of nurses was highest (43.78), and the mean of auxiliary personnel was lowest (39.56). Mean total MBI emotional exhaustion scores were highest in nurses (19.73) and lowest in auxiliary personnel (14.61). The mean total MBI depersonalization point was highest in physicians (8.76) and lowest in auxiliary personnel (5.28) (Table 5). An association between satisfaction with payments and PSS was detected. Individuals who found their payments insufficient had the highest mean PSS scores (44.46), whereas individuals who were satisfied with their payments had the lowest mean scores (39.91). Regarding satisfaction over payments categories, individuals who find their payments unsatisfactory have the highest means of MBI depersonalization (9.52), and individuals who find their payments satisfactory have the lowest means of MBI depersonalization (5.73) (Table 6).

Table 2. Results of T-test Analyses for PSS and MBI Subdivisions Total Points over Sex Categories

Total Points	Sex	Number of People	Mean	Standard Deviation	t	Degrees of Freedom	P
Perceived Stress Scale	Female	57	41.89	4.850	-0.419	108	0.676
Total Point	Male	53	42.28	4.853			
MBI Emotional Exhaustion	Female	57	17.72	7.907	-0.255	108	0.799
Total Point	Male	53	18.11	8.292			
MBI Depersonalization	Female	57	6.53	4.355	-1.930	108	0.056
Total Point	Male	53	8.68	7.108			
MBI Personal Accomplishment	Female	57	20.51	5.268	3.491	108	0.001
Total Point	Male	53	17.06	5.089			

Table 3. Results of ANOVA analyses for PSS and MBI subdivisions total points over education levels

Education Level	Number of People	Mean	Standard Deviation	F	p
Perceived Stress Scale Total Point					
Primary/Middle School	7	38.71	3.904	2.914	0.038
High School	21	40.48	4.996		
University	39	42.26	5.538		
Master's Degree/PhD	43	43.26	3.768		
Total	110	42.08	4.833		
MBI Emotional Exhaustion Total Point					
Primary/Middle School	7	13.43	6.997	3.158	0.028
High School	21	14.57	7.600		
University	39	18.10	8.143		
Master's Degree/PhD	43	20.09	7.764		
Total	110	17.91	8.060		
MBI Depersonalization Total Point					
Primary/Middle School	7	5.43	4.429	2.971	0.035
High School	21	4.57	4.069		
University	39	8.33	7.908		
Master's Degree/PhD	43	8.67	4.069		
Total	110	7.56	5.918		
MBI Personal Accomplishment Total Point					
Primary/Middle School	7	16.43	4.614	1.688	0.174
High School	21	20.95	4.706		
University	39	18.74	5.144		
Master's Degree/PhD	43	18.30	5.986		
Total	110	18.85	5.442		

Table 4. Results of ANOVA analyses for PSS and MBI subdivisions total points over marital status categories

Marital Status	Number of People	Mean	Standard Deviation	F	p
Perceived Stress Scale Total Point					
Married	65	42.26	5.091	0.198	0.820
Single	34	41.65	4.935		
Divorced	11	42.36	2.730		
Total	110	42.08	4.833		
MBI Emotional Exhaustion Total Point					
Married	65	18.26	8.146	1.008	0.368
Single	34	18.29	8.081		
Divorced	11	14.64	7.406		
Total	110	17.91	8.060		
MBI Depersonalization Total Point					
Married	65	6.97	4.552	1.477	0.233
Single	34	9.00	8.209		
Divorced	11	6.64	4.056		
Total	110	7.56	5.918		
MBI Personal Accomplishment Total Point					
Married	65	20.14	5.108	6.895	0.002
Single	34	16.12	4.766		
Divorced	11	19.64	6.637		
Total	110	18.85	5.442		

Table 5. Results of ANOVA analyses for PSS and MBI subdivisions total points over professional title categories

Professional Title	Number of People	Mean	Standard Deviation	F	p
Perceived Stress Scale Total Point					
Physician	37	42.84	3.797	8.755	0.000
Nurse	37	43.78	4.866		
Auxiliary Personnel	36	39.56	4.831		
Total	110	42.08	4.833		
MBI Emotional Exhaustion Total Point					
Physician	37	19.30	7.363	4.822	0.010
Nurse	37	19.73	8.258		
Auxiliary Personnel	36	14.61	7.725		
Total	110	17.91	8.060		
MBI Depersonalization Total Point					
Physician	37	8.76	3.947	4.237	0.017
Nurse	37	8.59	7.712		
Auxiliary Personnel	36	5.28	4.885		
Total	110	7.56	5.918		
MBI Personal Accomplishment					
Total Point					
Physician	37	18.11	5.953	1.145	0.322
Nurse	37	18.51	5.157		
Auxiliary Personnel	36	19.94	5.149		
Total	110	18.85	5.442		

Table 6. Results of ANOVA analyses for PSS and MBI subdivisions total points vs satisfaction over payments categories

Satisfaction Over Payment	Number of People	Mean	Standard Deviation	F	p
Perceived Stress Scale Total Point					
Satisfactory	11	39.91	3.477	13.694	0.000
Partially Satisfied	49	40.14	4.721		
Unsatisfactory	50	44.46	4.132		
Total	110	42.08	4.833		
MBI Depersonalization Total Point					
Satisfactory	11	5.73	5.934	5.425	0.006
Partially Satisfied	49	5.98	3.677		
Unsatisfactory	50	9.52	7.092		
Total	110	7.56	5.918		
MBI Personal Accomplishment					
Total Point					
Satisfactory	11	17.09	7.176	2.708	0.071
Partially Satisfied	49	20.14	5.264		
Unsatisfactory	50	17.96	5.006		
Total	110	18.85	5.442		

DISCUSSION

Of healthcare workers participating in our study, 52% were female and 48% were male. PSS, MBI emotional exhaustion, and MBI depersonalization scores did not show a significant difference between males and females (Table 2). The reason behind this is possibly the fact that healthcare workers in the hospital during the COVID-19 pandemic are working under the same circumstances. Many studies on burnout also reported similar results. However, personal accomplishment, a sub-dimension of burnout level, has been demonstrated to be higher in females. Studies demonstrate that personal success points are associated with lower burnout levels. Therefore, the higher personal success of female personnel decreases their burnout levels compared to males. In a study conducted by Helvacı et

al.[10] in 2013, contrary to expectations, the burnout levels of males were found to be higher than in females. With regards to depersonalization, many studies point out that depersonalization is more common in males. On the other hand, personal success is not associated with sex.

In a study that investigates female and male physicians' work-related stress and physical activity levels by Passey et al.,[11] female physicians had high levels of physical activity and perceived stress levels, whereas male physicians had higher measurable stress but low physical activity levels. In another study done in India, perceived stress levels of physicians and nurses were reported to be similar (physicians = 18.35, nurses = 17.15). Our findings show that perceived stress levels are similar for females and males. In the study of Passey et al.,[11] stress levels of female and male physicians were similar.

According to our studies, Post-Hoc (LSD) multiple comparisons results; mean MBI personal accomplishment points of married and single individuals were different. Other studies on marital status and personal accomplishment did not find any significant difference. The study of Çelmece et al.[12] reports that the continuous anxiety point is higher in married individuals when compared to singles. Discrepancies between single and married individuals in our study can be described by the fact that married individuals have increased responsibilities towards their partners and children, whereas single individuals are only responsible for themselves, which leads to a more comfortable life economically and morally. In a study done with healthcare workers during the COVID-19 pandemic, emotional exhaustion was found to be higher in married participants.[12]

In a meta-analysis done by Salari et al.,[13] a linear correlation between higher education level and anxiety was found. This was explained by increased awareness associated with higher education. Higher levels of awareness of self, situations, and health could be the reason behind higher levels of anxiety.[2] In another study supporting this data, individuals with primary school education have higher perceived social support.[14,15] In our study, the mean PSS total point is significantly different concerning education levels. The mean total PSS scores of participants with master's degrees and Ph.D. vs. primary and middle school graduates were different. Participants with master's degrees and Ph.D. have the highest (43.26) and primary and middle school graduates have the lowest mean (38.71). Higher perceived stress in participants with higher education. Participants with higher education have higher expectations at their workplaces, and a mismatch between expectations and reality for these people can be a facilitating factor for higher stress levels.

Our study also signifies differences due to professional titles. Especially in auxiliary personnel (cleaning staff, technicians, secretaries, anesthesia technicians, security personnel), stress levels are different than physicians and nurses. Perceived stress levels of physicians and nurses are higher than auxiliary personnel. This can be explained by increased direct contact with patients, treatment, and responsibilities brought on by patients, and involvement in every process in deteriorating patients. Similarly, when data on burnout subdivisions, including emotional exhaustion and depersonalization points, are evaluated, they are higher for physicians and nurses.

Payments (salaries) of workers associated with their jobs affect job satisfaction. Participants finding their payments satisfactory have lower PSS scores when compared to participants finding their payments unsatisfactory. Stress levels of individuals increase when they think that their payments don't meet their work. Similarly, when burnout levels are considered, unsatisfied healthcare workers have higher points. To sum up, personnel's payment satisfaction affects occupational burnout levels. The limitation of our study is the small sample size; thus, larger studies should be conducted in the following years. Higher burnout levels in physicians and nurses than auxiliary healthcare personnel are evaluated similarly to other studies in the literature.[6,10,12] A similar situation is found in married participants who have lower levels of perceived stress when compared to singles. This situation, also seen in other studies, can be caused by relatively lower levels of responsibilities.[12] Increased occupational burnout associated with higher educational levels can be due to the higher awareness of these participants, and some other studies in the literature report similar findings.[16]

Ethics Committee Approval

This study approved by the Umraniye Training and Research Hospital Ethics Committee (Date: 23.06.2022, Decision No: 223).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: E.V.; Design: Y.E.Ç.; Supervision: E.V., S.O.A.; Materials: F.A.; Data: F.A., Y.E.Ç.; Analysis: S.O.A.; Literature search: E.V.; Writing: E.V., F.A.; Critical revision: E.V., F.A.

Conflict of Interest

None declared.

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COVID-19 Pandemi Sürecinde Nöroşirürjideki Sağlık Çalışanlarının Algılanan Stres Seviyeleri ve Tükenmişlik Sendromları Arasındaki İlişkinin İncelenmesi

Amaç: COVID-19 hastalığı son dönemde tüm dünyayı etkisi altına almış ve ortaya çıkmasıyla birlikte insanların hayatında köklü değişikliklere neden olmuştur. Hastaneler ve sağlık personeli en çok etkilenen gruplar arasında yer almaktadır. Bu çalışmada, salgının sağlık çalışanları üzerindeki etkisinin; algılanan stres ve tükenmişlik düzeyleri değerlendirilerek araştırılması hedeflenmiştir.

Gereç ve Yöntem: Beyin ve Sinir Cerrahisi Kliniğinde görevli, doktorlar, hemşireler ve sağlık personelinden oluşan 110 kişilik grup çalışmaya dahil edildi. Veri toplama aşamasında demografik bilgi formu, Algılanan Stres Ölçeği-14 (ASS) ve Maslach Tükenmişlik Endeksi (MTE) kullanılmıştır.

Bulgular: Kadın ve erkek katılımcılar arasında ASS ve MTE skorları arasında anlamlı fark bulunamadı. Mesleğini değiştirmek isteyen katılımcılar, daha yüksek MTE skorlarına sahiptiler. Evli katılımcıların bekarlara göre daha yüksek kişisel başarı puanlarına sahip olduğu görüldü. Eğitim düzeyi arttıkça ASS skorunda artışın olduğu izlendi. Aldığı ücreti yetersiz bulan katılımcıların daha yüksek stres ve tükenmişlik seviyelerine sahip oldukları bulundu.

Sonuç: Doktor ve hemşire gruplarında diğer sağlık personeline oranla görülen yüksek tükenmişlik oranı önceki çalışmalar ile uyumlu bulundu. Bekarlara göre evli katılımcıların daha düşük stres oranlarına sahip olması da literatürle uyumlu izlendi. Bu bulgunun evli ve bekarlar arasındaki sorumluluk farkıyla ilgili olduğu düşünülüyor.

Anahtar Sözcükler: Algılanan stres; COVID-19; sağlık çalışanları; stres; tükenmişlik.

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Original Article

Relationship of Personality and Temperament Traits with Pain and Function in Patients with Knee Osteoarthritis

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Keywords: Function; osteoarthritis; pain; personality; temperament.

ABSTRACT

Objective: There are a few studies on the relationship between personality and temperament types and functionality and pain felt in patients with knee osteoarthritis (OA). This study aimed to determine the relationship between personality and temperament characteristics and pain and function in patients with knee OA.

Methods: The study included 126 patients diagnosed with knee OA who met the inclusion criteria. Eysenck Personality Questionnaire Revised-Short Form (EPQR-S) and Type D Personality Scale (DS-14) were used for personality assessment, Temperament Evaluation of Memphis, Pisa, and San Diego Auto-questionnaire (TEMPS-A) was employed for temperament assessment, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used for OA pain and general function assessment.

Results: Of the participants, 58 (46%) showed Type D personality traits, while depressive temperament was dominant in 18 (14.3%) participants, irritable temperament in 12 (9.5%), and anxious temperament in 16 (17.3%) participants. Those with Type D personality had worse functions, and Type D personality was positively associated with pain and total WOMAC score. Total WOMAC score showed a positive correlation with neuroticism and psychoticism personality traits and cyclothymic and nervous temperament traits.

Conclusion: This study demonstrates that pain and total WOMAC score are associated with personality and temperament characteristics in patients with knee OA. In addition to pharmacological and physical therapy, interventions in these areas may be beneficial.

INTRODUCTION

Chronic pain is one of the rapidly growing public health problems with a significant social burden. The chronic pain costs are estimated to exceed the total costs spent on diabetes, heart disease, and cancer.[1] Overall, osteoarthritis (OA) affected 303 million people worldwide in 2017 and was one of the leading causes of disability among chronic pain sufferers.[2] Although it can be seen in any diarthrodial joint, OA most commonly occurs in the hands, knees, and hip joints, with the highest prevalence in the knee.[3] When it is symptomatic, OA leads to significant declines in emotional and physical health, social functioning, and daily life activities. Hip and knee OA ranked as the eleventh leading cause of global disability out of 291 conditions, and OA pain is considered to be a leading cause of mobility impairment in older adults.[4] These rates are projected to rise as a result of longer life expectancy, increasing prevalence of obesity, and a growing elderly population.

Personality and temperament describe how individuals perceive their environment, relate, and think about the environment. In addition, they may be affected by traumas that may cause depression or anxiety.[5] Anxiety can be defined as state anxiety and trait anxiety. State anxiety is a transient emotional state and can be reflected in thought, emotion, and behavior at a given moment. However, trait anxiety persists for a long time and may reflect a persistent pattern of emotions, thoughts, and behaviors. These different thoughts and behaviors can change the perception of pain, disability, and quality of life. Many of these can be found in various personality types and can affect the severity of pain, quality of life, and functionality of the person.

Studies investigating chronic pain and personality traits have shown that higher harm avoidance and lower self-management may be leading personality traits in chronic pain sufferers, with an association between neuroticism and pain.[6-11] However, to the best of our knowledge, including these studies, few studies examine the patient group with OA, one of the most common causes of chronic pain, as a sample. This study investigated the rela-

tionship between personality and temperament characteristics and pain and functionality in patients with knee OA.

MATERIALS AND METHODS

A priori power analysis was performed with G*Power version 3.1.9.4 to determine the minimum sample size required for the study. The results showed that at α=0.05 significance criterion for correlation analysis, the required sample size was N=84 to reach 80% power to detect a medium effect. The study included 126 patients who presented to the physical therapy and rehabilitation clinic of Oltu State Hospital with knee pain and were diagnosed with idiopathic knee OA according to the classification criteria[12] for the subgroups of OA. Uncooperative patients who had secondary OA, low back or hip pain, systemic inflammatory disease, and cancer and had received physical therapy or intra-articular injections within the last six months were excluded from the study. Written informed consent was obtained from the patients. Ethics committee approval was obtained from the Erzurum Regional Training and Research Hospital Ethics Committee. (Number: 37732058-514.10). The study was conducted under the 1964 Declaration of Helsinki principles and its later amendments.

Data Collection Tools

Sociodemographic Data Form: A questionnaire form was prepared by the authors to obtain information on patients' sociodemographic data characteristics such as age, gender, education, employment status, and disease duration.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): It is a scale recommended by Outcome Measures in Rheumatology Clinical Trials (OMERACT) for studies on OA. The Turkish validity and reliability study of the scale was conducted by Tuzun et al.[13] The scale consists of three subscales: pain, stiffness, and physical function, with a total of 24 questions. High scores indicate increased pain and stiffness and deterioration in physical function.[13]

Eysenck Personality Questionnaire Revised-Short Form (EPQR-S): This 24-item questionnaire evaluates three dimensions of personality: extraversion (more participation in social activities, more talkative), neuroticism (stressed, anxious, over-focusing on somatic sensations and interpreting somatic sensations as harmful or threatening), and psychoticism (low social functioning). In addition to these three domains, it aims to prevent bias and increase the validity of the questionnaire with the lying subscale. The score that can be obtained for each personality trait varies between 0 and 6. The Turkish validity and reliability study of the scale was conducted by Karanci et al.[14]

Temperament Evaluation of Memphis, Pisa, and San Diego Auto-questionnaire (TEMPS-A): The scale evaluating dominant affective temperament types such as depressive, cyclothymic, hyperthymic, nervous, and anxious was developed by Akiskal et al.[15] The cut-off score of the 9-item scale was found to be 13 for depressive, 18 for cyclothymic, 20 for hyperthymic, 13 for nervous, and 18 for anxious temperament.[16]

Type D Personality Scale (DS-14): Individuals with negative affect usually have a depressed mood, feel less well, and exhibit more physical symptoms. Socially introverted individuals feel nervous, insecure, and suppressed. Negative affectivity and social introversion are seen together in individuals with type D personality. The scale was developed to assess Type D personality. It consists of 14 items and two subscales of negative affectivity and social inhibition. Those who score ≥10 points on the two subscales are considered to have a Type D personality. The Turkish validity and reliability study of the scale developed by Denollet[17] was conducted by Alcelik et al.[18]

Statistical Analysis

The data used were analyzed with SPSS version 24.0. Mean and standard deviation were used to summarize the data. The Kolmogorov-Smirnov test was used to analyze the normality of the data. The independent samples t-test was used to compare WOMAC data between groups. Pearson's correlation analysis was used for normally distributed data, while Spearman's correlation analysis was used for non-normally distributed data. A p-value less than 0.05 was considered statistically significant.

RESULTS

There were 84 female and 42 male participants with knee OA. The mean age of the participants was 59.37±9.29 years, the educational level was 6.06±2.19 years, the disease duration was 3.60±4.17 years, and the body mass index (BMI) was 31.17±6.28. Only 18 (14.3%) participants were employed. The evaluation by the DS-14 cut-off score

Table 1. Socio-demographic and other characteristics of the participants

Variables	Value, n (%)
Gender (female/male)	84/42 (66.7/33.3)
Employed/Non-employed	18/108 (14.3/85.7)
Unilateral knee/Bilateral knee	52/74 (41.3/58.7)
Age, mean±SD	59.37±9.29
Educational level (year), mean±SD	6.06±2.19
Disease duration (year), mean±SD	3.60±4.17
BMI, mean±SD	31.17±6.28
Dominant temperament	
Depressive	18 (14.3)
Cyclothymic	0 (0)
Hyperthymic	0 (0)
Irritable	12 (9.5)
Anxious	16 (17.3)
Type D personality (yes/none)	58/68 (46/54)

SD: Standard deviation; BMI: Body mass index.

Table 2. Comparison of VOMAC scores of the groups

Group	Pain	p	Stiffness	p	Function	p	Total VOMAC score	p
Female	12.29±4.38	0.497	4.68±2.17	0.252	43.14±13.39	0.234	60.49±18.16	0.209
Male	11.71±4.55		4.21±2.06		40.09±13.68		56.21±17.41	
Unilateral knee	11.15±4.30	0.045	4.08±2.13	0.049	39.62±13.50	0.080	55.15±18.19	0.040
Bilateral knee	12.76±4.42		4.84±2.10		43.90±13.52		61.81±17.39	
Type D personality (+)	12.48±4.37	0.366	5.21±1.44	<0.001	43.31±11.66	0.357	61.41±15.69	0.168
Type D personality (-)	11.76±4.47		3.94±2.45		41.12±14.92		57.06±19.58	

Table 3. Correlation of variables with pain

	R	P
Age	0.102	0.254*
Educational level	-0.252	0.004*
Disease duration	0.114	0.205**
BMI	-0.148	0.098*
Personality		
Type D personality	0.226	0.011*
Extraversion	-0.126	0.160*
Neuroticism	0.098	0.274*
Psychoticism	0.053	0.552**
Temperament		
Depresive	0.050	0.575*
Cyclothymic	0.105	0.241*
Hyperthymic	-0.14	0.874*
Irritabl	0.124	0.165**
Anxious	0.102	0.256*

BMI: Body mass index; *:Pearson correlation analysis; **: Spearmen correlation analysis.

Table 4. Correlation of variables with total VOMAC score

	r	P
Age	0.148	0.099*
Educational level	-0.301	0.001*
Disease duration	0.241	0.006**
BMI	0.16	0.856*
Personality		
Type D personality	0.336	<0.001*
Extraversion	-0.115	0.201*
Neuroticism	0.223	0.012*
Psychoticism	0.180	0.044**
Temperament		
Depresive	0.175	0.05*
Cyclothymic	0.212	0.017*
Hyperthymic	-0.99	0.271*
Irritablr	0.309	<0.001**
Anxious	0.144	0.109*

BMI: Body mass index; *:Pearson correlation analysis; **: Spearmen correlation analysis.

revealed that 58 (46%) participants had Type D personality traits. The evaluation of the dominant temperament by the TEMPS-A cut-off scores showed that depressive temperament was dominant in 18 (14.3%) participants, irritable temperament in 12 (9.5%) participants, and anxious temperament in 16 (17.3%) participants (Table 1).

The classification of the participants by gender revealed no significant difference between the female and male groups in terms of pain, stiffness, function, and total WOMAC scores (p>0.05 for all). The classification of the participants as unilateral and bilateral knee OA showed a significant difference in terms of pain, stiffness, and total WOMAC scores in the bilateral knee OA group (p=0.045, p=0.049, p=0.040, respectively), while there was no significant difference in terms of function (p=0.080). The classification of those with and without Type D personality revealed a significant difference in terms of function, which was worse in those with Type D personality (p<0.001), while there was no significant difference between the groups in terms of pain, stiffness, and total WOMAC scores (p>0.05 for all) (Table 2).

The evaluation of the correlation of pain level with some variables and personality temperament characteristics showed a negative correlation (r=-0.252, p=0.004) with the duration of education and a positive correlation (r=0.226, p=0.011) with Type D personality (Table 3).

The evaluation of the correlation of total WOMAC score with some variables and personality temperament characteristics revealed a negative correlation with the duration of education (r=-0.301, p=0.001), a positive correlation with disease duration (r=0.241, p=0.006), a positive correlation with Type D personality, neuroticism, and psychoticism (r=0.336, p<0.001; r=0.223, p=0.012; r=0.180, p=0.044, respectively), and a positive correlation with cyclothymic and irritable temperament (r=0.212, p=0.017; r=0.309, p<0.001, respectively) (Table 4).

DISCUSSION

In the study, it was demonstrated that there was a negative correlation between pain level and education and a positive correlation between pain level and Type D personality in patients with knee OA. The results revealed a negative correlation between total WOMAC score and

duration of education, a positive correlation between total WOMAC score and Type D personality traits, neuroticism, psychoticism personality traits, and a positive correlation between total WOMAC score and cyclothymic and irritable temperament traits.

Previous studies on personality traits found that negative affective states, depression, and neuroticism were highly associated with pain and disability in OA patients.[19,20] Moreover, a prospective study on neuroticism predicted higher joint pain levels after 23 years.[21] Our study showed no correlation with pain, but there was a positive correlation between neuroticism and psychoticism and total WOMAC score, which also evaluates pain, stiffness, and functionality. Personality traits such as neuroticism and psychoticism may have a negative effect on diverting situational pain-related attention response from pain sensation to another direction and on cognitive distraction mechanisms.[22] In addition, it has been suggested that psychoticism is a personality trait that is a predictor of bodily symptoms.[23] These negative effects may be associated with the results of our study.

Our study is the first to assess Type D personality in patients with knee OA. Previous studies with fibromyalgia and ankylosing spondylitis patient groups found that patients with Type D personality were worse in terms of pain, physical mobility, sleep, and social and emotional functions compared to patients without Type D personality.[24,25] Furthermore, Type D personality, including chronic pain, has been associated with increased the number or severity of reported health complaints. The comparison of the groups with and without Type D personality in our study showed a significant difference only in terms of the WOMAC stiffness score, while there was a positive correlation between the Type D personality score and both pain and total WOMAC score.

A previous study conducted in our country evaluated temperament characteristics of OA patients and found a higher rate of depressive and anxious dominant temperament and no correlation with pain.[26] In our study, the dominant temperament rates were similar, and no correlation was found with pain. Moreover, there was a positive correlation between total WOMAC score and cyclothymic and irritable temperament. Individuals with a depressive temperament have low energy and exhibit negative cognitions and emotions. In anxious temperament, the person tends to constantly worry about the well-being of himself/herself and his/her relatives. It involves hyperthymic temperament, enthusiastic temperament, and behavioral excesses. Irritable temperament is characterized by a highly unbalanced mixture of dysthymic and hyperthymic characteristics, exhibiting characteristics such as overly critical attitudes and outbursts of anger. Cyclothymic temperament is characterized by mood swings between depressive and hyperthymic characteristics.[27,28] The prevalence of depressive and anxious temperament in patients with knee OA and the positive correlation of total WOMAC score with cyclothymic and irritable temperament may be the subject of research for future studies. There is a need for further research on these issues.

Consistently with previous studies,[29,30] there was no difference between the gender groups in terms of pain and other WOMAC scores in our study. Interestingly, our study showed no correlation between age and pain and the WOMAC sub-scores, although the prevalence of knee OA increased with age. This may be due to the higher prevalence of life stress and hypochondriasis, which are associated with higher pain scores in young people.[31] Obesity, which is a known risk factor for the development of OA, has been associated with increased severity of OA-related pain.[32] However, in our study, as in the study of Somers et al.,[33] it was found that BMI was not correlated with pain scale scores. In line with another study conducted in our country,[34] there was a negative correlation between educational level and the WOMAC scores. This may be related to the association of a low level of education with the inability to interpret pain sensation and to cope with pain and disability. As expected, pain, stiffness, and total WOMAC scores were significantly higher in those with bilateral knee OA than those with unilateral knee OA. As an unexpected result, there was no difference in function between the groups. Thus, it can be interpreted that functionality will be significantly affected in both cases in patients with knee OA, whether unilateral or bilateral.

Our study has some limitations. The study sample is relatively small. Since the sample size was insufficient, a group could not be created according to dominant temperament characteristics, and no statistical evaluation could be made. In addition, since an observational study was conducted by taking sections containing a certain period in a long-term disease, it only includes the state within the study period.

Conclusions

Our study demonstrated a positive correlation between Type D personality and pain, a positive relationship between the total WOMAC score and Type D personality, neuroticism, and psychoticism personality traits, and a positive correlation between the total WOMAC score and cyclothymic and irritable temperament traits. In addition to pharmacological and physical therapy, psychosocial interventions for these domains may help treat OA.

Ethics Committee Approval

This study approved by the Erzurum Regional Training and Research Hospital Ethics Committee (Date: 07.12.2020, Decision No: 2020/22-214).

Informed Consent

Prospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.İ., K.S.; Design: A.İ., K.S; Supervision: A.İ., K.S.; Fundings: A.İ., K.S.; Materials: K.S.; Data: A.İ., K.S.; Analysis: A.İ.; Literature search: A.İ., K.S.; Writing: A.İ., K.S.;

Critical revision: A.İ., K.S.

Conflict of Interest

None declared.

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Diz Osteoartritli Hastalarda Kişilik ve Mizaç Özelliklerinin Ağrı ve Fonksiyonla İlişkisi

Amaç: Diz osteoartritli hastalarda kişilik ve mizaç tipleri ile işlevsellik ve hissedilen ağrı arasındaki ilişkiyi inceleyen az sayıda çalışma bulunmaktadır. Bu çalışmada diz osteoartritli hastalarda kişilik ve mizaç özellikleri ile ağrı ve fonksiyon arasındaki ilişkinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya dahil edilme kriterlerini karşılayan diz osteoartrit tanısı alan 126 hasta dahil edildi. Kişilik değerlendirmesi için Eysenck Kişilik Anketi Revize Edilmiş Kısa Formu (EPQR-S) ve D Tipi Kişilik Ölçeği (DS-14), mizaç değerlendirmesi için Memphis, Pisa ve San Diego Mizaç Değerlendirmesi Anketi (TEMPS-A) kullanıldı. OA ağrısı ve genel fonksiyon değerlendirmesi için Western Ontario ve McMaster Üniversiteleri Osteoartrit İndeksi (WOMAC) kullanıldı.

Bulgular: Katılımcıların 58'i (%46) D Tipi kişilik özellikleri gösterirken, 18'inde (%14.3) depresif mizaç, 12'sinde (%9.5) sinirli mizaç ve 16'sında (%17.3) endişeli mizaç baskındı. D Tipi kişiliğe sahip olanlar daha kötü işlevlere sahipti ve D Tipi kişilik, ağrı ve toplam WOMAC puanı ile pozitif olarak ilişkiliydi. Toplam WOMAC puanı, nevrotiklik ve psikotisizm kişilik özellikleri ve siklotimik ve sinirli mizaç özellikleri ile pozitif bir korelasyon gösterdi.

Sonuç: Bu çalışma, diz osteoartritli hastalarda ağrı ve toplam WOMAC skorunun kişilik ve mizaç özellikleri ile ilişkili olduğunu göstermektedir. Farmakolojik ve fizik tedaviye ek olarak, bu alanlara yönelik müdahaleler faydalı olabilir.

Anahtar Sözcükler: Ağrı; fonksiyon; kişilik; mizaç; osteoartrit.

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Original Article

Comparison of Laparoscopic Surgery and Expectant Management in Patients with Adnexal Masses During Pregnancy in A High-Volume Tertiary Center

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Keywords: Adnexal mass, dermoid cyst; laparoscopy; ovarian cyst; pregnancy.

ABSTRACT

Objective: To describe the characteristics of pregnant women diagnosed with adnexal masses and review our experience with diagnosis, management and treatment modalities in this area for which there are no definitive treatment guidelines.

Methods: All women with adnexal masses during pregnancy whose management and follow-up was completed at a large tertiary referral center between January 2018 and September 2023 were retrospectively evaluated. After applying the exclusion criteria, a total of 19 women who underwent antepartum laparoscopic adnexal surgery (group 1) and 34 women who underwent expectant management (group 2) were included.

Results: Gestational age at birth, cesarean section rates, birthweight and APGAR-5 scores were similar, while the largest mass diameter and CA-125 levels were significantly higher in group 1 ($p<0.001$ and $p=0.014$, respectively). Of the patients in group 1, 15 (78.9%) had unilateral complex cysts and 4 (21.1%) had unilateral simple cysts, while there were no bilateral masses. Emergency laparoscopy was performed in 6 (31.6%) of patients for adnexal torsion and in 7 (36.8%) for cyst rupture, while elective laparoscopy was performed in 6 (31.6%) asymptomatic patients with suspected malignancy. While functional cyst was the most common histopathologic finding, malignancy was found in 2 cases (granulosa cell tumor and endometrioid adenocarcinoma). Preterm births occurred in 8 (41.1%) women, of whom 5 (26.3%) gave birth before 34 weeks' gestation and 3 (15.7%) between 34-36 weeks and 6 days.

Conclusion: Parallel to the increase in ultrasound examinations in early pregnancy, both the overdiagnosis and early detection of adnexal masses during pregnancy have increased. Given the high rate of spontaneous regression in most lesions and the fact that bleeding in ruptured cases is usually self-limiting, an expectant approach would be appropriate in cases without hemodynamic instability, acute abdomen and/or suspected malignancy. Laparoscopy is a safe and efficient surgical approach for surgery.

INTRODUCTION

Adnexal masses are cystic and/or solid lesions of the adnexal structures consisting of bilateral ovaries, fallopian tubes, adjacent ligaments, and connective tissue. Adnexal masses are one of the most common gynecological problems and can affect women of almost any age. The incidence varies between 0.1-2.4% of pregnant women.[1] The malignancy rate of adnexal masses during pregnancy is reported to be 1-6%.[1] Before the widespread use of ultrasound, most adnexal masses during pregnancy, especially asymptomatic ones, were only noticed when they were identified during a cesarean section or when patients became symptomatic in the postpartum period. The diagnosability of adnexal masses during pregnancy has increased in recent years as ultrasound examinations in the first trimester have become widely available, the number of patients attending healthcare facilities for antenatal care has increased, and detailed sonographic anatomic examination of the fetus in the second trimester has become more important.[2] About 70% of cystic masses are functional cysts with a benign course, which usually regress spontaneously at the beginning of the second trimester. Most of them are detected incidentally during an ultrasound examination in the first trimester.[3] The majority of persistent adnexal masses with a diameter of 5 cm or more are dermoid cysts.[4]

There are no established guidelines for the management of adnexal masses during pregnancy, and approaches may vary from clinic to clinic. There are basically two types of treatment approaches: expectant management and surgery. Many factors should be considered when making a treatment plan, including the patient's age, general condition, presence of symptoms, gestational age, ultrasound findings, and laboratory results. While the diagnosis and treatment of a potentially malignant lesion may be delayed by expectant management leading to an advanced stage, surgery must be performed for lesions causing dystocia, adnexal torsion, and life-threatening rupture with intra-abdominal hemorrhage.[2]

Despite advances in surgical techniques, including minimally invasive methods, many questions remain about the adverse effects and benefits of unnecessary adnexal surgery during pregnancy. Recognizing the need for studies that bridge the gap between theory and practice regarding perinatal and maternal outcomes in such pregnancy populations, we conducted this study to share our five years of experience.

MATERIALS AND METHODS

Study Design

We conducted a retrospective cohort study at a large tertiary center between January 1, 2018, and September 30, 2023, that included all patients diagnosed and treated for an adnexal mass during pregnancy. After approval by the Kartal Dr. Lütfi Kırdar State Hospital's ethics committee for medical research (Date: 29.11.2023, Decision No: 2023/514/262/2), the medical records and patient files were examined retrospectively. Our study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent could not be obtained from the participants, as not all participants could be

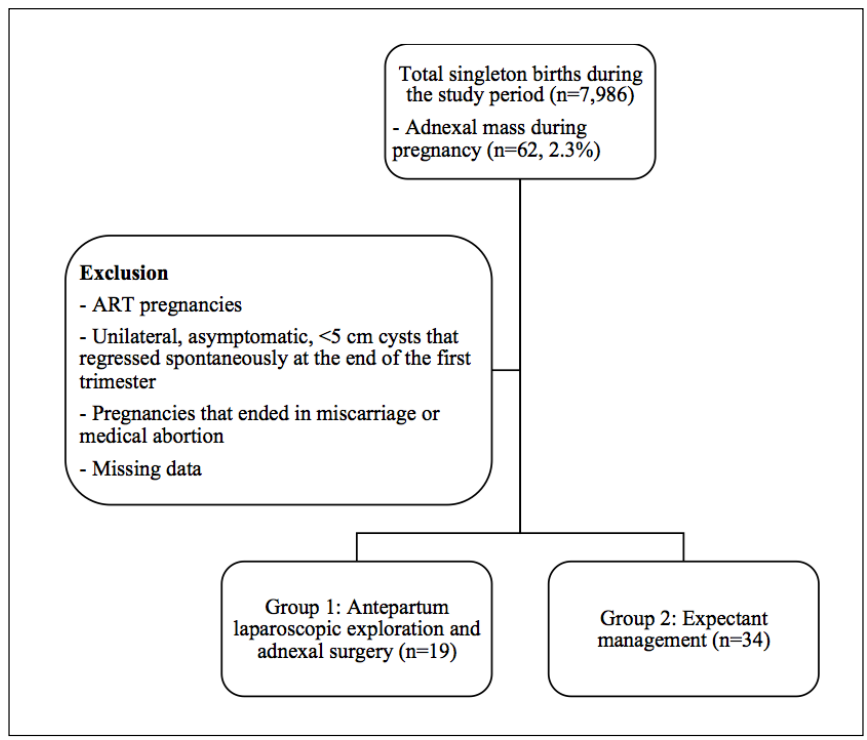

Figure 1. Flow chart of the study.

reached and the study was planned retrospectively.

Characteristics of Study Population, Patient Selection, and Data Collection

Multiple pregnancies; pregnancies conceived with assisted reproductive techniques; pregnancies that ended in miscarriage or medical abortion; pregnant women with unilateral, asymptomatic cysts <5 cm in size that disappear spontaneously at the end of the first trimester and indicate a corpus luteum; patients whose adnexal mass persists on postnatal ultrasound examinations; patients with missing data were not included in the study. All data, including age, medical history, pregnancy history, body mass index (BMI), gestational age at diagnosis, symptoms, examination findings, ultrasound findings, cancer antigen-125 (CA-125) levels, gestational age at delivery, and mode of delivery, 5-minute Apgar scores,[5] postpartum ultrasound findings, treatment method of adnexal mass, surgical and histopathologic findings in patients who underwent surgery were obtained from the hospital database and patient records.

Definitions, Diagnostic Methods, and Surgery

Gestational age was calculated based on the first day of the last menstrual period and confirmed by sonographic dating based on measurement of the crown-rump length of the fetus in the first trimester. If the calculated gestational age contained fractions of days, the gestational age is rounded up or down to the nearest whole week. Sonographic assessment and measurement, including size, echogenicity, wall thickness, presence of papillary extensions and septation, margin features, and vascularity of adnexal masses, and presence of free intraperitoneal fluid were performed with the same sonographic system [GE Voluson 730 Expert System (General Electric Medical Systems, Milwaukee, WI, USA) with a 4-8 MHz transabdominal probe or a 5-9 MHz transvaginal transducer, if necessary]. Adnexal cystic masses with septation, solid components, and/or papillary structures were referred to as 'complex' cysts. Serum CA-125 measurements were performed with the Roche Cobas e801 (Roche Diagnostics International Limited, Rotkreuz, Switzerland) immunoassay analyzer.

In the patients for whom surgery was decided, a mass excision or salpingo-oophorectomy was performed with a laparoscopic approach in the lithotomy position after general anesthesia with intratracheal intubation. For prophylaxis, a single dose of 1 gram of intramuscular cefazolin was administered as standard 60 minutes before the procedure. While care is taken to maintain the integrity of the lesion, the resection is performed in an eb-0100 disposable endoscopic bag (Segimedical Surgitools Medical Instruments Co., Ltd., Shanghai, China) to prevent possible iatrogenic spillage of malignant cells. After completion of the resection, the specimen is removed in an endobag through an 11-mm trocar. If necessary, the liquid contents of the mass in the endobag are aspirated or the mass is cut to reduce its volume so that it can be removed more easily from the laparoscopic port.

Table 1. Demographic and clinical characteristics of the study population

Variable	Group 1 (n=19)	Group 2 (n=34)	Total (n=53)	p
Age (years)	28 (24-30)	29 (24-36)	28 (34-31)	0.248
BMI (kg/m^2)	26.9±3.01	27.9±3.61	27.5±3.41	0.340
Gravida (number)	3 (2-3)	2 (2-3)	2 (2-3)	0.924
Parity (number)	1 (0-2)	1 (1-1)	1 (1-2)	0.866
Nulliparity (number)	6 (31.6)	7 (20.6)	13 (24.5)	0.507
Miscarriage (number)	0 (0-1)	0 (0-1)	0 (0-1)	0.839
Gestational age at diagnosis (weeks)	18 (14-23)	14 (14-19)	15 (14-20)	0.175
Largest mass diameter (cm)	9 (7-10)	6 (5-7)	6 (5.5-8)	**<0.001**
Gestational age at birth (weeks)	37 (33-39)	38 (35-39)	38 (34-39)	0.328
PTB (<34 weeks)	5 (26.3)	6 (17.6)	11 (20.8)	1.000
PTB (34 – 36 weeks 6 days)	3 (15.8)	5 (17.4)	8 (15.0)	
CA-125 (IU/mL)	58 (29-118)	30 (23-37)	30 (25-41)	**0.014**
Mode of delivery				
Vaginal	13 (68.4)	28 (82.4)	41 (77.4)	0.311
Cesarean Section	6 (31.6)	6 (17.6)	12 (22.6)	
APGAR				
APGAR-1	9 (8-9)	9 (8-10)	9 (8-9)	0.137
APGAR-5	10 (9-10)	9 (9-10)	10 (9-10)	0.895
Birthweight (grams)	2890 (2110-3240)	2970 (2510-3330)	2950 (2440-3290)	0.427

APGAR: Appearance, pulse, grimace, activity and respiration; BMI: Body-mass index; CA-125: Cancer antigen-125; cm: Centimeters; IU/mL: International unit/milliliters; kg/m^2: kilograms/square meter; PTB: Preterm birth. Data are expressed as mean ± standard deviation, median (quartile1-quartile3), or number (percentage) where appropriate. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

Table 2. Clinical and sonographic characteristics of patients in antepartum laparoscopic exploration and adnexal surgery group (n=19)

Variable	Number (%)
Symptom	
Abdominal pain	12 (63.2)
Incidental	7 (36.8)
Sonographic characteristics	
Simple	4 (21.1)
Complex	15 (78.9)
Torsion	
Yes	6 (31.6)
No	13 (61.4)
Intraperitoneal free fluid	
Yes	7 (36.8)
No	12 (63.2)
Preterm Birth	
<34 weeks	5 (26.3)
34 – 36 weeks 6 days	3 (15.7)

Table 3. Histopathological findings (n=53)

Histopathology	Number (%)
Cystic lesion with spontaneous resolution	34 (64.2)
Functional ovarian cyst	5 (9.4)
Dermoid cyst	5 (9.4)
Endometrioma	2 (3.8)
Serous cyst adenoma	2 (3.8)
Paraovarian cyst	1 (1.9)
Fibroadenoma	1 (1.9)
Borderline ovarian tumor	1 (1.9)
Granulosa-cell ovarian tumor	1 (1.9)
Endometrioid adenocarcinoma	1 (1.9)

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA). Shapiro-Wilk tests were used to assess normality. Normally distributed continuous variables were described by the means and standard deviations, and the independent-samples t-test was used to compare these parameters between groups. For numerical data that did not have a normal distribution, descriptive analyses were performed using medians and quartiles (quartile 1-quartile 3), and the Mann-Whitney U test was used to compare these parameters between groups. For categorical variables, descriptive analyses were performed using frequency and percentage. Relationships between categorical variables were analyzed with the chi-square test. A type I error level of 5% overall was used to derive statistical significance. A p-value of less than 0.05 was considered a statistically significant result.

RESULTS

During the study period, there were a total of 7,986 singleton births, of which 62 (2.3%) were diagnosed with an adnexal mass during pregnancy. After applying the exclusion criteria, a total of 54 cases were included in the study: 20 patients who underwent antepartum laparoscopic exploration and adnexal surgery (group 1) and 34 patients whose adnexal mass regressed spontaneously after expectant management (group 2). No statistically significant difference was found between the groups in terms of demographic characteristics such as age, BMI, gravidity, parity, nulliparity, early pregnancy loss, and gestational age at diagnosis, as well as obstetric outcomes such as gestational age at delivery, mode of delivery, birthweight, and 5-minute Apgar scores, while the largest mass diameter and CA-125 levels were significantly higher in group 1 ($p<0.001$ and $p=0.014$, respectively). The median values of the largest adnexal mass diameter and CA-125 were 9 cm (range 7-10 cm) and 58 IU/mL (range 29-118) for group 1; 6 cm (range 5-7 cm) and 30 IU/mL (23-37), for group 2, respectively. The cesarean section rate among all cases was 22.6% (n=12). The indications for cesarean section were non-reassuring fetal status (n=2), malpresentation (n=1), previous cesarean section (n=7), fetal macrosomia (n=1), and non-progressive labor (n=1). The median gestational age at delivery was 38 weeks (range 34-39 weeks) (Table 1).

The clinical and sonographic characteristics of the patients who underwent laparoscopic surgery are shown in Table 2. Accordingly, 15 (78.9%) of the masses were complex, and 4 (21.1%) were simple cysts. There was no patient with bilateral adnexal masses. Emergency laparoscopy was performed in 12 (63.2%) patients with abdominal pain, of whom 6 (31.6%) were diagnosed with ovarian torsion and 7 (36.8%) with intraperitoneal hemorrhage due to cyst rupture. Elective laparoscopy was performed in 6 (31.6%) patients who were asymptomatic and in whom incidental adnexal lesions were detected on ultrasound by decision of the joint council of perinatology and gynecologic oncology departments. Preterm births occurred in a total of 8 (41.1%) patients, of whom 5 (26.3%) were before 34 weeks' gestation and 3 (15.7%) were between 34 and 36 weeks and 6 days. There was no significant difference between the groups in terms of preterm births.

In our study, the histopathologic results of the patients diagnosed with adnexal masses are listed in Table 3, and the lesions that spontaneously regressed during the follow-up period were designated as "cystic lesions with spontaneous resolution." Accordingly, the most common adnexal lesions occurring during pregnancy were cystic lesions with spontaneous resolution (64.2%), while the least common were paraovarian cysts, fibroadenomas, borderline ovarian tumors, granulosa cell tumors, and endometrioid adenocarcinomas (1.9% each). In the patients diagnosed with granulosa cell ovarian tumor and endometrioid adenocarcinoma, the final histopathological examination revealed grade 1 and stage 1A disease in both patients. The

postpartum follow-up of these two patients continues in our clinic, and so far, none of the patients have been diagnosed with a recurrence.

DISCUSSION

Before the widespread use of ultrasound, most adnexal masses during pregnancy were often not diagnosed in the prepartum period or could only be detected if the patient developed symptoms or by chance during a cesarean section. Early diagnosis of adnexal masses during pregnancy is increasing as more and more pregnant women are examined by gynecologists in the first weeks of pregnancy, ultrasound is widely used in obstetric practice, and there are advances in ultrasound technology. At the same time, however, the rate of overdiagnosis due to misdiagnosis of physiological adnexal structures as adnexal masses may also increase.[6] The prevalence of adnexal lesions detected during pregnancy varies widely, as there is no consensus on which lesions should be defined as "adnexal masses".[1,4,7-10] Therefore, to obtain more accurate results in our study, cysts that persist due to ovarian hyperstimulation, simple cystic lesions of less than 5 centimeters suggestive of a corpus luteum, and cysts that disappear spontaneously at the end of the first trimester were not considered adnexal masses. In our study, the diagnosis of adnexal masses was mostly made in the second trimester (between 14 and 20 weeks), and the earliest week of diagnosis was 10 weeks in the laparoscopic surgery group and 12 weeks in the expectant management group.

Most adnexal cystic masses that occur during pregnancy are benign, simple cysts with a diameter of less than 5 cm. These are follicular cysts or corpus luteum cysts that occur as part of the normal physiological function of the ovaries and are referred to as functional cysts. As in our study (the proportion of cases that regressed spontaneously and whose pathologic diagnosis was reported as a functional cyst was 73.6%), about 70% of all adnexal cystic masses detected in the first trimester are functional cysts.[6] Other benign adnexal lesions have been reported as dermoid cyst, endometrioma, serous cystadenoma, and mucinous cystadenoma, in order of frequency.[6] Less common benign lesions such as borderline ovarian tumors, fibroadenomas, and paraovarian cysts may also occur as adnexal masses during pregnancy.

Although the most common type of cancer diagnosed during pregnancy is breast cancer, ovarian cancer is the fifth most common type of cancer after thyroid cancer, cervical cancer, and Hodgkin's lymphoma. Malignant ovarian tumors account for 1-6% of adnexal masses detected during pregnancy.[1,4,7] In our study, this incidence was 3.8%, which is consistent with the literature. In addition to suspected malignant disease, torsion, which causes severe pain, and rupture, which can result in both pain and impaired hemodynamic stability due to bleeding, may also require surgery. The probability of adnexal masses causing ovarian torsion is higher during pregnancy and is between 5-22%.[4,11] Torsion occurs most frequently between 10-17 weeks of gestation (60%), while the risk of torsion decreases to about 6% of cases after 20 weeks. It was found that adnexal masses with a size of 6-8 cm have a significantly higher risk of torsion than other sizes.[11] In our study, torsion was observed in 6 of 53 patients (11.3%). The size of the torsed masses varied between 7-12 cm. Ovarian torsion occurred in 2 cases after 20 weeks of gestation and in 4 cases before 20 weeks. On the other hand, 7 (13.2%) cases underwent laparoscopy due to abdominal pain and free intra-abdominal fluid due to rupture of the adnexal mass.

In our study, none of the patients had to be converted to open surgery, and only one case resulted in an intraoperative complication. In this case with intra-abdominal adhesions due to endometriosis, the dissection of the adhesions between the bladder and the endometrioma resulted in a linear injury of approximately 1 cm in the bladder wall, which was successfully repaired with laparoscopy. With the exception of cases that require very rapid intervention and extensive exploration, such as severe vascular injuries, many complications can be treated laparoscopically without the need for open surgery.[12] The main limitations of the present study are its retrospective nature and the relatively small sample sizes. The major strength is that it was conducted in a large tertiary referral hospital that has an experienced surgery team using the same algorithms for diagnosis, management, and follow-up.

Conclusion

Parallel to the increase in ultrasound examinations in early pregnancy, both the overdiagnosis and early detection of adnexal masses during pregnancy have increased. Given the high rate of spontaneous regression in most lesions and the fact that bleeding in ruptured cases is usually self-limiting, an expectant approach would be appropriate in cases without hemodynamic instability, acute abdomen, and/or suspected malignancy. Laparoscopy is a safe and efficient surgical approach for surgery in patients with an adnexal mass during pregnancy. Further randomized, prospective, and multicenter studies on this topic are needed to substantiate our findings.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar State Hospital Ethics Committee (Date: 29.11.2023, Decision No: 2023/514/262/2).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.L.D., E.M.; Design: E.M., G.Y., S.Ö.; Supervision: E.M., G.Y., U.S.,; Fundings: None. Materials: Y.A., Ö.K.; Data: E.M., Y.A.; Analysis: P.Y., M.L.D., A.K.; Literature search: M.L.D., P.Y., S.T.S.; Writing: M.L.D.; Critical revision: E.M., G.Y., U.S.

Conflict of Interest

None declared.

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Yüksek Hacimli Üçüncü Basamak Bir Merkezde Gebelikte Adneksiyel Kitlelere Yaklaşım: Laparoskopik Cerrahi ve Ekspektan Yönetimin Karşılaştırılması

Amaç: Adneksiyel kitle tanısı alan gebelerin özelliklerini tanımlamak ve kesin bir yönetim kılavuzu bulunmayan bu alanda tanı, yönetim ve tedavi yöntemlerine ilişkin deneyimlerimizi gözden geçirmek.

Gereç ve Yöntem: Ocak 2018 ile Eylül 2023 tarihleri arasında hasta yoğunluğunun fazla olduğu bir üçüncü basamak sevk merkezinde yönetim ve takipleri tamamlanan, gebelikte adneksiyel kitle tanısı alan tüm kadınlar retrospektif olarak değerlendirildi. Dışlama kriterleri uygulandıktan sonra, antepartum laparoskopik adneksiyel cerrahi uygulanan 19 kadın (grup 1) ve ekspektan yönetim uygulanan 34 kadın (grup 2) çalışmaya dahil edildi.

Bulgular: Doğum haftası, sezaryen oranları, doğum ağırlığı ve Apgar-5 skorları benzer olup en büyük kitle çapı ve CA-125 düzeyleri grup 1'de anlamlı olarak yüksekti (sırasıyla p<0.001 ve p=0.014). Grup 1'deki hastaların 15'inde (%78.9) tek taraflı kompleks kist, 4'ünde (%21.1) tek taraflı basit kist mevcuttu, iki taraflı kitle yoktu. Hastaların 6'sına (%31.6) adneksiyel torsiyon, 7'sine (%36.8) kist rüptürü nedeniyle acil laparoskopi yapılırken, asemptomatik olan 6 (%31.6) hastaya malignite şüphesi ile elektif laparoskopi yapıldı. Fonksiyonel kist en sık görülen histopatolojik bulgu iken, 2 olguda (granüloza hücreli tümör ve endometrioid adenokarsinom) malignite saptandı. 8 (%41.1) kadında erken doğum meydana geldi; bunların 5'i (%26.3) 34. gebelik haftasından önce, 3'ü (%15.7) 34-36 hafta 6 gün arasında doğum yaptı.

Sonuç: Günümüzde gebeliğin erken haftalarında ultrasonografik muayenelerin artmasına paralel olarak gebelikte adneksiyel kitlelerin erken tanısında olduğu gibi aşırı tanıda da bir artış söz konusudur. Benign karakterli lezyonların kendiliğinden gerileme oranının yüksekliği; rüptüre olan vakalardaki kanamanın da kendini sınırlayabileceği göz önünde bulundurulduğunda hemodinamik instabilite, akut batın veya malignite şüphesi olmayan vakalarda ekspektan yaklaşım uygun olacaktır. Cerrahi gerektiren hastalarda tercih edilmesi gereken cerrahi yaklaşım, güvenli ve minimal invazif bir yaklaşım olan laparoskopi olmalıdır.

Anahtar Sözcükler: Adneksiyel kitle; dermoid kist; gebelik; laparoskopi; over kisti.

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Original Article

The Role of Vitamin D Status on Initial Characteristics of Primary Hyperparathyroidism: Current Clinical Experience from a Tertiary Center

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Keywords: Estimated glomerular filtration rate; parathyroid hormone; primary hyperparathyroidism; vitamin D status.

ABSTRACT

Objective: The aim of this study was to assess vitamin D status and its impact on the initial characteristics of primary hyperparathyroidism (PHPT).

Methods: This study included consecutive participants diagnosed with PHPT aged 18 years and/or older at a tertiary center between November 2017 and December 2023. A total of 195 subjects not taking vitamin D replacement were reviewed retrospectively. The study population was categorized into three groups according to their vitamin D levels at the time of admission: Group 1: vitamin D ≤19 ng/mL, Group 2: vitamin D 20-29 ng/mL, and Group 3: vitamin D ≥30 ng/mL. Demographic, clinical, biochemical, radiological findings, and post-operative complications were compared between the three groups.

Results: Among 195 patients, 157 (80.5%) were women, and 38 (19.5%) were men. The mean age was 56.4±14.5 years. Sixty-five patients (33.3%) had vitamin D deficiency (VDD), and 48 patients (24.7%) had vitamin D insufficiency. Of the 195 patients, 74 (37.9%) had kidney stones, and 90 (46.2%) had osteoporosis. Fracture frequency was 9.7% (n=19). VDD was associated with higher parathyroid hormone (PTH) levels (p=0.000) and better estimated glomerular filtration rate (p=0.021). When all groups were compared, there were no differences in terms of nephrolithiasis, osteoporosis, and fractures.

Conclusion: The present study revealed that VDD was associated with higher PTH levels and better renal function. However, vitamin D status was not associated with classical target organ involvement in PHPT.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is one of the most frequent endocrine diseases, with a higher predominance in postmenopausal women. PHPT is defined by hypercalcemia and increased or inappropriately normal serum parathyroid hormone (PTH) resulting from the excessive release of PTH in at least one parathyroid gland.[1,2] The most common cause is solitary parathyroid adenoma.[1,2] Three clinical phenotypes are described in PHPT. Symptomatic PHPT presents with overt kidney or bone complications. Asymptomatic PHPT presents no overt signs or symptoms, but patients may be affected by target organ involvement, for example, osteoporosis or nephrolithiasis.[1,2] Normocalcemic PHPT is defined as both normal albumin-corrected serum calcium levels and increased PTH. Patients in this classification may or may not have renal or skeletal complications.[1,2] In Western countries, most patients are asymptomatic due to increased recognition of PHPT with common biochemical screening tests and earlier diagnosis.[3] In contrast, in some developing countries, the majority of primary hyperparathyroid patients (PHPP) have the classical symptomatic phenotypes with kidney and bone presentations.[4]

25-hydroxyvitamin D (25OHD) deficiency (VDD) and insufficiency (VDI) are still widespread comorbidities in patients with PHPT.[5,6] The mechanism behind the higher frequency of VDD is multifactorial, including decreased synthesis of vitamin D, accelerated conversion of 25OHD into other vitamin D compounds, increased metabolic clearance rate of vitamin D, shorter half-life of vitamin D, low vitamin D intake, and low vitamin D-binding protein level.[7] Vitamin D status should be considered to explain the different clinical and biochemical presentations of PHPT. There are studies investigating the relationship be-

tween vitamin D status and its impact on the initial characteristics in PHPT.[5,6,8-14] Effects of vitamin D status on initial biochemical and clinical characteristics remain controversial. Lower vitamin D is associated with higher serum PTH,[4,6,8-10,12-14] higher serum calcium,[4,8,12,13] lower serum phosphate,[8,9] increased bone turnover markers,[4,6,8,10,12-14] lower bone mineral density (BMD),[8,10,11,13] higher rates of pathological fractures,[11,15] and higher urinary calcium excretion.[14] Patients with VDD tend to have larger parathyroid adenoma size or higher weight of excised parathyroid gland.[6,14,16-18] Preoperative VDD is also associated with the development of postoperative hypocalcemia.[19] Measurement and repletion to adequate levels of 25OHD in patients with PHPT are recommended in the current clinical guidelines for PHPT.[2] Vitamin D level should be maintained above 30 ng/mL before surgical or medical treatment.[2] The prevalence of VDD has become less common in recent years due to increased repletion in PHPT.[9,15,20]

There is limited available data on vitamin D status and its impact on the initial presentations of PHPP in our country. The aim of this present study is to explore the relationship between vitamin D status and initial characteristics of PHPT.

MATERIALS AND METHODS

Ethical committee approval for this present study was obtained on March 25, 2024, with decision number 2024.137. IRB2.062. This retrospective cohort study was conducted in a single tertiary center. Consecutive PHPP aged 18 years and/or older not taking vitamin D replacement between November 2017 and December 2023 were included in the study. Patients treated with bisphosphonates and/or denosumab at the time of admission were excluded.

A total of 195 subjects with PHPT, verified in accordance with current clinical guidelines, were analyzed retrospectively.[1,2] The diagnosis of PHPT was made by both elevated serum calcium and elevated or unsuppressed serum PTH levels. Abnormal PTH level was defined above 65 pg/mL in this study. Demographic, clinical, and biochemical characteristics of the subjects, including age, gender, body mass index (BMI), history of smoking, laboratory findings [(fasting blood samples for serum calcium, phosphate, PTH, 25OHD), estimated glomerular filtration rate (eGFR), and 24-hour urinary calcium excretion], complications of PHPT (osteoporosis, kidney stone, and fracture history), radiological imaging findings, histopathological findings, and complications after surgery were reviewed. Data of the patients were obtained from the hospital record system. Patients were categorized into three groups according to their serum concentration of vitamin D at the time of diagnosis. Group 1: vitamin D ≤19 ng/mL (VDD), group 2: vitamin D 20-29 ng/mL (VDI), and group 3: vitamin D ≥30 ng/mL [vitamin D sufficiency (VDS)].[1,2] The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate eGFR.[21] Neck and urinary tract ultrasonographic examinations were performed by experienced operators. Technetium-99m-labelled sestamibi parathyroid scintigraphy scan imaging was used in the identification of the hyperfunctioning parathyroid gland. BMD values were measured on the lumbar spine (L1-L4), femoral neck, total hip, and 1/3 distal radius using

Table 1. Baseline characteristics of patients with PHPT

Parameters	Total (n=195)
Age (years), mean±SD	56.4±14.5
Gender, n (%)	
Female	157 (80.5)
Male	38 (19.5)
BMI (kg/m^2), mean±SD	26.9±4.6
Smoking, n (%)	38 (19.5)
25OHD (ng/mL), mean±SD	29.2±18.1
25OHD status, n (%)	
≤19	65 (33.3)
20-29	48 (24.7)
≥30	82 (42.0)
Albumin-corrected calcium (mg/dL), mean±SD	11.4±0.8
Hypercalcemia, n (%)	
Mild (10-<12 mg/dL)	158 (81.0)
Moderate (12-<14 mg/dL)	34 (17.4)
Severe (≥14 mg/dL)	3 (1.6)
Phosphate (mg/dL), mean±SD	2.7±0.5
PTH (pg/mL), mean±SD	169.1±135.8
24-h urinary calcium excretion (mg/24h), mean±SD	326.5±164.6
eGFR (ml/min/1.73 m^2), mean±SD	100.4±28.0
Complications of PHPT, n (%)	
Kidney stone	74 (37.9)
Osteoporosis	90 (46.2)
Fracture	19 (9.7)
Acute Pancreatitis	3 (1.5)
Parathyroid lesion size (mm), mean±SD	13.8±6.2
Localization of abnormal parathyroid gland, n (%)	
Neck	171 (87.7)
Ectopic	24 (12.3)
Ectopic localization, n (%)	
Neck	17 (70.8)
Superior mediastinum	7 (29.2)
Surgical approach, n (%) (n=174)	
MIPS	168 (96.6)
Thoracostomy	6 (3.4)
Postoperative complication, n (%) (n=174)	20 (11.5)
Postoperative complication, n (%) (n=174)	
Temporary hypocalcemia	16 (80.0)
Permanent hypocalcemia	3 (15.0)
Hungry bone syndrome	1 (5.0)
Pathology report, n (%) (n=174)	
Adenoma	167 (96.0)
Atypical adenoma	7 (4.0)

PHPT: Primary hyperparathyroidism,; SD: Standard deviation; BMI: Body mass index; PTH: Parathyroid hormone; 25OHD: 25-hydroxyvitamin D; h: hour; eGFR: Estimated glomerular filtration rate; MIPS: Minimally invasive parathyroid surgery.

a dual-energy X-ray absorptiometry system with a Hologic device. Osteoporosis is defined as a BMD T-score ≤-2.5 at any of the above-mentioned sites. Parathyroid surgery was performed by experienced parathyroid surgeons according to recommendations of current clinical guidelines for PHPT.[1,2] Demographic, clinical, biochemical, radiological findings, and postoperative complications were compared in the three vitamin D groups.

The electrochemiluminescence immunoassay method was used to measure serum PTH and 25OHD. Adjusted total serum calcium concentration, phosphate, and 24-hour urinary calcium were measured by spectrophotometric assay. Albumin-corrected calcium was calculated using the formula: [(4-albumin)x0.8]+calcium. Serum creatinine concentration and 24-hour urinary creatinine excretion were measured with an enzymatic colorimetric test. These measurements were performed using a Roche Cobas 6000 analyzer device.

Statistical Analysis

IBM SPSS Statistics (version 27, Chicago, USA) program was used to analyze data. Descriptive statistics of variables were represented by percentages (%), frequencies, and means and standard deviations. The distribution of variables was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. A comparative analysis of independent groups studied by quantitative characteristics was carried out using ANOVA (Tukey test), Independent Samples T test, Kruskal-Wallis, and Mann-Whitney U test. Chi-Square test was used in the comparison of independent groups by qualitative characteristics. If the Chi-Square test did not meet the criteria, Fisher's Exact test was used. The statistical significance level was defined as $p<0.05$.

RESULTS

A total of 195 patients were analyzed in the study. Among them, 157 (80.5%) were women, and 38 (19.5%) were men with a mean BMI of 26.9±4.6 kg/m². Mean age was 56.4±14.5 years. The current smokers' rate was 19.5%. Mean 25OHD level was 29.2±18.1 ng/mL. Among participants, 65 (33.3%) had VDD, 48 (24.7%) had VDI, and 82 (42.0%) had VDS. Only 7.2% of patients (n=14) had severe VDD (vitamin D <10 ng/mL). Mean serum calcium concentration adjusted for albumin was 11.4±0.8 mg/dL. Participants had predominantly mild hypercalcemia (81%). Mean phosphate and PTH levels were 2.7±0.5 mg/dL and 169.1±135.8 pg/mL, respectively. Mean 24-hour urinary calcium excretion was 326.5±164.6 mg/day, and eGFR was 100.4±28 ml/min/1.73 m². Of the 195 patients, 74 (37.9%) had kidney stones, and 90 (46.2%) had osteoporosis. Fracture frequency was 9.7% (n=19). Three patients (1.5%) had a history of acute pancreatitis. Mean parathyroid lesion size was 13.8±6.2 mm. A group of 174 patients were operated on for PHPT. One hundred sixty-eight patients were operated with minimally invasive parathyroid surgery and 6 patients with thoracostomy. Baseline characteristics of the 195 patients with PHPT are summarized in Table 1.

The comparison of vitamin D groups [group 1: ≤19 ng/mL (VDD), group 2: 20-29 ng/mL (VDI), and group 3: ≥30 ng/mL (VDS)] is shown in Table 2. Patients who were in group 1 tended to have higher serum PTH levels than group 2 and group 3 (p=0.000) (Fig. 1). PTH levels did not differ between group 2 and group 3. Mean serum calcium and phos-

Table 2. Characteristics of patients with PHPT according to their vitamin D levels

Parameters	Group 1 (n=65) Deficient	Group 2 (n=48) Insufficient	Group 3 (n=82) Sufficient	P value
Age (years), mean±SD	52.5±14.7	58.0±16.3	58.5±12.7	0.064[K]
Gender, n (%)				
Female	52 (78.8)	38 (80.9)	67 (81.7)	0.903[x2]
Male	14 (21.2)	9 (19.1)	15 (18.3)	
BMI (kg/m²), mean±SD	27.6±5.6	25.8±4.3	27.0±3.8	0.208[K]
Smoking, n (%)	14 (21.2)	8 (17.0)	16 (19.5)	0.858[X2]
Albumin-corrected calcium (mg/dL), mean±SD	11.5±1.0	11.3±0.7	11.3±0.8	0.280[K]
Phosphate (mg/dL), mean±SD	2.6±0.5	2.7±0.6	2.8±0.5	0.069[K]
PTH (pg/mL), mean±SD	221.2±207.9	149.3±76.9	138.5±52.3	0.000[K]
24-h urinary calcium excretion (mg/24h), mean±SD	351.4±188.3	312.9±158.8	314.4±146.9	0.377[A]
eGFR (ml/min/1.73m²), mean±SD	109.7±31.8	91.9±26.8	99.1±24.1	0.021[A]
Kidney stone, n (%)	26 (39.4)	16 (34.0)	32 (39.0)	0.817[x2]
Osteoporosis, n (%)	26 (39.4)	22 (46.8)	42 (51.2)	0.356[x2]
Fracture, n (%)	5 (7.6)	4 (8.5)	10 (12.2)	0.608[x2]
Acute Pancreatitis, n (%)	1 (1.5)	0 (0.0)	2 (2.4)	>0.05[x2]
Parathyroid lesion size (mm), mean±SD	15.6±7.4	13.2±6.4	12.9±4.5	0.116[K]
Postoperative complication, n (%)	8 (13.6)	3 (7.3)	9 (12.2)	0.612[x2]

PHPT: Primary hyperparathyroidism; SD: Standard deviation; BMI: Body mass index; PTH: Parathyroid hormone; 25OHD: 25-hydroxyvitamin D; h: hour; eGFR: Estimated glomerular filtration rate. [A]ANOVA / [K]Kruskal-wallis (Mann-whitney u test) / [X2]Chi-Square test (Fisher's test).

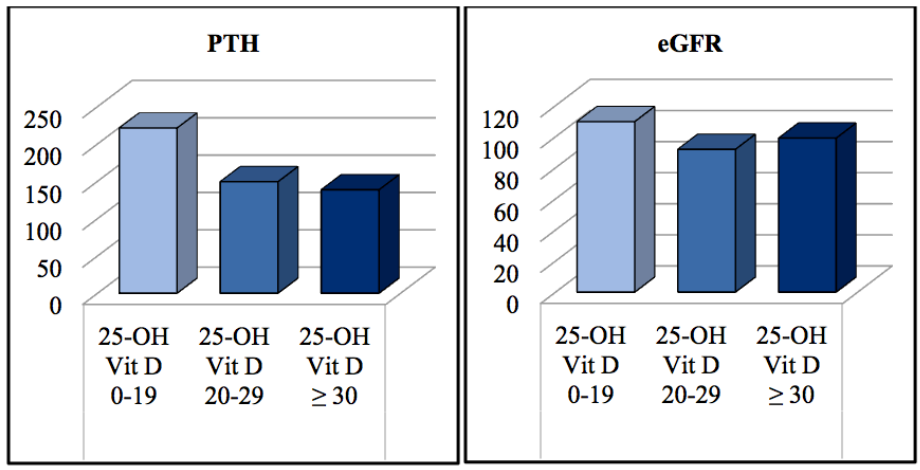

Figure 1. PTH and eGFR levels according to vitamin D thresholds: <20 (light blue), 20-29 (medium blue), and ≥30 (dark blue) ng/mL.

PTH: parathyroid hormone; 25-OH Vit D: 25-hydroxyvitamin D; eGFR: estimated glomerular filtration rate.

phate levels were comparable in all groups. Mean eGFR was better in group 1 than in group 2 (p=0.021). Renal functions did not differ in group 3 from group 1 and group 2 (Fig. 1). Vitamin D levels were not associated with age, gender, BMI, serum calcium, phosphate levels, 24-hour urinary calcium excretion, parathyroid adenoma size, osteoporosis, nephrolithiasis, fracture, and postoperative complications.

DISCUSSION

The present study, which included 195 patients with PHPT, described the relationship between vitamin D status and PHPT-related comorbidities at the time of diagnosis. Findings of this study showed that thirty-three percent of the study population had a lower than 20 ng/mL vitamin D level. Furthermore, VDD was associated with higher PTH levels and better renal function. We found no difference between vitamin D status and PHPT-related classical bone or kidney complications.

There are contradicting study results about the frequency of VDD in PHPT. Walker et al.[20] showed that VDD is less common in recent cohorts when compared to previous cohorts because vitamin D supplementation has become more widespread in today's Western World.[1,2] On the other hand, VDD and VDI are both common comorbidities in PHPT in different geographical areas.[5,8,9,18] Liu et al.[12] compared the vitamin D levels in PHPT patients between Shanghai and New York. The average vitamin D levels were significantly lower in the Shanghai cohort than in the New York cohort.[12] One study conducted in Turkey showed nearly 52% of the study group had VDD.[5] However, their sample size was smaller than ours. Walker et al.[9] reported that 19% of patients had lower than 20 ng/mL vitamin D levels. Another study from Italy reported that there was VDD in about one-third of patients with PHPT.[8] Vitamin D replacement therapy is still not at the optimal level, but there appears to be improvement.[22] Nowadays, more patients are insufficient when compared to the previous deficient status.[22] A similar VDD rate to the Italian cohort has been noted in our study. We think that the frequency of VDD will be less prevalent in PHPT if vitamin D replacement becomes widespread with the recommendation of current clinical guidelines for PHPT in our country.

Lower vitamin D levels are associated with more severe biochemical presentation. Liu et al.[12] reported that serum PTH and calcium levels were significantly higher in PHPP with lower vitamin D status. Some authors similarly showed that a lower vitamin D level was associated with higher PTH and calcium levels.[4,8,12,13] A study reported that vitamin D treatment for 1 year reduced PTH levels by 26% without exacerbating hypercalcemia.[23] Other studies confirmed the reduction in PTH levels with vitamin D repletion.[14,16] Serum calcium level also remained stable after vitamin D replacement.[16] These study results might be associated with the presence of mild hypercalcemia in the majority of PHPP.[1,2] There were studies that showed opposite results about the association between serum PTH and vitamin D levels.[5] In our study population, those with vitamin D levels below 20 ng/mL had higher PTH levels. We found no correlation between vitamin D status and serum calcium levels. It was thought that this finding might be related to earlier diagnosis.

PHPP with VDD present more severe skeletal manifestations at the time of diagnosis.[8,12,15,24] Signs of severe bone disease in PHPT include increased bone turnover markers,[4,6,8,10,12-14] lower BMD,[8,10,11,13] and increased fracture risk.[11,15] Brown tumors and osteolytic bone lesions are now very rare complications of PHPT in developed countries.[15] A study from India reported that most of the PHPP who presented with osteitis fibrosa cystica had severe VDD.[13] However, a recent study from India reported that VDD was associated with only increased serum alkaline phosphatase levels.[6] Walker et al.[9] reported that 39% of subjects had osteoporosis and 15% had a history of fragility fracture. They showed no difference between vitamin D levels and the presence of osteoporosis and fracture.[9] In their study, the vitamin D effect was only limited to cor-

tical 1/3 radius.[9] Their findings may be explained by the mean age being younger in the vitamin D deficient group than in the vitamin D insufficient and sufficient groups.[9] Furthermore, there was male predominance in these two groups.[9] Other studies found no significant correlation between vitamin D status and bone signs.[5] We observed that 46.2% of patients had osteoporosis, and 9.7% had a fragility fracture. Vitamin D status was not related to age, gender, presence of osteoporosis, and fragility fracture in our cohort. The lower fracture rate in our cohort may be associated with short-term VDD due to early diagnosis of PHPT and the presence of a few patients with severe VDD. Previous studies reported that patients with severe bone disease had prolonged PHPT coexisting with VDD.[13] The amount of nutritional daily calcium intake of the cases may be higher in our cohort. We also did not investigate the silent vertebral fractures with radiographic imaging modalities in patients who did not have a fracture history. In addition, we found a low smoking rate in our study population.

Hypercalciuria, nephrolithiasis, and chronic kidney disease are classical renal involvements of PHPT.[1,2,25] One study reported elevated urinary calcium excretion in PHPP with VDD.[14] In contrast to these findings, vitamin D was higher in patients with nephrolithiasis than in those without nephrolithiasis.[10] There were studies that found no differences between vitamin D status and the presence of nephrolithiasis or hypercalciuria.[5,9,25] In the comparison of PHPP according to their vitamin D status, we demonstrated no difference in nephrolithiasis and 24-hour urinary calcium excretion. Lower vitamin D was associated with better renal function in some studies.[9,10] We found that PHPP with VDD had higher eGFR. Rolighed et al.[26] found that daily supplementation with 2800 IU vitamin D was safe and associated without any change in urinary calcium and serum creatinine. In our study, renal functions did not differ in the vitamin D sufficient group from the deficient and insufficient groups. We think that vitamin D repletion could be safe in PHPP with VDD and VDI.

There is an inverse relationship between the size/weight of parathyroid adenoma and vitamin D levels.[8,14,15] VDD stimulates the proliferation of parathyroid cells, which may cause larger parathyroid adenoma size.[17] In most of the studies, the excised parathyroid gland weight was evaluated.[6,14,17,18] We evaluated the greatest size of the parathyroid lesion on ultrasonography examination because we did not have the weight of the parathyroid gland on pathology reports. In our study results, there was no relationship between parathyroid adenoma size and vitamin D levels. Ayçiçek et al.[5] confirmed our findings. In their study, the mean parathyroid adenoma size was similar in the vitamin D deficient and vitamin D sufficient groups. These findings may be related to the quicker diagnosis of PHPT in recent years compared to previous years.

Preoperative VDD and VDI are associated with the development of transient hypoparathyroidism.[19] One retrospective study showed that vitamin D supplementation in PHPT undergoing parathyroid surgery reduced hypocalcemia and the duration of hospitalization.[27] In this study, bilateral neck exploration was also associated with increased postoperative hypocalcemia risk.[27] Most of the postoperative complications were temporary hypocalcemia in our study. We found no correlation between vitamin D status and postoperative complications. Our findings may be related to a targeted surgical approach to the parathyroid lesion with experienced surgeons. We also began vitamin D replacement before the surgical approach in PHPP with VDD and VDI.

Some limitations exist within our study. It was a single-center study. Our study had a small sample size. We also did not have a control group. Calcium intake may play a role in the bone and kidney characteristics of the PHPP. We could not evaluate the amount of nutritional daily calcium intake of the cases. In addition, we did not assess bone turnover markers and silent fractures of the subjects. Finally, we did not have the excised weight of the parathyroid adenoma. Despite these limitations, we think that our study is important to show current vitamin D status and its effects on biochemical and clinical characteristics in PHPT. It seems that although VDD was a common condition in PHPP, vitamin D status was not associated with classical target organ involvement in PHPT. We think that our study results are related to earlier diagnosis and treatment in our country. Based on our study results, we suggest that PHPP with VDD and VDI should be treated with vitamin D replacement before the management plan for PHPT.

Conclusion

This present study showed that VDD was still a common condition in PHPP in our country. VDD was associated with higher PTH levels and better renal function. Furthermore, we found no difference between vitamin D status and PHPT-related classical skeletal and kidney complications.

Ethics Committee Approval

This study approved by the Koç University Ethics Committee (Date: 25.03.2024, Decision No: 2024.137.IRB2.062).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Conflict of Interest

None declared.

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Primer Hiperparatiroidinin Başlangıç Özelliklerinde D Vitamini Durumunun Rolü: Üçüncü Basamak Bir Merkezden Güncel Klinik Deneyim

Amaç: Bu çalışmanın amacı, D vitamini durumunu ve bunun primer hiperparatiroidinin (PHPT) başlangıç özellikleri üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Bu çalışma, Kasım 2017 ve Aralık 2023 tarihleri arasında üçüncü basamak bir merkezdeki 18 yaş ve/veya üzeri PHPT tanısı alan ardışık katılımcıları içermektedir. D vitamini replasmanı almayan toplam 195 hasta geriye dönük olarak incelendi. Çalışma popülasyonu başvuru anındaki D vitamini düzeylerine göre 3 gruba kategorize edildi. Grup 1: D vitamini ≤19 ng/mL, grup 2: D vitamini 20-29 ng/mL, ve grup 3: D vitamini ≥30 ng/mL. Demografik, klinik, biyokimyasal, radyolojik bulgular ve operasyon sonrası komplikasyonlar üç grup arasında karşılaştırıldı.

Bulgular: Yüz doksan beş hastanın, 157'si (%80.5) kadın, 38'i (%19.5) erkekti. Ortalama yaş 56.4+14.5 yıldı. Altmış beş hastada (%33.3) D vitamini eksikliği (DVE) ve 48 hastada (%24.7) D vitamini yetersizliği vardı. Yüz doksan beş hastanın, 74'ünde (%37.9) böbrek taşı ve 90'ında (%46.2) osteoporoz vardı. Kırık sıklığı %9.7 (n=19) idi. DVE daha yüksek paratiroid hormon (PTH) seviyesi (p=0.000) ve daha iyi tahmini glomerüler filtrasyon hızı (p=0.021) ile ilişkilendirildi. Tüm grublar karşılaştırıldığında böbrek taşı, osteoporoz ve kırık dağılımı açısından fark yoktu.

Sonuç: Mevcut çalışma DVE'nin daha yüksek PTH seviyesi ve daha iyi böbrek fonksiyonu ile ilişkili olduğunu ortaya çıkardı. Ancak, D vitamini durumu PHPT'de klasik hedef organ tutulumuyla ilişkili değildi.

Anahtar Sözcükler: D vitamini durumu; eGFR; paratiroid hormon; primer hiperparatiroidi.

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Original Article

Factors That Influence the Length of Hospital Stay After an Appendectomy

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ABSTRACT

Objective: Acute appendicitis is a surgical emergency that causes acute abdominal pain. After laparoscopic appendectomy, standard hospital care is nearly 24-h, although some patients need a longer length of hospital stay (LOS). This study aimed to evaluate the factors that influence LOS after appendectomy by examining biochemical and radiologic parameters.

Methods: This study retrospectively analyzed the data of 185 patients who underwent appendectomy in 2020-2024 in our hospital. Patient files were examined, and preoperative biochemical values such as white blood cell count, lymphocyte count, neutrophil count, C reactive protein (CRP) value, and neutrophil-lymphocyte ratio (NLR) were recorded. Preoperative radiologic examinations, appendix diameter, and presence of periappendiceal free fluid were assessed.

Results: A total of 163 patients were in early discharge group, and 22 patients were in late discharge group. The mean age of the patients was 34.5±8.5 years, and 53.5% were male. The mean discharge was 1.8±1.4 days. Lymphocyte count was statistically significantly lower in late discharge group, and NLR, CRP value, and appendix diameter were statistically significantly higher in late discharge group ($p<0.005$). Multivariate analysis showed a significant independent effect of NLR and CRP values ($p<0.05$).

Conclusion: Decreased lymphocytes, elevated NLR and CRP values, increased appendix diameter, and presence of periappendiceal free fluid on CT affected patients' LOS after appendectomy. Patients with these risk factors could be preferentially selected for laparoscopic approach, routine drain placement, late start of normal food, planned late discharge time and should be informed about longer hospitalization.

INTRODUCTION

Acute appendicitis (AA) is one of the causes of acute abdomen that requires urgent surgical intervention. The lifetime risk of AA is 7% to 8%, although it is more dominantly seen in males, with a rate of 8.6% to 6.7% in females. In the U.S., appendicitis, and related complications are responsible for 0.6% of all hospitalizations.[1-3] At the time of diagnosis of AA, in addition to the typical physical examinations, biochemical markers and radiologic examinations are diagnostic tools to decide the correct treatment options. Elevated C-reactive protein (CRP) value, white blood cell (WBC) count, neutrophil count and neutrophil percentage, and neutrophile-lymphocyte ratio (NLR) have been shown to predict the diagnosis of AA in previous studies.[1,4,5] Notably, computerized tomography (CT) imaging can accurately diagnose AA and identify perforation in AA with high specificity and sensitivity. The fact that postoperative complication rates of AA are observed at rates of 2% to 23% in studies makes correct diagnosis and treatment algorithms important.[2]

Laparoscopic appendectomy (LA) or the traditional open surgery approach are the surgical options, and antibiotic therapy is medical management in patients with high risk or comorbidity. With the integration of laparoscopy into surgical life, the most common approach in treatment is LA, which is increasingly applied at a higher rate, approaching nearly 90%.[1,2,6,7] Nowadays, with minimally invasive technology and a new anesthetic modality, there is a tendency for single-day discharge surgery and hospital stay to decrease. The LA technique enhances shorter length of hospital stay (LOS) by decreasing postoperative pain, nausea, and wound infection rates, providing early ambulation.

This is directly linked to reducing costs and increasing the utilization capacity of potential hospital beds.[2,3,8] However, rehospitalization of patients is related to intra-abdominal abscesses, ileus due to peritonitis, hematoma in the right lower quadrant, and deep surgical site infections. All of these outcomes cause a longer LOS and higher costs,[3] as patients require longer hospitalization after appendectomy for further evaluations.

The aim of this study was to evaluate the factors that influence the LOS in patients with AA.

MATERIALS AND METHODS

The study was designed as a retrospective data analysis study. Patients who were diagnosed with AA and underwent surgery in our hospital (private clinic) between January 2020 and January 2024 were included in the study. Patient data were collected and analyzed retrospectively, including patients' age, gender, biochemical values such as preoperative leukocyte count, neutrophil count, neutrophil-lymphocyte ratio (NLR), CRP value, preoperative radiological images including appendicitis diameter, and presence of periappendiceal free fluid in abdomen. In addition, the type of surgeries, including open, laparoscopic, conversion from laparoscopic to open surgery, pathological evaluations, LOS, and need for rehospitalization were recorded from the patient files.

Inclusion and exclusion criteria

Patients who had an appendectomy between January 2020 and January 2024 and patients over 16 years of age were included. We excluded patients who had incidental appendectomy without diagnosis with AA (especially at the time of gynecological operations), lacked data records, or whose data were inaccessible.

A total of 202 patients who underwent appendectomies between January 2020 and January 2024 were evaluated. Four patients were excluded because an appendectomy was performed incidentally during gynecologic surgery. Thirteen patients' data were not collected properly, and 17 patients were excluded. Finally, 185 patients were included in the study (Figure 1).

The patients were divided into two groups: the early discharge group, which had an LOS of under 48 h, and the late discharge group, which had an LOS of over 48 h or re-admission.

Primary outcome and ethical approval

The primary outcome of this study was to evaluate the factors that affect LOS or readmission after appendectomy. Before the study, ethical committee approval was obtained by Training and Research Hospital Ethics Committe e(E-46059653-050.99-242070323). Due to the retrospective study design, informed consent was not applicable.

Statistical analysis

Mean, standard deviation, median, lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The distributions of variables were measured by Kolmogorov–Smirnov and Shapiro–Wilk tests. The Mann–Whitney U test was used in the analysis of quantitative independent data. A chi-square test was used to analyze the qualitative independent data. The effect level and cut-off value were investigated using the receiver operating characteristic (ROC) curve. The effect level was investigated using univariate and multivariate logistic regressions. The SPSS 28.0 program was used for the analyses.

Complications

There was no mortality in the study. We observed a 30-day re-admission to the hospital in six patients. One patient needed percutaneous drainage for an abdominal abscess. All the included patients were discharged. No major bleeding or transfusion was seen.

RESULTS

Patient demographical features are shown in Table 1, including age, gender, operation type, radiological features such as appendix diameter and periappendiceal free fluid, biochemical results such as WBC, neutrophil count, lymphocyte count, NLR, CRP value, pathological evaluations, discharge day, and readmissions.

Patient median age was 33 years, with 53.5% of the patients being males. Overall, 96.2% of the surgeries were completed by laparoscopic. The median WBC value was $12.3x10^3$ /µl, lymphocyte value was $1.9x10^3$ /µl, and neutrophil value was $9.7x10^3$ /µl. The mean NLR value was 6.1±4.4, and the mean CRP value was 33.4±54.3 mg/l. Mean discharge day 1.8±1.4 and rate of readmission was

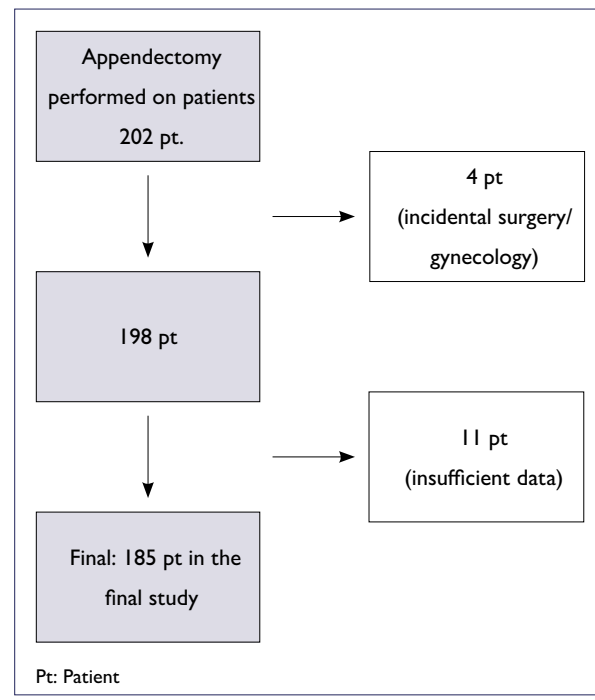

Figure 1. Patient selection data and exclusion process.

Table 1. Patients' demographic features

	Min–Max	Median	Mean±ss/n%	
Age	17.0 - 64.0	33.0	34.3±8.5	
Gender				
Female			86	46.5%
Male			99	53.5%
Operation type				
Laparoscopic appendectomy			178	96.2%
Conversion laparoscopic to open surgery			2	1.1%
Conventional (open) surgery			5	2.7%
Radiology				
CT			137	74.1%
USG			48	25.9%
WBC	4.9 - 23.5	12.3	12.6±3.9	
Neutrophil	2.4 - 19.9	9.3	9.7±3.9	
Lymphocyte	0.6 - 5.3	1.8	1.9±0.8	
NLR	1.0 - 23.0	5.1	6.1±4.4	
CRP	0.7 - 298.9	11.4	33.4±54.3	
Appendix diameter (mm)	1.0 - 19.0	11.0	10.9±3.0	
Periappendiceal free fluid				
(-)			161	87.0%
(+)			24	13.0%
Pathologic Evaluation				
Acute appendicitis			123	66,5%
Phlegmonous/suppurative appendicitis			32	17.3%
Gangrenous appendicitis			22	11.9%
Lymphoid hyperplasia			6	3.2%
Malignancy			2	1.1%
Discharge day	1.0 - 9.0	1.0	1.8±1.4	
Rehospitalization				
(-)			179	96.8%
(+)			6	3.2%

3.2% (6 patients). According to this information, patients were divided into two groups: the early discharge group (under 48h) and the late discharge group (over 48h). The features of these groups are presented in Table 2.

The analysis of the age and gender of the patients did not reveal statistically significant differences between the early discharge groups and the late discharge groups ($p>0.005$). The ratio of conventional appendectomy was significantly higher in the late discharge group than in the early discharge group ($p<0.005$). A comparison of biochemical values showed no statistically significant difference between the two groups regarding WBC count and neutrophil count ($p>0.005$). However, lymphocyte count was statistically significantly lower ($p<0.005$), and NLR and CRP values were statistically significantly higher in the late discharge groups (<0.005). Appendix diameter was significantly statistically higher in late discharge groups, as was the presence of periappendiceal free fluid ($p<0.005$). The rehospitalization ratio was significantly higher in the late discharge group ($p<0.005$) (Table 2).

The results of the univariate and multivariate logistic regression analyses for factors effecting discharge day after appendectomy is shown in Table 3. We observed a significant ($p<0.05$) effect of lymphocyte, NLR, CRP value, appendix diameter, and periappendiceal free fluid in distinguishing between the early and the late discharge groups. In the multivariate model, a significant independent effect of NLR and CRP values was observed ($p<0.05$).

Further, we observed a significant effectiveness of an NLR cut-off value of 6.85 (area under the curve 0.684 [0.555–0.813]) and a CRP cut-off value of 16 mg/L (area under curve 0.745 [0.646–0.843]) in distinguishing between the early discharge and the late discharge group' patients as shown Tables 4 and 5.

DISCUSSION

Appendicitis is one of the most common surgical operations in emergency units and requires hospitalization. With laparoscopy and new anesthetic modalities, a single-day discharge program after an appendectomy is a trend issue. However, some patients need rehospitalization due to complications, such as intra-abdominal abscesses, he-

Table 2. Comparison of the early and late discharge groups

	Discharge day ≤ 2		Discharge day ≥ 3		
	Mean±ss/n%	Median	Mean ± ss/n%	Median	p
Age	34.0±8.1	33.0	36.0 ± 10.7	34.0	0.349[m]
Gender					
Female	72	44.2%	14	63.6%	0.086[X²]
Male	91	55.8%	8	36.4%	
Operation type					
Laparoscopic appendectomy	159	97.5%	19	86.4%	0.037[X²]
Conversion laparoscopic to open surgery	0	0.0%	2	9.1%	
Conventional (open) surgery	4	2.5%	1	4.5%	
Radiology					
BT	117	74.1%	20	90.9%	0.082[X²]
USG	46	29.1%	2	9.1%	
WBC	12.4±3.8	11.9	13.7±4.4	13.7	0.223[m]
Neutrophil	9.5±3.8	9.1	11.0±4.2	11.1	0.153[m]
Lymphocyte	2.0±0.8	1.9	1.6±1.0	1.3	0.006[m]
NLR	5.7±3.9	4.8	9.1±6.0	8.2	0.005[m]
CRP	23.4±35.5	7.9	107.6±97.9	73.8	0.000[m]
Appendix diameter (mm)	10.6±2.8	10.1	12.9±3.9	12.5	0.011[m]
Periappendiceal free fluid					
(-)	150	92.0%	11	50.0%	0.000[X²]
(+)	13	8.0%	11	50.0%	
Pathological evaluation					
Acute appendicitis	109	67.3%	14	63.6%	0.733[X²]
Phlegmonous/Suppurative	29	17.9%	3	13.6%	0.620[X²]
Gangrenous	17	10.5%	5	22.7%	0.097[X²]
Lymphoid Hyperplasia	5	3.1%	0	0.0%	1.000[X²]
Malignancy	2	1.2%	0	0.0%	1.000[X²]
Rehospitalization					
(-)	163	100.0%	16	72.7%	0.000[X²]
(+)	0	0.0%	6	27.3%	

[m]Mann-Whitney u test/X^2 Ki-Kare test (Fischer test)

Table 3. Factors that affect discharge day after appendectomy

	Univariate model			Multivariate model		
	OR	95% GA	p	OR	95% GA	p
Lymphocyte (K/uL)	0.453	0.220 – 0.933	0.032			
NLR	1.145	1.052 – 1.247	0.002	1.128	1.020 - 1.246	0.019
CRP (mg/L)	1.020	1.012 – 1.028	0.000	1.020	1.011 - 1.029	0.000
Appendix diameter (mm)	1.269	1.095 – 1.471	0.002			
Periapendiceal free fluid	11.538	4.204 – 31.671	0.000			

Logistic regression (forward LR). NLR: neutrophil-lymphocyte ratio; CRP: C reactive protein.

matomas, ileus with peritonitis, and surgical site infections. Some patients may also need surgical intervention or interventional radiologic procedures. We aimed to evaluate the factors that influenced the longer hospital stay and rehospitalization after an appendectomy by examining the laboratory findings, radiologic examination, and type of surgical procedure.

A study from Korea suggested that the LOS after an uncomplicated appendectomy was 1.6 to 4.2 days. Another study showed that the mean LOS was 2.1±0.7 days. Martínez-Pérez et al.[3] demonstrated that LOS in complicated appendectomy patients was 5 and called prolonged

Table 4. Critical value of neutrophil-lymphocyte ratio

	Area under the curve		95% Confidence interval	p
NLR	0.684		0.555 – 0.813	0.005
NLR 6.85 Cut off	0.676		0.549 – 0.803	0.007
	Early discharge	Late discharge		%
NLR				
≤6.85	124	9	Sensitivity	59.1%
>6.85	39	13	Positive prediction rate	25.0%
			Specificity	76.1%
			Negative prediction rate	93.2%

ROC Curve.

Table 5. Critical value of CRP

	Area under the curve		95% Confidence interval	p
CRP	0.815		0.717 – 0.913	0.000
CRP 16 Cut off	0.745		0.646 – 0.843	0.000
	Early discharge	Late discharge		%
CRP				
≤16	102	3		
>16	61	19		
			Sensitivity	86.4%
			Positive prediction rate	23.8%
			Specificity	62.6%
			Negative prediction rate	97.1%

ROC Curve.

LOS more than seven days. Worldwide, the LOS trend after LA tends to be single-day surgery.[2,3,9,10] The mean LOS in our study was 1.8±1.4 days, which is compatible with the literature.

In the time of diagnosis of AA, biochemical markers are commonly used. In the literature, elevated WBC and neutrophil counts are related to the diagnosis of AA.[1,4,7,8] In our study, WBC count and neutrophil count were found to be higher in the late discharge group than in the early discharge group, although there were no statistically significant differences between the groups, suggesting that WBC and neutrophil counts cannot be used for the decision of estimated hospitalization time.

A study suggested that a decrease in is associated with perforated appendicitis, whereas an increase in the percentage of lymphocytes may occur with a negative appendectomy.[9] Another study demonstrated a decreased level of lymphocyte count in complicated appendicitis, but there was no statistical difference.[1] In our study, we observed that decreased lymphocyte count was statistically significantly lower in the late discharge group ($p<0.005$). This could be explained by severe inflammation causing a decreased number of lymphocytes, which results in complicated cases and longer hospital stays.

Regarding the NLR, studies have demonstrated that the NLR is related to high inflammation in AA. Yardımcı et al.[1] showed that NLR values above 8 were significantly related to perforation and gangrenous appendicitis. Al Amri et al.[11] showed that the severity of appendicitis could be predicted by NLR. Another study suggested that the critical value of the NLR for diagnosing AA was 3.8, while the NLR in complicated appendicitis was 8.86. A meta-analysis consisting of 13 studies and over 7300 patients demonstrated that NLR was significantly higher in the complicated appendicitis group (10.39) than in the uncomplicated appendicitis group (6.63). A meta-analysis also showed that appendicitis could be distinguished from non-appendicitis cases, with a higher NLR value of 8.04 versus 3.34.[1,10,11] In our study, NLR in the late discharge group was statistically significantly higher than NLR in the early discharge group ($p<0.005$). Multivariate analysis showed that NLR could be used as a parameter to estimate hospitalization time pre-operatively. ROC curve analysis showed that the critical NLR value of 6.85 could distinguish between the early discharge group and the late discharge group in our study (Table 4; Figure 2).

One of the most commonly used nonspecific inflammatory markers is CRP, which is used in the diagnosis of an acute abdomen. Elevated CRP levels are strongly associated with the severity of inflammation. Many studies have shown that elevated CRP values predict complicated appendicitis that causes prolonged hospital stays.[2,4,6,12] A study showed that the percentage of negative appendectomy was 38% if the

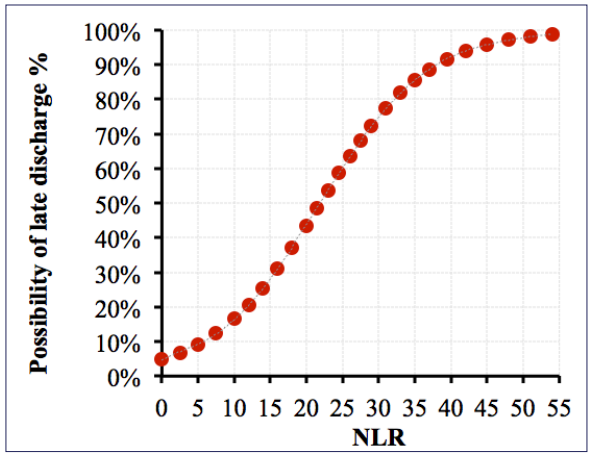

Figure 2. Relationship between NLR and discharge time.

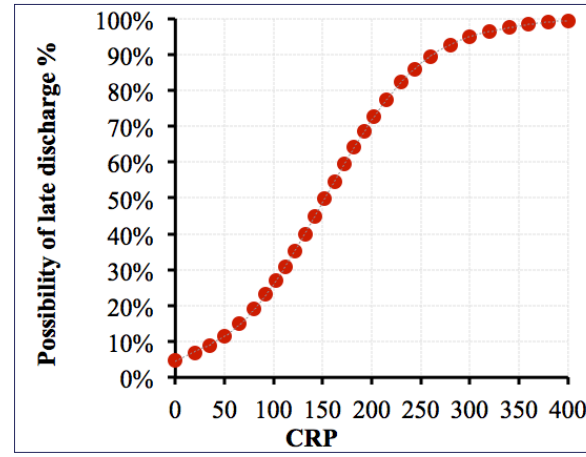

Figure 3. Relationship between CRP and discharge time.

CRP value <5 mg/l.[8] Another study suggested that a high CRP level was strongly associated with delayed treatment completion after appendectomy.[2] A prospective study consisting of 123 patients with LA showed that a CRP value <18 mg/l was significantly related to LOS of about 24 h.[12] Our study showed that a higher CRP value predicted a prolonged hospital stay after an appendectomy. There was a statistically significant difference between the early discharge group and the late discharge group regarding CRP levels ($p<0.005$). Univariate and multivariate analyzes showed that elevated CRP levels were independent risk factors for longer hospital stays, with the ROC curve suggesting a critical CRP level of 16 mg/l (Table 5; Figure 3).

Current methods for evaluating abdominal pain include CT, an indispensable radiologic evaluation tool. Kim et al.[13] suggested that independent risk factors on CT for early perforated appendicitis include focal defect in the appendiceal wall, circumferential periappendiceal changes, transverse diameter of the appendix (>11 mm), and the presence of an appendicolith. By contrast, some studies have shown that maximal appendix diameter does not change the LOS.[2] In our study, we observed that appendix diameter and the presence of periappendiceal free fluid were statistically significantly related with the late discharge group ($p<0.005$). The mean diameter of the appendix in patients in the late discharge group was 12.9±3.9 mm.

Around the world, appendectomies are performed laparoscopically to reduce hospital stays, costs, and complications related to surgery. During the COVID-19 pandemic, open surgeries were preferred, especially in patients with suspected COVID-19, until sufficient scientific data were obtained.[12,14,15] In our study, LA was performed on 96.2% of the patients. Only 2.2% of the patients were treated with traditional open surgery. The reason for this was that laparoscopic surgery was not recommended during the COVID-19 pandemic. Two patients (1.1%) required conversion from laparoscopic to open surgery, which affected their LOS, with statistical significance ($p=0.037$), consistent with the literature.

In the literature, readmission after an appendectomy differs from 1% to 9.3%. A large meta-analysis consisting of over 836,000 patients showed that the rate of re-admission was 4.3%. In our study, the re-admission rate was 3.2%, which is compatible with the literature.[16-19]

Our study has several limitations. First, this was a single-center retrospective study. Increasing the number of patients or using multi-center modalities may affect the results. Second, the complication rate of surgeries was very low, which directly affected the LOS. Third, the study design was retrospective, and some patients had to be excluded due to inaccessible data files. Notably, the COVID-19 pandemic negatively affected the patient sample size, as patients who had typical physical examinations with AA may not have presented to the hospital because of fear of the COVID-19 pandemic. Further, some patients also need to be operated on by open traditional surgery instead of the laparoscopic approach.

Conclusion

We showed that a decreased number of lymphocytes, increased NLR and CRP value, increased diameter of appendix, and presence of periappendiceal free fluid on CT were statistically significant findings that affected patients' LOS after appendectomy. Further, an NLR cut-off value >6.85 and a CRP value >16 mg/l were independent risk factors for longer hospitalization. Therefore, patients with these risk factors could be preferentially selected for laparoscopic approach, routine drain placement, late start to normal food, and planned late discharge time and should be informed about longer hospitalization.

Ethics Committee Approval

This study approved by the Sancaktape Sehit Prof. Dr.İlhan Varank Training and Research Hospital Ethics Committee (Date: 17.04.2024, Decision No: 122).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.K.; Design: B.K.; Supervision: Y.Ö., S.Ç.E.; Ma-

terials: B.K.; Data: B.K.; Analysis: S.Ç.E.; Literature search: Y.Ö. Writing: B.K.; Critical revision: B.K., D.E.

Conflict of Interest

The authors declare no conflicts of interest.

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Apendektomi Sonrası Hastanede Kalış Süresini Etkileyen Faktörler

Amaç: Akut apandisit, akut karın ağrısına neden olan cerrahi bir acil durumudur. Laparoskopik apendektomiden sonra standart hastane bakımı yaklaşık 24 saattir, ancak bazı hastaların hastanede daha uzun kalış süresine ihtiyacı vardır. Bu çalışmada apendektomi sonrası hastanede yatış süresini etkileyen faktörlerin biyokimyasal ve radyolojik parametreler incelenerek değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Bu çalışmada Medical Park Pendik Hastanesi'nde 2020-2024 yılları arasında apendektomi yapılan 185 hastanın verileri retrospektif olarak analiz edildi. Hasta dosyaları incelenerek ameliyat öncesi beyaz küre sayısı, lenfosit sayısı, nötrofil sayısı, C reaktif protein (CRP) değeri, nötrofil-lenfosit oranı (NLR) gibi biyokimyasal değerler kaydedildi. Ameliyat öncesi radyolojik incelemeler, apendiks çapı ve periapendikste serbest sıvı varlığı değerlendirildi. Hastaların yatış süreleri incelenerek; hastalar 48-saat ya da daha az yatanlar ve 48-saatten daha uzun yatanlar olarak iki gruba ayrılarak karşılaştırılarak incelendi.

Bulgular: Toplam 185 hasta; 163'ü erken taburculuk grubunda, 22'si geç taburculuk grubunda olmak üzere iki grupta incelendi. Hastaların yaş ortalaması 34.5±8.5 olup %53.5'i erkek cinsiyetti. Ortalama taburculuk süresi 1.8±1.4 gündü. Geç taburcu olan grupta lenfosit sayısı istatistiksel olarak anlamlı derecede düşük bulundu. NLR, CRP değeri ve apendiks çapı ise geç taburcu olan grupta istatistiksel olarak anlamlı derecede yüksekti ($p<0.005$). Çok değişkenli analiz, NLR ve CRP değerlerinin anlamlı bağımsız etkisini gösterdi ($p<0.05$).

Sonuç: Çalışmada; lenfositlerin azalması, NLR ve CRP değerlerinin yükselmesi, apendiks çapının artması ve BT'de periapendiks çevresinde serbest sıvı bulunmasının hastaların apendektomi sonrası hastane yatış süresini etkilediği görüldü. Bu risk faktörlerine sahip hastalara; rutin dren yerleştirilmesi, normal gıdaya geç başlanması, taburculuk süresinin geç planlanması ve daha uzun hastanede kalış süresi konusunda bilgilendirilmeleri için öncelikli olarak seçilmelidir.

Anahtar Sözcükler: Apendektomi; CRP değeri; hastanede yatış süresi; nötrofil-lenfosit oranı.

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Original Article

Multivariate Analysis of Emergency Department Related Deaths in Europe and Türkiye

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Keywords: Accident, disease mortality, emergency related deaths, suicide.

ABSTRACT

Objective: In this research, it was aimed to evaluate Multivariate analysis of emergency department related deaths in the Europe (the EU) and Türkiye.

Methods: Data set was collected from the World Bank Country Reports for the EU and Türkiye from 2002 to 2021. Accident, suicide and disease related mortality rates were used as dependent variables. Independent variables were heath expenditure, rural population and population growth.

Results: Disease mortality, rural population and population growth were significantly higher in Türkiye, whereas suicide mortality and health expenditure were significantly higher in the EU ($p<0.05$). Location had significant correlation with suicide mortality ($r=0.868$; $p<0.01$), disease mortality ($r=-0.728$; $p<0.01$), health expenditure ($r=0.866$; $p<0.01$) and population growth ($r=-0.866$; $p<0.01$). In year-controlled correlation, location had significant correlation with suicide mortality ($r=0.997$; $p<0.01$), disease mortality ($r=-0.976$; $p<0.01$), health expenditure ($r=0.957$; $p<0.01$), rural population ($r=-0.745$; $p<0.01$) and population growth ($r=-0.939$; $p<0.01$). For Türkiye, accident mortality was significantly and positively correlated with population growth ($r=0.572$; $p<0.01$). Suicide mortality was significantly and negatively correlated with health expenditure ($r=-0.710$; $p<0.01$), and positively correlated with rural population ($r=0.836$; $p<0.01$). Disease mortality was significantly and negatively correlated with health expenditure ($r=-0.486$; $p<0.01$), and positively correlated with rural population ($r=0.980$; $p<0.01$). For the EU, accident mortality was significantly and negatively correlated with health expenditure ($r=-0.798$; $p<0.01$), and positively correlated with rural population ($r=0.998$; $p<0.01$). Suicide mortality was significantly and negatively correlated with health expenditure ($r=-0.683$; $p<0.01$), and positively correlated with rural population ($r=0.889$; $p<0.01$). Disease mortality was significantly and negatively correlated with health expenditure ($r=-0.821$; $p<0.01$), and positively correlated with rural population ($r=0.998$; $p<0.01$).

Conclusion: Mutual information exchange and health system model analyzes may be useful to prevent deaths due to disease in Türkiye and deaths due to suicide in the EU countries.

INTRODUCTION

Although health events requiring acute intervention are at the forefront in emergency departments, patients are directed to relevant units after the first intervention, and as a result, follow-up after the first intervention cannot be performed adequately.[1] Therefore, it is possible to state that there are some difficulties in evaluating the quality of emergency department services based on patient outcomes.[2] In general, birth and death statistics in health services are accepted as an indicator of the health system and social welfare level, and when associated with emergency services, it can be said that the statistical evaluation of death rates is more appropriate compared to birth rates.[3] The main reason for this is that the services provided in emergency departments are mostly related to postpartum processes and acute situations.[4-6] Therefore, it is possible to evaluate mortality rates as an indicator of emergency services.[7-9] Among the mortality rates, the most relevant ones can be classified as accident, suicide, and disease statistics, which are also related to the content of emergency services.

Health is one of the important public services in Türkiye's EU harmonization process.[10-11] The European Union, as an indicator of social welfare and peace, shows the social structure in which individuals aim to receive a higher

quality and more egalitarian service.[12,13] In health services, compared to elective health services, compulsory health processes are among the health processes that individuals must receive and are a constitutional right. Among these, the health services provided in emergency departments are one of the most prominent health service areas, both financially, as they are financed from public resources, and because they involve urgent, acute health problems with high mortality rates.[14] In this regard, in terms of both Türkiye's compliance with the EU harmonization process and the performance of emergency services, the study included a multivariate analysis of the factors affecting deaths caused by emergency services through mortality rates.

Although studies have been conducted on the quality and cost of the service provided in emergency services, how many people it reaches, and what benefits it provides, today there is no consensus on a generally accepted performance measurement method and indicators for emergency services. For this reason, this research aimed to compare and reveal the mortality rates in emergency services in Türkiye and the EU in a multidimensional manner.

MATERIALS AND METHODS

Research Design

The research is a longitudinal study designed in a descriptive survey model. In this model, the relationship between variables over time is described in detail with the help of quantitative data, without intervention by the researcher. In this context, the study provided a multivariate description of the relationship between mortality levels associated with emergency services and basic indicators.

Data Set

The data set was collected from the World Bank Country Reports for the EU and Türkiye from 2002 to 2021. Accident, suicide, and disease-related mortality rates were used as dependent variables. Independent variables were health expenditure, rural population, and population growth. Details of variables were as follows:

Dependent variables

- Accident Mortality: Mortality caused by road traffic injury (per 100,000 population)

- Suicide Mortality: Suicide mortality rate (per 100,000 population)

- Disease mortality: Mortality from CVD, cancer, diabetes, or CRD between exact ages 30 and 70 (%)

Independent variables

- Health expenditure: Current health expenditure per capita (current US$)

- Rural population: Rural population (% of total population)

- Population growth: Population growth (annual %)

Statistical Methods

Scale variable descriptions were given by means and standard deviations. Kolmogorov-Smirnov test was used for normality of variables. Mann-Whitney U test was used for non-normally distributed variable differences, and independent samples t-test was used for normally distributed parameters. Because of linearization deviations,[15-17] Spearman's rho and year-controlled partial correlation analysis were used for relationship analysis. SPSS 25.0 for Windows was used for analysis at 95% Confidence Interval with 0.05 significance level.

Ethical Considerations

Because of the nature of the research, no ethical approval or informed consent was applicable. The data set used in the research is public data and may be reached on the official website of the World Bank Country Reports.

RESULTS

The same data or information given in a Table must not be repeated in a Figure and vice versa. It is not acceptable to repeat extensively the numbers from Tables in the text or to give lengthy explanations of Tables or Figures.

Tables and Figures

The difference between accident mortality per 100,000 population of the EU and Türkiye was similar, and the difference was insignificant (p>0.05). Suicide mortality per

Table 1. Mortality and related factors of Türkiye and the EU and difference analysis results

	Location		
	Türkiye	**Europe**	**p**
Accident mortality per 100.000 population	8.1±1.6	8.6±2.8	0.968[a]
Suicide mortality per 100.000 population	2.64±0.50	13.30±1.00	0.000[a]
Disease mortality, %	17.67±1.56	14.53±1.56	0.000[b]
Health Expenditure, current US$	413.25±132.30	2870.28±715.90	0.000[a]
Rural population, % of total population	29.06±3.69	26.98±1.33	0.017[b]
Population growth, annual %	1.34±0.33	0.19±0.14	0.000[a]

[a]Mann Whitney U Test. [b]Independent Samples t-test. SD: Standard Deviation.

Table 2. Spearman's rho correlation analysis for correlation between location and mortality with related factors

	r	p
Accident mortality per 100.000 population	-0.009	0.958
Suicide mortality per 100.000 population	0.868**	0.000
Disease mortality, %	-0.728**	0.000
Health Expenditure, current US$	0.866**	0.000
Rural population, % of total population	-0.276	0.070
Population growth, annual %	-0.866**	0.000

**p<0.01

Table 3. Year controlled partial correlation analysis for correlation between location and mortality with related factors

	r	p
Accident mortality per 100.000 population	0.125	0.450
Suicide mortality per 100.000 population	0.997**	0.000
Disease mortality, %	-0.976**	0.000
Health Expenditure, current US$	0.957**	0.000
Rural population, % of total population	-0.745**	0.000
Population growth, annual %	-0.939**	0.000

**p<0.01

Table 4. Spearman's rho correlation between mortality and related factors for Türkiye and the Europe

	Türkiye			Europe		
	Accident mortality	Suicide mortality	Disease mortality	Accident mortality	Suicide mortality	Disease mortality
Health Expenditure, current US$	0.277	-0.710**	-0.486**	-0.798**	-0.683**	-0.821**
Rural population, % of total population	-0.376	0.836**	0.980**	0.998**	0.889**	0.998**
Population growth, annual %	0.572**	-0.101	0.131	0.311	0.146	0.304

**p<0.01

100,000 population in the EU (13.30±1.00) was higher than in Türkiye (2.64±0.50), and the difference was statistically significant (p<0.05). Disease mortality percent in Türkiye (17.67±1.56) was higher than in the EU (14.53±1.56), and the difference was statistically significant (p<0.05). Health expenditure of the EU (2870.28±715.90) was higher than of Türkiye (413.25±132.30) with statistically significant difference (p<0.05). Rural population percentage and annual population growth in Türkiye were also significantly higher than in the EU (p<0.05) (Table 1).

Spearman's rho correlation analysis results for correlation between location and mortality with related factors showed that location had significant correlation with suicide mortality (r=0.868; p<0.01), disease mortality (r=-0.728; p<0.01), health expenditure (r=0.866; p<0.01), and population growth (r=-0.866; p<0.01) (Table 2).

Year-controlled partial correlation analysis results for correlation between location and mortality with related factors showed that location had significant correlation with suicide mortality (r=0.997; p<0.01), disease mortality (r=-0.976; p<0.01), health expenditure (r=0.957; p<0.01), rural population (r=-0.745; p<0.01), and population growth (r=-0.939; p<0.01) (Table 3).

For Türkiye, accident mortality was significantly and positively correlated with population growth (r=0.572; p<0.01). Suicide mortality was significantly and negatively correlated with health expenditure (r=-0.710; p<0.01), and positively correlated with rural population (r=0.836; p<0.01). Disease mortality was significantly and negatively correlated with health expenditure (r=-0.486; p<0.01), and positively correlated with rural population (r=0.980; p<0.01) (Table 4).

For the EU, accident mortality was significantly and negatively correlated with health expenditure (r=-0.798; p<0.01), and positively correlated with rural population (r=0.998; p<0.01). Suicide mortality was significantly and negatively correlated with health expenditure (r=-0.683; p<0.01), and positively correlated with rural population

(r=0.889; p<0.01). Disease mortality was significantly and negatively correlated with health expenditure (r=-0.821; p<0.01), and positively correlated with rural population (r=0.998; p<0.01) (Table 4).

DISCUSSION

This study aimed to multidimensionally examine and compare emergency department-related deaths and basic health and population-related variables in Türkiye and the EU countries. In this context, the research analyzed deaths due to accidents, suicides, and diseases, and the effects of health expenditures, urbanization, and population growth rates on these deaths, including the time effect.

The main events that are subject to emergency services are accidents, injuries, suicides, febrile seizures of diseases, intense pain, or similar acute health problems. The most basic feature of these diseases and health conditions is that they have life-threatening mortality and morbidity.[18] For this reason, although not all of them end in death in emergency departments, it is possible to state that there are more health situations with a high risk of death, followed by events with a high risk of organ loss. Although emergency services are used for other purposes than for individuals to get priority in a busy healthcare system, basically, emergency services are units that provide services for health problems with high mortality and morbidity rates.[19-20] Therefore, it is possible to argue that the services provided in emergency departments are related to mortality rates. These mortality rates include deaths due to accidents, suicide, and disease.

The World Bank (WB) and the World Health Organization (WHO) take mortality and birth rates as basic indicators when making an evaluation about a disease or health problem or determining the welfare levels of societies. Among these, birth rates mostly concern the relevant clinics of family health centers and hospitals, while mortality is related to health conditions that are subject to emergency services. Both WB and WHO keep and share mortality rates regularly and share these data anonymously. In this regard, it is possible to state that mortality rates are among the most important and reliable health indicators internationally.[22-24] The comparison made in this regard between Türkiye and the EU, which is shown as a welfare project and which Türkiye has wanted to join for a long time, reveals the mortality rates and relevant population variables subject to emergency services.

Although health is seen as a social right, health services, especially elective ones and some compulsory health services, are seriously dependent on the economy. Therefore, the cost of health is measured as both public and private expenditures, and it is accepted that there is a significant relationship between health and the economy. In the comparison between Türkiye and the EU, health expenditures have differed significantly since 2002, and the average general health expenditure for the EU is much higher than Türkiye's health expenditures. This may be due to the higher cost of health services in EU countries or the provision of more services. However, evaluating per capita health expenditures in USD indicates that more intensive and high-cost health services are provided.

Population density and age structure of the population are also important variables in health services, and it can be stated that the health expenditures and needs of the elderly population are higher than the young population. The age structure of the population in EU countries is higher than in Türkiye, and the population growth rate in Türkiye is significantly higher than in EU countries. This situation also affects health expenditures and may be one of the reasons why health expenditures are higher in EU countries.

Mortality rates are not only related to the quality of health services, but also to the age, urbanization, and economic structure of the population. Therefore, when evaluating mortality rates, it is necessary to take into account not only the quality of health services, but also the annual growth rate, which is an indicator of health expenditures and the urbanization structure of the population and age. In the comparison between Türkiye and the EU, although deaths due to accidents do not show a statistically significant difference, deaths due to disease are statistically significantly higher in Türkiye and deaths due to suicide in EU countries. Correlation analysis results showed that deaths due to suicide and disease were related to location between Türkiye and the EU. Therefore, while living in EU countries increases suicide rates, living in Türkiye increases deaths due to disease. A similar situation exists in time-dependent partial correlation analyses, and deaths due to suicide are significantly higher in EU countries than in Türkiye.

Limitations of the Study

The most important limitation of the study is that there is not enough data to determine how many of the deaths caused by the emergency department are related to the emergency department and how many are related to other services. Therefore, instead of directly comparing deaths in emergency departments, mortality rates for the types of deaths most common in emergency departments were compared. This situation is valid not only for Türkiye or the World Bank, where research data are obtained, but also for the World Health Organization and the whole world. Therefore, more advanced data collection and evaluation systems are needed in emergency departments.

Another important limitation of the research is the possibility that social and cultural differences between Türkiye and the EU may affect the research results. Many variables such as family structure, economic structure, and social structure may be important, especially in deaths caused by suicide. Therefore, further studies are needed on this subject, especially in the EU countries. Although deaths due to disease are very high in Türkiye, the solution is a little clearer compared to the EU countries; it is possible to solve this situation with higher health services.

Contribution of the Research to the Literature

The most important contribution of the research to the literature is that it covers the mortality rates in a broad scope by comparing the mortality rates regarding the diseases and health conditions subject to the emergency department between the EU and Türkiye. In this way, the impact of health expenditures and population and urbanization on health services was revealed both in the EU and in Türkiye. In this respect, the research can serve as a source in the literature.

Another importance of the research comes from its findings. In the light of real data obtained directly from the field in the research, deaths due to suicide are more common in EU countries compared to Türkiye, by a very high difference. This situation reveals Türkiye's potential to be an important role model in correcting this situation in EU countries. In this respect, the research contributes to both field practice and literature.

Conclusion

According to the research results, health expenditures and urbanization have an impact on deaths due to disease and suicide in the EU and Türkiye. While health expenditures and urbanization significantly affect accident-related deaths in EU countries, no significant effect was detected in Türkiye. As a result, mutual information exchange and health system model analyses may be useful to prevent deaths due to disease in Türkiye and deaths due to suicide in the EU countries.

Ethics Committee Approval

Since data used in the study are anonymous and may be reached by public, neither ethical approval nor institute permission is not applicable.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: E.B.; Design: E.B.; Supervision: E.B.; Fundings: E.B.; Materials: E.B.; Data: E.B., K.Y.; Analysis: E.B., K.Y.; Literature search: E.B.; Writing: E.B.; Critical revision: E.B.

Conflict of Interest

None declared.

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Avrupa ve Türkiye'de Acil Servise Bağlı Ölümlerin Çok Değişkenli Analizi

Amaç: Bu araştırmada Avrupa (AB) ve Türkiye'de acil servise bağlı ölümlerin çok değişkenli analizinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Veri seti olarak, 2002-2021 yılları arasında AB ve Türkiye için Dünya Bankası Ülke Raporlarından derlenmdi. Bağımlı değişken olarak kaza, intihar ve hastalığa bağlı ölüm oranları kullanıldı. Bağımsız değişkenler sağlık harcamaları, kırsal nüfus ve nüfus artışı seçildi.

Bulgular: Hastalık mortalitesi, kırsal nüfus ve nüfus artışı Türkiye'de anlamlı derecede yüksekken, intihar mortalitesi ve sağlık harcamaları AB'de anlamlı derecede yüksekti ($p<0.05$). Lokasyonun intihar mortalitesi ($r=0.868$; $p<0.01$), hastalık mortalitesi ($r=-0.728$; $p<0.01$), sağlık harcamaları ($r=0.866$; $p<0.01$) ve nüfus artışı ($r=-0.866$; $p<0.01$) ile ilişkisi istatistiksel olarak anlamlıydı. Yıl kontrollü korelasyon analizi sonuçlarına göre lokasyon ile intihar mortalitesi ($r=0.997$; $p<0.01$), hastalık mortalitesi ($r=-0.976$; $p<0.01$), sağlık harcamaları ($r=0.957$; $p<0.01$), kırsal nüfus ($r=-0.745$; $p<0.01$) ve nüfus artışı ($r=-0.939$; $p<0.01$) ile anlamlı ilişkisi vardı. Türkiye için kaza ölümleri ile nüfus artışı arasında anlamlı ve pozitif bir korelasyon vardı ($r=0.572$; $p<0.01$). İntihar mortalitesi ile sağlık harcamaları arasında anlamlı ve negatif bir korelasyon ($r=-0.710$; $p<0.01$), kırsal nüfusla ise pozitif bir korelasyon vardı ($r=0.836$; $p<0.01$). Hastalık mortalitesi ile sağlık harcamaları arasında anlamlı ve negatif bir korelasyon ($r=-0,486$; $p<0,01$), kırsal nüfusla ise pozitif bir korelasyon vardı ($r=0.980$; $p<0.01$). AB için kaza ölümleri sağlık harcamaları ile anlamlı ve negatif bir korelasyona sahipken ($r=-0.798$; $p<0.01$), kırsal nüfus ile pozitif bir korelasyona sahipti ($r=0.998$; $p<0.01$). İntihar mortalitesi ile sağlık harcamaları arasında anlamlı ve negatif bir korelasyon ($r=-0.683$; $p<0.01$), kırsal nüfusla ise pozitif bir korelasyon vardı ($r=0.889$; $p<0.01$). Hastalık mortalitesi ile sağlık harcamaları arasında anlamlı ve negatif bir korelasyon ($r=-0.821$; $p<0.01$), kırsal nüfusla ise pozitif bir korelasyon vardı ($r=0.998$; $p<0.01$).

Sonuç: Karşılıklı bilgi alışverişi ve sağlık sistemi modeli analizleri, Türkiye'de hastalık kaynaklı ölümlerin, AB ülkelerinde ise intihar kaynaklı ölümlerin önlenmesinde faydalı olabilir.

Anahtar Sözcükler: Acil duruma bağlı ölümler; hastalıktan ölümler; intihar; kaza.

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Original Article

Pediatric Trauma in a Tertiary Care Center: A Comprehensive Analysis Evaluation of Trauma Cases in Pediatric Intensive Care Unit

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Keywords: Falls from a height; intracranial hemorrhage; mortality; pediatric trauma; prognosis.

ABSTRACT

Objective: In this study, the demographic characteristics, causes of trauma, prognosis, and types of trauma of pediatric trauma patients followed in a single center over a period of three years were retrospectively examined.

Methods: Data of pediatric patients admitted to our (single-center, 8-bed) pediatric intensive care unit due to trauma between January 2020 and January 2023 were retrospectively reviewed from computer records.

Results: This study includes 122 pediatric trauma cases (37 females and 85 males) with an average age of 75±59 months admitted to intensive care with a diagnosis of trauma. The most frequently observed type of trauma was falls from a height in 68 cases (55.7%), the most affected anatomical region was the head and neck region in 75 cases (61.5%), and the most common pathology was intracranial hemorrhage in 55 cases (45.1%). Surgery was necessary for 36% of the cases, and the predominant reason for surgical intervention was observed in 22 cases (18%), primarily attributed to falls from a height. During the course of their stay in the intensive care unit, 13 cases (10.6%) experienced mortality, indicating a mortality rate of 10.6%.

Conclusion: Traumas remain a significant cause of mortality and morbidity in the pediatric age group today.

INTRODUCTION

Despite significant advancements in the field of health over the years, trauma-related deaths in children remain a substantial health concern in both developed and developing countries.[1,2] In the United States, approximately 10 million children seek emergency care due to trauma each year, with over 10,000 children losing their lives due to severe trauma.[3] According to the Turkish Statistical Institute (TÜİK) data for the year 2018, the mortality rate in the 0-14 age group in Turkey, attributed to external injuries or poisoning, is 6.9%, ranking second among

the causes of child mortality.[4] The TÜİK reports for the years 2019,[5] and 2020,[6] further indicate that 1,326 and 1,348 children, respectively, died as a result of external injuries and poisonings. Despite preventive measures, injuries, which are preventable causes of death, have not significantly decreased.[7]

Injuries resulting from trauma are leading causes of emergency department visits and intensive care admissions.[3] Easy access of traumatically injured children to healthcare facilities and specialized trauma centers, coupled with improved therapeutic services, has contributed to reduced in-hospital survival rates and deaths.[8]

The aim of this study is to evaluate the demographic and epidemiological characteristics, as well as treatment outcomes, of pediatric trauma cases admitted to our pediatric intensive care unit. This research seeks to contribute to our national data on the subject.

MATERIALS AND METHODS

The data of pediatric patients monitored due to trauma in the Pediatric Intensive Care Clinic of Health Sciences University Bağcılar Training and Research Hospital were retrospectively examined from computer records between January 2020 and January 2023. The study included cases with a primary admission reason of trauma, specifically those related to motor vehicle accidents, falls from height, penetrating injuries, and drowning, all of which were followed in our Pediatric Intensive Care Unit (PICU). Patients with incomplete records and those with PICU stays of less than 24 hours were excluded from the study.

During the retrospective review of the files of identified trauma cases, demographic characteristics, etiology of trauma, duration of intensive care and hospital stay, clinical features, Pediatric Risk of Mortality (PRISM-3) and Glasgow Coma Scale (GCS) scores, laboratory values detected at the time of admission to the PICU, administered treatments, need for blood and blood product transfusion, requirement for invasive mechanical ventilation (IMV) support, need for inotropic infusion, continuous renal replacement therapy (CRRT) requirement, therapeutic plasma exchange (TPE) requirement, need for surgical operation, and discharge status were recorded by examining hospital information systems. Surgical interventions performed in the operating room conditions specifically targeting pathologies resulting from trauma were taken into account.

This study was evaluated and approved by the Bağcılar Training and Research Hospital Clinical Research Ethics Committee on May 10, 2023, with decision number 2023/05/07/026. Informed consent was obtained from the parents of the cases included in the study. It was conducted in accordance with the Declaration of Helsinki.

For statistical analyses, the SPSS software package version 28.0 (IBM SPSS, Armonk, NY, USA) was used. The data collected for the study were initially entered into the Microsoft Excel® database and then transferred to SPSS. Descriptive statistics were presented as mean ± standard deviation, median, frequency, percentage, minimum, and maximum values. The normal distribution of the data was examined with the Shapiro-Wilk and Kolmogorov-Smirnov tests. For continuous variables showing normal distribution, the Student t-test was used for comparisons between two groups, and one-way analysis of variance (ANOVA) was used for comparisons between more than two groups. The Mann-Whitney U test was employed for the analysis of continuous variables not showing normal distribution between two groups, and the Kruskal-Wallis test was used for comparisons between more than two groups. Pearson chi-square test and Fisher's exact test were used for the comparison of categorical variables.

RESULTS

A total of 122 patients (37 females and 85 males) were included in the study. The mean age of the cases was 75±59 months. By age groups, 0-4 years accounted for 52 cases (42.6%), 4-9 years for 38 cases (31.1%), 10-14 years for 18 cases (14.8%), and 15 years and above for 14 cases (11.5%).

The most common cause of trauma was falls from height, accounting for 55.7%. This was followed by motor vehicle accidents at 36.1%, penetrating injuries at 4.9%, and drowning at 3.3%. The distribution according to trauma types is shown in Figure 1 (Table 1).

Multisystemic trauma affecting more than one system was present in 87 cases (71.3%). Out of the total cases, 13 (10.6%) died, with 8 (61.5%) being male and 5 (38.5%) female. Looking at the etiology of trauma in the 13 lost children, 8 (61.5%) were due to falls from height, 4 cases (30.8%) were due to motor vehicle accidents, and one case (7.7%) was due to penetrating injury. However, no significant relationship was found between the type of trauma and mortality (p:0.891) (Table 1).

When comparing the treatment requirements of survivors and nonsurvivors, all nonsurvivors required blood transfusion, whereas only 45% of the survivors needed it, and

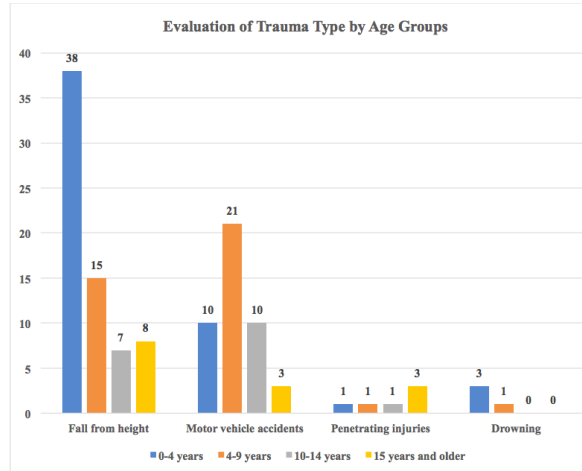

Figure 1. Evaluation of trauma by age groups.

Table 1. Evaluation of trauma etiology, clinical characteristics, and treatment needs in surviving and deceased trauma cases

	Survivors (n=109)	Nonsurvivors (n=13)	All patients (n=122)	P value
Age, years, mean ± SD	74.84±58.25	77±67.7	75.08±59.02	0.891[1]
Sex				
Male	77 (70.6%)	8 (61.5%)	85(69.7%)	0.500[2]
Female	32 (29.4%)	5 (38.5%)	37 (30.3%)	
Etiology of Trauma				
Fall from height	60 (54.1%)	8 (61.5%)	68 (55.7%)	0.891[2]
Motor vehicle accident	40 (33.9%)	4 (30.8%)	44 (36.1%)	
Penetrating injury	5 (3.7%)	1 (7.7%)	6 (4.9%)	
Drowning	4 (3.7%)	-	4 (3.3%)	
Need for transfusion	49 (45.0%)	13 (100%)	62 (50.8%)	[2]<0.001**
Need of Invasive Mechanical Ventilation	28 (25.7%)	13 (100%)	41 (33.6%)	[2]<0.001**
Need of Inotropic Agent Infusion	1 (0.9%)	10 (76.9%)	11 (9.0%)	[2]<0.001**
Need of TPE	1 (0.9%)	2 (15.4%)	3 (2.5%)	[2]0.001**
Need of CRRT	1 (0.9%)	4 (30.8%)	5 (4.1%)	[2]<0.001**
Need of Surgical Intervention	42 (38.5%)	2 (15.4%)	44 (36.1%)	0.100[2]

T-test1, Pearson chi-squres test2, significant p-values are highlighted in bold and indicated with the ** symbol. Abbreviations: SD: Standard deviation; CT: Computerized Tomography; MR: Magnetic Resonance; TPE: Therapeutic Plasma Exchange; CRRT: Continuous Renal Replacement Therapy.

Table 2. Evaluation of surgical need according to the type of trauma

Type of Trauma	No Need for Surgery (n=78)	Surgery Required (n=44)
Fall from height	46 (59%)	22 (50%)
Motor vehicle accident	28 (35.9%)	16 (36.4%)
Penetrating injury	-	6 (13.6%)
Drowning	4 (5.1%)	0 (0%)
P value	0.006**	

The Pearson chi-square test was utilized in the intergroup comparison, significant p-values are highlighted in bold and indicated with the **symbol.

this difference was statistically significant (p<0.001). Of the nonsurvivors, 84.6% required massive blood transfusion, while only 3.7% of the survivors needed it, and this difference was statistically significant (p<0.001). All nonsurvivors (100%) required invasive mechanical ventilation (IMV), while only 25.7% of the survivors received IMV support, and this difference was statistically significant (p<0.001). Inotropic infusion was required in 76.9% of nonsurvivors, whereas only 0.9% of the survivors needed it, and this difference was statistically significant (p<0.001). TPE was needed in 15.4% of nonsurvivors and 0.9% of survivors, while CRRT was required in 30.8% of nonsurvivors and 0.9% of survivors, and these differences were also statistically significant (p<0.001) (Table 1).

Among the 44 cases requiring surgical intervention, 50% were due to falls from height, and this trauma type was found to have a statistically significant higher need for surgical intervention compared to other trauma types, details are shown in Table 2.

The mean hemoglobin levels (8.3±2.9) and platelet levels (202.2±117.7) of nonsurvivors were significantly lower than survivors (p<0.001, p:0.001, respectively). The mean albumin level of survivors (3.95±0.6) was significantly higher than that of nonsurvivors (2.29±0.76) (p<0.001). The mean INR value of survivors (1.32±0.3) was significantly lower than that of nonsurvivors (3.81±2.95) (p<0.001) (Table 3).

The mean GCS score of nonsurvivors (4.2±1.96) and PRISM-3 score (40.8±16) were significantly lower than those of survivors (p<0.001) (Table 3).

Head trauma, thoracic trauma, intracranial bleeding, brain edema, lung contusion, and spleen laceration were significantly more common in nonsurvivors. A comparison of survivors and nonsurvivors based on the organ systems affected by trauma is shown in Table 4.

DISCUSSION

Trauma remains a significant public health concern worldwide across all age groups. Recent reports from the Turkish Statistical Institute (TÜİK) between 2018-2020 highlight childhood deaths due to trauma as a leading cause, emphasizing an age-specific distribution with increased mortality rates in the 15 and above age group. Our study,

Table 3. Comparison of laboratory values, GCS, PRISM scores, and duration of stay between survivors and non-survivors

	Survivors (n=109) Mean±SD	Nonsurvivors (n=13) Mean±SD	All patients (n=122) Mean±SD	P
Hemoglobin, g/dl	10.9±1.8	8.3±2.9	10.6±2.1	<0.001
Platelets, 10^3/ml	333±123.5	202.2±117.7	319.06±128.98	0.001
Albumin, g/dl	3.95±0.6	2.29±0.76	3.77±0.81	<0.001
Creatinine, mg/dl	0.43±0.25	0.65±0.25	0.45±0.26	<0.001
INR	1.32±0.3	3.81±2.95	1.59±1.24	<0.001
GCS	12.4±3.45	4.2±1.96	11.5 ± 4.17	<0.001**
PRISM-3	3.5±5.1	40.8±16	7.5±13.5	<0.001**
PICU Stay, days	7.51±8.19	4.46±4.79	7.19±7.94	0.048
Ward Stay, days	4.48±7.97	0	4±7.65	--

The independent t-test was utilized in the intergroup comparison, significant p-values are highlighted in bold and indicated with the **symbol. Abbreviations: SD: Standard deviation; INR: International Normalized Ratio; GCS: Glasgow Coma Scale; PRISM-3: Pediatric Risk of Mortality Score; PICU: Pediatric Intensive Care Unit.

Table 4. Comparison of anatomical regions and pathologies affected by trauma in survivors and non-survivors

	Survivors (n=109)	Nonsurvivors (n=13)	All patients (n=122)	P
Head	63 (57.8%)	12 (92.3%)	75 (61.5%)	0.016**
Brain Edema	12 (11.0%)	6 (46.2%)	18 (14.8%)	<0.001**
Intracranial Hemorrhage	44 (40.4%)	11 (84.6%)	55 (45.1%)	0.002**
Chest	60 (55.0%)	12 (92.3%)	72 (59.0%)	0.010**
Pneumothorax	39 (35.8%)	4 (30.8%)	43 (35.2%)	0.721
Hemothorax	12 (11.0%)	2 (15.4%)	14 (11.5%)	0.64
Lung Contusion	52 (47.7%)	10 (76.9%)	62 (50.8%)	0.046**
Abdomen	35 (321.%)	7 (53.8%)	42 (34.4%)	0.119
Liver Laceration	23 (21.1%)	1 (7.7%)	24 (19.7%)	0.25
Splenic Laceration	13 (11.9%)	6 (46.2%)	19 (15.6%)	0.001**
Extremities	47 (43.1%)	8 (61.5%)	55 (45.1%)	0.207
Closed Fracture	45 (41.3%)	8 (61.5%)	53 (43.4%)	0.164
Open Fracture	4 (3.7%)	0 (0%)	4 (3.3%)	0.482

The Pearson chi-square test was utilized in the intergroup comparison, significant p-values are highlighted in bold and indicated with the **symbol.

conducted in a tertiary care center, revealed an average age of 77±67.7 months for non-survivors, potentially linked to trauma-related deaths occurring on-site, during hospital transfers, or in emergency services, particularly in the adolescent age group.

In most studies in the literature, cases exposed to trauma are observed to be predominantly male.[8-11] Our study also revealed a similar predominance of males (69.7%), consistent with the literature. The higher incidence of trauma in male children compared to female children can be attributed to the fact that boys tend to be more active and engage in outdoor activities more frequently than girls.

Falls from height are the most common cause of childhood trauma and rank second among causes of death after motor vehicle accidents.[8,11-14] Our study results, similar to other studies, identified falls from height (55.7%) as the leading cause. Among our cases, 42.6% were in the 0-4 age group, with falls from height being the most frequent trauma type (72%). In the 4-9 age group, non-traffic accidents were most commonly observed. The prevalence of falls from height in the under-4 age group contributed to it being the most common trauma etiology in the overall distribution. As a tertiary care center receiving traumatic patients from the region, especially adolescent cases are managed in adult intensive care units in surrounding hospitals, while younger patients are referred to our center. This situation significantly contributes to the lower aver-

age age observed in our study. We believe that the high density of immigrant populations and crowded family structures in our region may hinder the implementation of sufficient preventive measures within households, leading to a higher incidence of fatal falls in the 0-4 age group.

The mortality rate of our study is 10.8%, and 8 out of the 13 cases (61.5%) that were nonsurvivors were those admitted to our unit due to falls from height. Interestingly, in contrast to the literature, the most common trauma etiology in the nonsurvivors was falls from height, followed by motor vehicle accidents as the second most common cause.[15] This discrepancy can be attributed to the fact that approximately half of our cases were under the age of 4, and deaths in this age group were frequently associated with falls from height.

The severe clinical conditions resulting from multiorgan failure in the nonsurvivors necessitated aggressive treatment. Treatments such as blood product transfusion (84.6%), endotracheal intubation (100%), inotropic infusion (76.9%), therapeutic plasma exchange (TPE) (15.4%), and continuous renal replacement therapy (CRRT) (30.8%) were more frequently applied in the nonsurvivors to halt the decompensation process.

Head injuries are the most commonly affected region in pediatric trauma, and trauma-related mortality and morbidity are primarily attributed to head injuries.[16] The higher incidence of head trauma in children following falls is due to their higher head-to-body ratio compared to adults, increasing the likelihood of head injuries.[17,18] In the United States, it is reported that 62% of childhood deaths are trauma-related, with head injuries constituting more than 50% of this proportion.[19] In a study by Doğan et al.[20] examining pediatric cases presenting to the emergency department due to trauma, the most frequently injured region was identified as the head (42%), followed by extremities at a rate of 33.4%. In another study conducted by Kıhtır and colleagues, evaluating children with trauma followed up and treated at PICU, the most commonly injured region was the head with 49.1%, and the abdomen region ranked second with 22.6%.[8] Our study aligns with the literature, with the head (61.5%) being the most frequently affected region, followed by the thoracic region (59%). Notably, in nonsurvivors, the head was the most commonly affected region (92.3%).

The necessity for surgical intervention following trauma in children has been reported at varying rates in different studies. In a study of 588 children by Chabok et al.[13] 46% of trauma-affected cases evaluated in the emergency department required surgical intervention.[13] Another study by McGaha et al.[21] involving 526 children exposed to trauma, reported a surgical intervention requirement of 13.6% in cases evaluated in the emergency department. In a study compiling trauma cases monitored in pediatric intensive care, the reported rate of necessity for surgical intervention was 28%.[22] In another study conducted in Antalya province, surgical intervention requirement was observed in 29.2% of 106 children exposed to trauma and followed up at the Pediatric Intensive Care Unit.[8] Our study reported a surgical intervention rate of 36%, considerably higher than the literature. The significant difference in our study may be attributed to our cases being critically managed in the pediatric intensive care unit. We believe that if all traumatic pediatric cases presenting to our emergency department were considered, this rate would be lower. Moreover, differences in trauma etiology and resulting pathologies may contribute to the higher surgical requirement observed in our study compared to other pediatric intensive care studies.

Our study has some limitations, including its retrospective design, single-center nature, and a limited number of cases.

Conclusion

Trauma remains a significant cause of mortality and morbidity today. Our study emphasizes that falls are the most common etiology for trauma admissions to our unit, and the head is the most commonly affected anatomical region. Both our study and literature findings suggest that a substantial portion of childhood traumas may be preventable. Simultaneously, we believe that a multidisciplinary approach involving medical and surgical treatment methods, implemented in specialized healthcare centers, could reduce mortality and morbidity associated with traumatic pediatric conditions.

Ethics Committee Approval

This study approved by the Bağcılar Training And Research Hospital Ethics Committee (Date: 10.05.2023, Decision No: 2023/05/07/026).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: C.G., A.Ö., E.C.; Design: C.G., A.Ö., E.C., S.Y.; Supervision: M.E., A.Ö., E.C.; Fundings: A.Ö., S.Y., E.C.; Materials: C.G., A.Ö., S.Y.; Data: C.G., A.Ö.; Analysis: C.G., A.Ö., S.Y.; Literature search: C.G., A.Ö., M.E.; Writing: C.G., A.Ö., S.Y., E.C., M.E.; Critical revision: A.Ö., M.E., S.Y.

Conflict of Interest

None declared.

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Çocuk Yoğun Bakım Ünitesindeki Pediatrik Travma Vakalarının Kapsamlı Bir Analizi

Amaç: Bu çalışmada, tek merkezde üç yıl boyunca takip edilen çocuk travma hastalarının demografik özellikleri, travma nedenleri, prognozları ve travma tipleri retrospektif olarak incelenmiştir.

Gereç ve Yöntem: Ocak 2020 ve Ocak 2023 tarihleri arasında travma nedeniyle çocuk yoğun bakım ünitemize (tek merkezli, 8 yataklı) kabul edilen çocuk hastaların verileri bilgisayar kayıtlarından retrospektif olarak incelendi.

Bulgular: Bu çalışma, travma tanısı ile yoğun bakıma kabul edilen yaş ortalaması 75±59 ay olan 122 çocuk travma olgusunu (37 kız ve 85 erkek) içermektedir. En sık gözlenen travma tipi 68 olguda (%55.7) yüksekten düşme, en sık etkilenen anatomik bölge 75 olguda (%61.5) baş ve boyun bölgesi ve en sık görülen patoloji 55 olguda (%45.1) intrakraniyal hemorajiydi. Olguların %36'sında cerrahi müdahale gerekmiştir ve 22 olguda (%18) cerrahi müdahalenin en önemli nedeni yüksekten düşme olarak görülmüştür. Yoğun bakım ünitesinde 13 hasta (%10.6) exitus olmuştur, bu da %10.6'lık bir mortalite oranına işaret etmektedir.

Sonuç: Travmalar, günümüzde pediatrik yaş grubunda önemli bir mortalite ve morbidite nedeni olmaya devam etmektedir.

Anahtar Sözcükler: Mortalite; pediatrik travma; prognoz; yüksekten düşme.

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Original Article

Prevalence of Vitamin D Deficiency and Seasonality Effect in First Trimester Pregnant Women Referring to a Tertiary Health Care Institution

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Keywords: Hypovitaminosis D; pregnancy; prevalence; seasonal; vitamin D.

ABSTRACT

Objective: We aim to investigate the prevalence of low vitamin D levels in pregnant women receiving medical care at a tertiary hospital by analyzing the seasonal variations in these levels.

Methods: This study was conducted at the Obstetrics and Gynecology outpatient facility of a tertiary medical institution between February 2020 and February 2024. The demographic data, including maternal age, parity, gestational age, smoking status, vitamin D level, and seasonal information, were duly captured from the first antenatal medical examination records.

Results: After the exclusion of individuals who did not meet the predetermined criteria, a total of 1101 pregnant women were selected to partake in the study. Among the pregnant women, a large proportion (866, 79%) had serum 25(OH)D concentrations lower than 20 ng/mL, with an additional 132 out of 866 (15.2%) having levels below 5 ng/mL. The overall sample group showed a mean vitamin level of 13.71±9.18, while the subset of participants with a vitamin D deficiency had a recorded value of 9.85±4.62. During the fall and summer seasons, a considerable 82% and 72.8% respectively exhibited a significant prevalence of hypovitaminosis D. The trend curve for the seasonal vitamin D levels of the vitamin D-deficient group shows a relatively flat pattern, with an R^2=0.0097 score.

Conclusion: The findings from our investigation corroborate the implementation of prenatal multivitamins enriched with vitamin D as a preventive measure against musculoskeletal and non-musculoskeletal conditions for maternal and neonatal health.

INTRODUCTION

Vitamin D is a fat-soluble steroid that has historically been known for its role in calcium and phosphorus homeostasis and bone maintenance. Additionally, lung, muscle, heart, bone marrow, blood vessels, brain, breast, colon, prostate, thyroid, parathyroid glands, pancreas, gonads, placenta, skin, fat tissue, and activated B- and T-lymphocytes contain vitamin D receptors and activating enzymes (1-alpha-hydroxylase) for synthesizing 1,25-dihydroxy-vitamin D [1,25(OH)2D], which is a precursor of vitamin D. These organs and cells are thought to carry out a local vitamin D function, potentially through autocrine or paracrine pathways.[1,2]

Vitamin D deficiency is a worldwide public health concern affecting all ages, races, and geographic regions. An estimated over one billion people suffer from vitamin D deficiency since dietary nutrients cannot counterbalance the requirements of the body.[3,4] Vitamin D deficiency impairs bone mineralization and causes rickets in children and osteomalacia in adults. Probably depending on the function of vitamin D among the aforementioned organs and cells, several observational studies have shown that vitamin D deficiency or insufficiency is associated with various non-musculoskeletal diseases such as cardiovascular and metabolic diseases, male and female infertility, cancer, autoimmune, and neurological diseases.[5,6]

Likewise, several studies showed pregnant women have a greater risk for hypovitaminosis D.[7] In pregnancy, 18-99% of inadequate 25-hydroxy-vitamin [25(OH)D] levels have been reported in different populations.[8,9] Vitamin D deficiency during pregnancy not only leads to maternal and fetal musculoskeletal problems but also a higher risk of preeclampsia, gestational diabetes, preterm birth, low birth weight, and cesarean sections. These were accused

of being results of vitamin D deficiency by observational studies. It is a foregone conclusion when the mother is deficient, the fetus is concluded to be deficient.[10,11] In the same way, however, it is inconsistent yet, suffering from fetal and neonatal vitamin D deficiency can predispose to bronchiolitis, asthma, autism spectrum disorder, attention deficit hyperactivity disorder, multiple sclerosis, and lower cognitive and psychomotor outcomes.[12,13]

In this present article, we aimed to evaluate the prevalence of vitamin D deficiency changes throughout the seasons among pregnant women attending a tertiary care facility. For this purpose, we collected the vitamin D levels of pregnant women on the first antenatal examination and sorted the data into the seasons.

MATERIALS AND METHODS

The study was conducted between February 2020 and February 2024 at the Obstetrics and Gynecology outpatient clinic of a tertiary hospital. The study was descriptive and made retrospectively. The study sample was pregnant women in the first trimester attending their first antenatal examination. Data were extracted from antenatal care records.

Inclusion criteria were pregnancy, a minimum age of 18 years, singleton pregnancies, and current residency of at least six months before the start of pregnancy. The exclusion criteria of the study were multiple pregnancies, age below 18 years, pregnancy more than 14 weeks, known or suspected drug or alcohol abuse, HIV infection, bone disease, lithium therapy, or known conditions of a history of renal or liver disease, and chronic malabsorption syndromes. Multivitamin consumption before pregnancy was not an exclusion criterion.

This study was approved by the local ethics committee (Date: 27.05.2020, Decision No: 2020/514/178/24).

The vitamin D status was evaluated by measuring 25(OH) D concentrations. The reason for selecting 25(OH)D as a biomarker of vitamin D status is because the nature of 25(OH)D reflects vitamin D obtained from both dietary intake and ultraviolet (UV) skin synthesis. Total 25(OH) D was measured using electrochemiluminescence immunoassay.

There is no universally accepted definition of vitamin D deficiency; therefore, the recommendations of the Institute of Medicine (IOM) were followed as a determinant, which vitamin D deficiency was defined as a 25(OH)D concentration of <20 ng/mL (50 nmol/L), while a serum 25(OH)D concentration of ≥20 ng/mL (50 nmol/L) was considered sufficient.[14]

Age, parity, gestational week, smoking status, and the season at the first antenatal examination were recorded. The 25OH(D) measurements were recorded as 'ng/mL'.

All statistical analyses were conducted using IBM® SPSS® software version 24 (IBM SPSS Armonk, NY). Continuous variables were described as the mean with standard deviation, minimum, and maximum, while categorical variables were given as counts with percentages.

RESULTS

After exclusion criteria, a total of 1101 pregnant women remained for the study. 5.8% of the pregnant women were smokers (n=64). The characteristics of the women are summarized in Table 1.

The mean age of the pregnant women on the blood sample day was 29.79±5.97. The mean parity was 1.22±1.07 and 298 (27%) women were nulliparous.

866 (79%) of the pregnant women had lower serum 25(OH)D concentrations of less than 20 ng/mL (Table 2). Among the pregnant women with low serum 25(OH)D

Table 1. The characteristics of the pregnant women

	Mean	Min	Max	SD
Serum 25(OH)D (ng/mL)	13.71	3	75	9.18
Age	29.79	18	47	5.97
Gestational Week	7.35	4	13	1.67
Parity	1.22	0	6	1.07

Min: minimum; Max: maximum, SD: standard deviation.

Table 2. Pregnant women were divided into groups for vitamin D status

Serum 25(OH)D (ng/mL)	N	Mean	Min	Max	SD
≥20	235	27.94	20	75	7.79
<20	866	9.85	3	19.9	4.62

N: count; Min: minimum; Max: maximum, SD: standard deviation.

Table 3. Vitamin D levels throughout the seasons

Serum 25(OH)D (ng/mL)	Fall	Winter	Spring	Summer
≥20	65 (18%)	32 (18.8%)	58 (21.4%)	80 (27.2%)
<20	300 (82%)	138 (81.2%)	213 (78.6%)	215 (72.8%)

Shown as counts, and percentages.

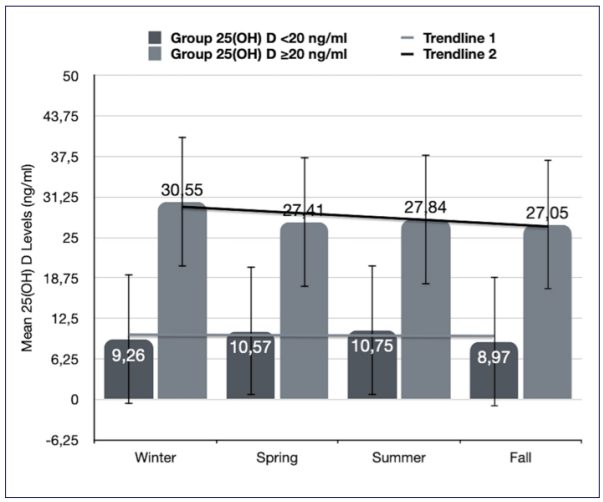

Figure 1. Seasonal variations in the mean serum 25-hydroxyvitamin D concentration.

concentrations, 132 (15.2%) women had less than 5 ng/mL serum 25(OH)D concentrations.

Vitamin D deficiency prevalence in spring and fall was 82% and 72.8%, respectively. Table 3 shows the deficiency prevalence throughout the seasons. Figure 1 demonstrates the trend analysis in mean values in the deficiency and sufficiency group between seasons. Group 25(OH)D <20 ng/mL R2 value of trendline is 0.0097 and Group 25(OH)D ≥20 ng/mL R2

DISCUSSION

In this article, we evaluated the vitamin D levels of pregnant women at their first antenatal visits, and the results were sorted by season. Based on our evaluation, our population has a very high prevalence (79%) of hypovitaminosis D, with a significant number of women (15.2%) suffering from severe vitamin D deficiency (<5 ng/mL).[15] Studies have shown that 18% of pregnant women in the United Kingdom, 25% in the United Arab Emirates, and almost 80% in the Netherlands had vitamin D levels of <25 nmol/L.[8] Another study from Taiwan showed a 99% deficiency in vitamin D with a cutoff point of 30 ng/mL.[9] One possible explanation for the vast differences in prevalence might be attributed to population disparities, such as their dietary intake habits, smoking, sociocultural status, body mass index (BMI), geographic region, sunlight exposure, genetic predisposition, and skin pigmentation. Besides, the high prevalence of vitamin D deficiency cannot be expounded by a single cause. For instance, Hagenau et al. reported that 25(OH)D levels decreased significantly among Caucasians with increasing latitude, whereas there was no change for non-Caucasians.[16] The combination of the reasons mentioned earlier can be the cause of differences between countries and even inter-regions within the same country.

Another possible explanation is that there is no clear consensus on the cutoff point for vitamin D deficiency among pregnant women; therefore, various studies have determined different cutoff points for hypovitaminosis D. On the other hand, investigators around the world suggest that maintaining a circulating 25(OH)D concentration of at least 40 ng/mL before a planned pregnancy or during the earliest time in pregnancy can reduce the risk of vitamin D-related pregnancy complications.[17,18,19,20] It's worth noting that the limit of 40 ng/mL in pregnancy vitamin D physiology is also an important point. The level of 1,25(OH)2D in pregnant blood continues to rise to supraphysiological levels until 25(OH)D has reached 40 ng/mL. The 1,25(OH)2D level remains constant at the same supraphysiological level it reached when the 25(OH)D level is above 40 ng/mL. According to these circumstances, it can be suggested that the 25(OH)D level required for pregnancy should be at least 40 ng/mL.

Depending on the same cutoff point for hypovitaminosis D as in our study, a study from a different region of Turkey evaluated that 90.3% of pregnant women in their last trimester had vitamin D deficiency.[21] Firstly, we can simply point out that even though both articles have studied pregnant women, our study focused on women in the first trimester. So that this variation in prevalence can be attributed to the increasing demand of the fetus for vitamin D as pregnancy progresses, with the mother being the primary source of this essential nutrient.[11] Also, the anticipated increase in weight for pregnant women with a normal BMI is projected to be between 11 and 18 kilograms.[22] Moreover, Tobias et al. showed that BMI was associated with a modified response to vitamin D supplementation and could explain the observed diminished outcomes of supplementation for various health outcomes among individuals with higher BMI. In light of this information, we can interpret that with each passing week of pregnancy, the BMI of the women increases, and even though the pregnant women take multivitamins containing vitamin D, that leads to lower 25(OH)D levels.[23]

Consequently, according to our research, the lowest prevalence of hypovitaminosis D was observed in summer

(72.8%), while the highest prevalence was observed in fall (82%). It is a well-established principle that the skin's reaction to UV radiation is fundamental for vitamin D synthesis. Although our country has four seasons and UV radiation wavelengths change over the year, we determined relatively steady vitamin D deficiency throughout the year. Likewise, Bromage et al. showed that even though the UV radiation changes throughout the year, vitamin D levels stayed almost consistent among pregnant women in Boston.[24] It is reasonable to hypothesize that this pertains to the enduring qualities of the participants, independent of seasonal fluctuations. However, another study from Bangladesh revealed that despite the country having ten hours of daily constant sunlight exposure during the entire year, the researchers observed a high prevalence of vitamin D deficiency.[25] Various studies have demonstrated a high occurrence of vitamin D deficiency in tropical countries, although these areas receive plenty of sunlight and have access to dietary sources of vitamin D (such as fatty fish and vegetables).[26] Adequate sun exposure is essential for the synthesis of vitamin D, as well as many other factors. Therefore, a meticulous examination before the treatment of vitamin D deficiency might be a more adequate and longstanding strategy.

To conclude, our study has two main limitations that must be acknowledged. We did not include information about the dietary and sunbathing habits and BMI of the pregnant women, which can predominantly be considered as the main determinants of vitamin D levels. The second limitation is that, as part of our national health strategy, we started vitamin D supplementation during the second trimester, but we did not monitor the treatment outcomes of all patients during the third trimester. However, our primary objective for this article was to evaluate the prevalence of vitamin D deficiency among our population and see the seasonality of hypovitaminosis D.

Despite these limitations, our study still holds validity. The importance of this work underlies in its extensive research, which involved multiple observations of different seasons over an extended period. The report presented significant data on the prevalence of vitamin D deficiency within a sizable patient population, providing valuable insights for our practice.

Conclusion

Vitamin D has a significant role in fertility, pregnancy, and neonatal outcomes. A public health problem arises from vitamin D deficiency and related illnesses caused by it. We evaluated a high prevalence of vitamin D deficiency among pregnant women. Determining hypovitaminosis D during pregnancy is easy and feasible. Vitamin D deficiency treatment is cheap, safe, and effective. Our study supports the importance of prenatal use of multivitamins containing vitamin D to prevent mothers and neonates from musculoskeletal and non-musculoskeletal diseases caused by hypovitaminosis D. Additional studies are necessary to identify what dose of vitamin D is optimal and when is the best time to start supplementation for pregnancy.

Ethics Committee Approval

This study approved by the Kartal Dr Lütfi Kırdar City Hospital Ethics Committee (Date: 27.05.2020, Decision No: 2020/514/178/24).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: K.T., B.K.; Design: K.T., B.K.; Supervision: K.T., B.K.; Data: B.K.; Analysis: B.K.; Literature search: B.K.; Writing: B.K.; Critical revision: K.T.

Conflict of Interest

None declared.

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Üçüncü Basamak Sağlık Kuruluşuna Başvuran İlk Trimesterdeki Gebe Kadınların D Vitamini Eksikliği Prevalansı ve Mevsimsellik Etkisi

Amaç: Üçüncü basamak bir hastanede tıbbi bakım alan gebe kadınlarda düşük D vitamini düzeylerinin prevalansını ve bu seviyelerdeki mevsimsel değişimleri analiz ederek değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışma, Şubat 2020 ile Şubat 2024 tarihleri arasında üçüncü basamak bir tıp kuruluşunun Kadın Hastalıkları ve Doğum polikliniğinde yürütüldü. İlk antenatal kontrol sırasında yaş, parite, gestasyonel hafta, sigara kullanımı bilgisi, D vitamini seviyesi ve mevsim bilgisi kayıt altına alındı.

Bulgular: Çalışmamıza 1101 gebe dahil edildi. Bu gebe kadınların 866'ında (%79) D vitamini eksikliği tespit edilirken, 866 gebenin 132'sinde D vitamini seviyesi 5 ng/ml'nin altında tespit edildi. Toplam çalışma grubunda vitamin D değeri ortalaması 13.71+/-9.18 iken, vitamin D eksikliği olan grupta 9.85+/-4.62 idi. Yaz ve sonbahar aylarındaki hipovitaminozis D prevalansı ise sırasıyla %72.8 ve %82 olarak tespit edildi. D vitamini eksikliği olan grubun mevsimsel D vitamini seviyelerinin ortalamasının eğilim eğrisi R2=0.0097 değeriyle rölatif olarak sabit kalmaktadır.

Sonuç: Araştırmamızdan elde edilen bulgular, anne ve yenidoğan kas-iskelet sistemi ve kas-iskelet sistemi dışı sağlığı için D vitamini ile zenginleştirilmiş doğum öncesi multivitaminlerin uygulanmasını desteklemektedir.

Anahtar Sözcükler: D vitamini; gebelik; hipovitaminozis D; mevsimsellik; prevalans.

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Original Article

The Prognostic Values of BCL-2, Caspase-3 and GSTP Expressions in Salivary Gland Tumors

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Keywords: Bcl-2; caspase-3; GSTP; salivary gland tumor.

ABSTRACT

Objective: There are numerous diagnostic, biological, and histological manifestations of salivary gland tumors, each of which offers concerns and difficulties in terms of diagnosis, grading, categorization, and therapy. The purpose of this study was to evaluate and compare the immunohistochemical expression of Bcl-2, caspase-3, and GSTP in benign and malignant salivary gland tumors, as well as how they are connected to a variety of clinicopathological variables.

Methods: A total of 61 cases of buffered formalin-fixed, paraffin-embedded tissues from previously identified cases of benign and malignant salivary gland tumors were included in this study. The immunohistochemistry staining process was carried out according to the manufacturer's recommendations, employing polyclonal anti-Bcl-2, anti-caspase-3, and anti-GST antibodies.

Results: The correlation between mean tumor diameter and Bcl-2 expression was shown to be statistically significant (rs=0.258, $p<0.05$). In pleomorphic adenoma tumor tissues, there were statistically significant correlations between the expression levels of Bcl-2 and caspase-3 (rs=0.66, $p<0.01$), Bcl-2 and GST (rs=0.61, $p<0.01$), and caspase-3 and GST (rs=0.73, $p<0.01$) when tumor types were compared. The tissues with pleomorphic adenoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma had the highest staining intensity of Bcl-2 expression, while the lowest staining intensity of GSTP expression was observed.

Conclusion: It seems probable to draw the conclusion that salivary gland tumors that resist apoptosis have elevated levels of Bcl-2 expression. The prognosis for salivary gland tumors may be poor due to the positive correlation between tumor diameter and high Bcl-2 expression.

INTRODUCTION

Salivary gland tumors occur in the head and neck region after squamous cell carcinoma.[1] They constitute 3-4% of all head and neck tumors. The most common sites of occurrence are the parotid gland, submandibular gland, and sublingual gland. They are heterogeneous tumoral formations and are difficult to diagnose due to the overlapping microscopic features among tumors and intra-tumor morphological diversity.[2] This situation complicates the studies to elucidate the etiopathogenesis of tumors and causes difficulties in diagnosis. As a result of advances in molecular techniques, various human tumors are being analyzed more extensively, and by virtue of a limited number of molecular studies on malignant salivary gland tumors, some genetic changes have been detected in proto-oncogenes, anti-oncogenes, and apoptotic genes.[3,4,5] Expressions of these genes in salivary gland tumor tissues have prognostic value. This information is important for understanding tumor biology, for clinical follow-up, and management of tumors.

Apoptosis, known as programmed cell death, occurs in normal and pathological conditions. As the target of treat-

ment strategies, apoptosis plays an important role in cancer therapy. Changes in the apoptotic pathway are often associated with cancer or a pathological condition.[6,7] It is thought that some apoptotic and anti-apoptotic markers play a role in the prognosis of oral tumors and are important in determining the behavior and pathogenesis of these tumors.[8,9]

Bcl-2 was carried by patients with the follicular variant of B-cell lymphoma.[10] It is expressed in many types of malignant tumors and protects cells from apoptosis-induced DNA damage.[11] Its increased expression reduces the susceptibility of cancer cells to apoptosis and is associated with the aggressiveness of tumor cells.[12] It also plays a role in maintaining mitochondrial membrane integrity and regulating caspase-3 activation.[13]

Caspase-3 is the enzyme responsible for the actual destruction of the cell after activation during apoptosis.[14] Caspases are implicated in nuclear changes in apoptosis in both the intrinsic and extrinsic pathways.[15] An alteration or loss of function of caspases leads to disruption of the apoptotic process and ultimately to cancer.[16]

Glutathione S-transferases (GST) are Phase-II enzymes that are primarily found in the cytosol. They are involved in cancer metabolism by metabolizing certain drug-active components and detoxifying a wide variety of chemical carcinogens in cells. Many human cancers frequently have overactive GST proteins.[17] The majority of GST proteins have complicated, multifaceted biology, and recent research has shown that these proteins actively contribute to tumorigenic processes like drug resistance, cell survival, and proliferation.[18,19] Among these enzymes, GST-Pi (also known as GSTP or GSTP1-1) is responsible for catalyzing the reaction between glutathione (GSH) and its electrophilic substrates when harmful free radicals are present. Additional investigation has also shown that GSTP is highly expressed in tumor cells and strongly linked to the development of tumors, carcinogenesis, and resistance to chemotherapy.[20,21]

This study aims to compare the expression of Bcl-2, caspase-3, and GSTP in benign and malignant salivary gland tumors and to evaluate their role in the development of these tumors by analyzing the clinical and demographic data of the patients.

MATERIALS AND METHODS

A total of 61 cases of buffered formalin-fixed, paraffin-embedded tissues from previously identified cases of benign and malignant salivary gland tumors is included in this study. The benign tumors, such as pleomorphic adenoma (PA, 31 cases) and malignant tumors, such as mucoepidermoid carcinoma (MEC, 10 cases) and adenoid cystic carcinoma (ACC, 20 cases), were taken for the study.

The clinical and pathological data of the patients were obtained from the hospital electronic database and patient reports. Tissue blocks that best represent the tumor were selected for this study. New sections were taken from each selected block for histological evaluation and stained with Hematoxylin & Eosin. The diagnoses were confirmed by reviewing the Hematoxylin & Eosin stained slides. After histological evaluation, 4-5µ thick thin sections were taken from each selected tumor block for immunohistochemistry.

Immunohistochemical Procedure

For immunohistochemical staining, 61 formalin-fixed, paraffin-embedded tissue sections, after deparaffinization, were incubated with 3% hydrogen peroxide for 10 minutes. The sections were boiled in a pressure cooker with citrate buffer pH 6.0 for 3 minutes. The sections were then incubated for 10 minutes at room temperature with protein blocking (SHP125; ScyTek Laboratories, West Logan, UT). Sections were incubated with diluted primary antibody anti-bcl-2 (E-AB-64075, Elabscience Biotechnology Inc, USA, dilution 1:50), anti-caspase-3 (E-AB-63602, Elabscience Biotechnology Inc, USA, dilution 1:100), and anti-GSTP (E-AB-40418, Elabscience Biotechnology Inc, USA, dilution 1:500) for 1 hour. The secondary antibody streptavidin-peroxidase complex (SHP 125) (ScyTek Laboratories, West Logan, UT, USA) was applied for 10 minutes. Diaminobenzidine (DAB) was then incubated to monitor peroxidase activity. Hematoxylin was used for counterstaining. Tissue sections were evaluated by two expert pathologists. Immunohistochemical evaluations according to the staining intensities of the tissues under the light microscope were as follows: (0) negative staining (no staining), (+1) mild staining (there is protein expression), (+2) moderate protein expression, (+3) severe staining.

Statistical Analysis

Analyses were made using RStudio version 1.4.1103. The relationship between age and mean tumor size and the relationship between expression levels for each tumor type were investigated using the Spearman's rho test. The relationship between tumor types and mean expression levels was investigated by the Kruskal-Wallis test.

RESULTS

Bcl-2, caspase-3, and GSTP protein expressions in salivary gland benign and malignant tumor samples of 61 patients were investigated using the immunohistochemical staining procedure. Some descriptive features of the patients included in the study are shown in Table 1.

Only the correlation between Bcl-2 expression and tumor size is statistically significant ($r_s=0.258$, $p=0.045<0.05$), whereas the correlation coefficient between the expression levels of each protein and age is not statistically significant ($p>0.05$) (Table 2).

When the expression levels of the monitored proteins were compared in each tissue group, statistically significant correlation rates were found only in PA tumor tissues; the Spearman correlation coefficients between Bcl-2 and caspase-3, Bcl-2 and GSTP, and caspase-3 and GSTP are

Table 1. Patients and treatment characteristics

	N	%
Gender		
Female	31	50.8
Male	30	49.2
Tumor Type		
Adenoid Cystic Carcinoma	20	32.8
Mucoepidermoid Carcinoma	10	16.4
Pleomorphic Adenoma	31	50.8
Relapse		
None	50	82.0
Yes	11	18.0
Age	47.3 (average) 61 (range)	
Tumor Size Mean	14.93 mm	

rs=0.66 (p<0.01), rs=0.61 (p<0.01), and rs=0.73 (p<0.01), respectively (Table 3).

There was no statistically significant difference between ACC, MEC, and PA tumor groups in terms of Bcl-2 (p=0.219>0.05), caspase-3 (p=0.451>0.05), and GSTP (p=0.142>0.05) scores (Table 4).

DISCUSSION

Salivary gland tumors have highly variable histological and biological behavior. Since they are not very common tumors in the clinic, they pose difficulties in terms of accurate diagnosis. In addition, while tumors have similar histological features, they could also show different histopathological features within the same tumor, and this fact becomes the source of complexity in their diagnosis. For this reason, molecular-based studies conducted in recent years are important for the diagnosis of tumors and targeted therapies.

Apoptosis is the cell death process that is responsible for the removal of senescent, injured, and altered cells in normal and some specific pathologies such as neoplasia. [22] Changes in apoptosis rates can result in oncogenic and pathological changes. Inhibition of the apoptotic pathway in the tumorigenesis process has provided new targets for molecular cancer therapy.[23]

Bcl-2 plays a role in protecting normal and neoplastic cells from apoptosis. Its higher expression in tumors is associated with resistance to treatment and tumor aggressiveness. [24] It has also been reported that high Bcl-2 expression in salivary gland tumors prevents salivary gland tumors from the apoptotic process.[25]

Yin et al.[26] studied 71 mucoepidermoid tumor tissues originating from minor salivary glands and compared Bcl-2

Table 2. Relationship between age and tumor size with Bcl-2, caspase-3 and GSTP. The values in parentheses indicate p-values

	Bcl-2	Caspase3	GSTP
Age	0.185 (0.153)	0.039 (0.763)	-0.041 (0.756)
Tumor Size	0.258* (0.045)	-0.001 (0.994)	0.112 (0.391)

*: Statistically significant.

Table 3. Relationship between the expressions of marker proteins according to tumor types. The values in parentheses indicate p-values

	Marker	Caspase-3	GSTP
Adenoid Cystic Carcinoma	Bcl-2	0.24 (0.32)	0.36 (0.12)
	Caspase-3	-	0.39 (0.09)
Mucoepidermoid Carcinoma	Bcl-2	0.05 (0.90)	0.05 (0.90)
	Caspase-3	-	0.14 (0.70)
Pleomorphic Adenoma	Bcl-2	0.66* (< 0.001)	0.61* (<0.001)
	Caspase-3	-	0.73* (<0.001)

*: Statistically significant.

Table 4. Mean ranks of expression levels (±SD)

	Bcl-2	Caspase3	GSTP
Adenoid Cystic Carcinoma	2.55±0.69	2.20±0.83	0.55±0.61
Mucoepidermoid Carcinoma	2.80±0.42	2.10±0.74	1.10±0.10
Pleomorphic Adenoma	2.32±0.87	1.90±0.83	0.84±0.58
Kruskall-Wallis test p-value	0.219	0.451	0.142

expression levels according to the degree of differentiation. They found that low-grade tumors expressed higher Bcl-2 compared to high and intermediate-grade tumors. da Cruz Perez et al.[27] also reported that low-grade MECs expressed more Bcl-2 than intermediate and high-grade MECs, implying that Bcl-2 might be used as a prognostic marker.

There is a relationship between Bcl-2 overexpression and salivary gland tumor types, with malignant tumors expressing higher Bcl-2 compared to benign tumors.[28,29] When Manjunatha et al.[30] compared Bcl-2 expression in a study of 50 benign and malignant salivary gland tumors, they found Bcl-2 expression in 55% of PA, 45% of MEC, and 100% of ACC. In this study, the most intense staining was observed in MEC, and the least intense staining was observed in PA when the average Bcl-2 protein expressions were compared.

It has been reported that Bcl-2 expression varies in epithelial neoplasms such as salivary gland tumors, and this expression difference is related to cell type and degree of differentiation.[31] It has been reported that Bcl-2 expression is negative in cells with terminal differentiation, such as salivary gland mucosa cells, normal acinar cells, and duct cells, whereas Bcl-2 expression is positive in basal cells of mucous and intermediate cells and normal oral epithelium.[31]

Atlı et al.[32] reported statistically significant increases in some of the GST isozymes in salivary gland tumors. In parallel with the current study, Zieper et al.[33] reported that the majority of salivary gland tumors, whether benign or malignant, displayed mild GSTP staining. Only MECs had considerably higher GSTP reactivity than other tumors, which could be due to the malignancy of the tumor. They also stated that a significant rise in GSTP activity in mucoepidermoid carcinomas should be relevant in recurrent and metastatic MECs. In our study, the comparatively modest immunostaining reactivity of GSTP in adenoid cystic carcinoma may be explained by the fact that as the size of the gland decreases, the incidence of tumor malignancy in the gland increases.

Caspase-3 is a key regulator of the apoptotic pathway. Some studies showed that high levels of caspase-3 lead to a favorable prognosis.[34] Koyun et al.[35] showed that the staining intensity of caspase-3 was lower in basal cell carcinoma samples than in normal tissues. Also, Winter et al.[36] indicated that low levels of caspase-3 were shown in poorly differentiated prostate cancers. Devarajan et al.[37] studied that low expression of caspase-3 may be related to the chemoresistance of breast cancer tissue. In the present study, we did not find any statistical differences in PA, MEC, and ACC salivary gland tumors.

The association of combined Bcl-2, caspase-3, and GSTP staining with salivary gland tumors may provide clinicians with useful information about tumor progression because the immune-reactivity of those proteins was associated with larger tumors, higher histologic grades, and greater invasion extension.

Conclusion

In the current study, all benign and malignant salivary gland tumors had high Bcl-2 expression and low GSTP expression. A link was discovered between tumor size and Bcl-2 expression. Increased Bcl-2 expression in benign and malignant cancers may block apoptosis and contribute to tumor cell immortalization. Because the number of patients in this study was modest and it was the first investigation with these tumor groupings, further comprehensive studies with larger sample sizes are required.

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Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 10.11.2021, Decision No: 2021/514/213/1).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.A., S.O.; Design: M.A., S.O.; Supervision: S.Ç., S.O.; Fundings: S.Ç.; Materials: K.B., S.A., M.G.D., G.K.A.; Data: M.G.D., K.B., G.K.A.; Analysis: F.K., C.Y.; Literature search: M.A., C.Y.; Writing: M.A.; Critical revision: S.O.

Conflict of Interest

None declared.

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Tükürük Bezi Tümörlerinde Bcl-2, Kaspaz-3 ve GSTP Ekspresyonlarının Prognostik Değerleri

Amaç: Tükürük bezi tümörlerinin çok sayıda tanısal, biyolojik ve histolojik belirtileri vardır; bunların her biri tanı, tedavi ve tümörlerin kategorize edilmesi açısından zorluklar oluşturmaktadır. Bu çalışmanın amacı, benign ve malign tükürük bezi tümörlerinde Bcl-2, kaspaz-3 ve GSTP'nin immünohistokimyasal ekspresyonlarını incelemek ve çeşitli klinikpatolojik değişkenlerle nasıl bağlantıları olduğunu değerlendirmektir.

Gereç ve Yöntem: Bu çalışmaya benign ve malign tükürük bezi tümörü tanısı almış, formalinle tamponlanmış ve parafine gömülü dokulardan oluşan 61 vaka dahil edilmiştir. İmmünohistokimya boyama işlemi, poliklonal anti-Bcl-2, anti-kaspaz-3 ve anti-GSTP antikorları kullanılarak üreticinin tavsiyelerine göre gerçekleştirildi.

Bulgular: Ortalama tümör çapı ile Bcl-2 ekspresyonu arasındaki korelasyonun istatistiksel olarak anlamlı olduğu gösterilmiştir (rs=0.258, p<0.05). Bcl-2 ve kaspaz-3 (rs=0.66, p<0.01), Bcl-2 ve GSTP (rs=0.61, p<0.01), kaspaz-3 ve GSTP (rs=0.73, p<0.01) ekspresyon düzeyleri tümör tipleri ile karşılaştırıldığında, pleomorfik adenoma tümör dokularında ekspresyon düzeyleri arasında anlamlı bir korelasyon bulunmuştur. Pleomorfik adenom, adenoid kistik karsinom ve mukoepidermoid karsinomlu dokularda Bcl-2 ekspresyonu en yüksek boyanma yoğunluğuna sahipken, GSTP ekspresyonu en düşük boyanma yoğunluğuna sahipti.

Sonuç: Apoptoza dirençli tükürük bezi tümörlerinin yüksek düzeyde Bcl-2 ekspresyonuna sahip olduğu sonucu çıkarılabilir. Tümör çapı ve yüksek Bcl-2 ekspresyonu arasındaki pozitif korelasyon, tükürük bezi tümörlerinde kötü prognoza neden olabilir.

Anahtar Sözcükler: Bcl-2; kaspaz-3; GSTP; tükürük bezi tümörü.