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ORIGINAL RESEARCH

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The Relationship Between Hematological Inflammatory Markers and Postoperative Hypocalcemia in Patients with Primary Hyperparathyroidism

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Abstract

Objective

Primary hyperparathyroidism (PHPT) is a common endocrine disease that is characterized by hypercalcemia and commonly associated with parathyroid adenoma (PTA). Hypocalcemia is a common postoperative complication in patients with PHPT. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inexpensive hematological inflammatory markers. We aimed to investigate the potential predictive risk factors, including the hemogram-derived inflammatory markers for early postoperative hypocalcemia in patients with PHPT.

Material and Method

Patients diagnosed with PHPT, underwent parathyroidectomy and histopathologically shown to be caused by a single PTA were included.

Results

NLR was significantly correlated with parathormone (PTH), while PLR was related considerably with only NLR. A significant positive correlation was shown between gland weight, volume, calcium (Ca), and PTH levels. A significant correlation of postoperative hypocalcemia with age, preoperative Ca, PTH, and NLR was also demonstrated.

Conclusion

We found that NLR was significantly higher in patients with PHPT who developed postoperative hypocalcemia; however, our regression analysis did not find elevated NLR as a significant predictive risk factor for postoperative hypocalcemia. To the best of our knowledge, this is the first study investigating the relationship between hemogram-derived inflammatory markers and clinical parameters, such as the development of postoperative hypocalcemia and preoperative nephrolithiasis, in patients with PHPT.

Keywords: Hyperparathyroidism, hypocalcemia, neutrophils, lymphocytes, platelets

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Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disease that is presented with hypercalcemia and is commonly associated with a parathyroid adenoma (PTA) (1). Parathyroidectomy has been described as the gold standard therapy for PHPT to normalize serum calcium (Ca) and parathyroid hormone (PTH) levels (2). Hypocalcemia is a common postoperative complication with a 2.3-42% incidence in patients with PHPT (3,4). Even if postoperative hypocalcemia is most commonly temporary, the outcome of this early postoperative complication might be life-threatening; therefore, hospitalization for several days after parathyroidectomy has been recommended by many experienced physicians (5,6). Multiple factors, such as age, PTH, alkaline phosphatase, preoperative serum calcium, osteocalcin, and vitamin D levels, were found to correlate with postoperative hypocalcemia in patients with secondary hyperparathyroidism. At the same time, there was no correlation between laboratory or other clinical factors and postoperative hypocalcemia in patients with primary hyperparathyroidism (4,7–9).

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inexpensive hematological inflammatory markers, and these markers are currently in use to indicate the severity of systemic inflammation or infectious complications (10,11). A relationship between PHPT and systemic inflammation has been described by several studies, as a possible consequence of elevated serum calcium levels, which might trigger systemic inflammation (12,13). Furthermore, PTH alone has been shown to stimulate interleukin-6 production and high PTH levels have been reported in septic patients (14,15). In line with these data, NLR has been found significantly related to various parameters, such as serum PTH, Ca, and P levels, white blood cell count, and parathyroid adenoma size (16–18). In this study, we aimed to investigate the potential predictive risk factors, including the hemogram-derived inflammatory markers for early postoperative hypocalcemia in patients with PHPT.

Material and Method

Patients aged >18 years and who were diagnosed with PHPT, underwent parathyroidectomy and histopathologically shown to be caused by a single PTA at our institute between 2010 and 2021 were included in our retrospective study. Demographics, preoperative albumin-corrected serum Ca, phosphorus (P), PTH, 25-hydroxy vitamin D (25OH-D), 24-hour urine calcium (24hr UCa), neutrophil, platelet, and lymphocyte counts, gonadal status of patients, lowest postoperative corrected calcium, the presence of nephrolithiasis demonstrated by any imaging technique and weight of the surgically removed parathyroid gland were recorded. Additionally, lengths of 3 dimensions of PTA given by our pathology department were recorded to calculate the volume of PTA. The volume of a parathyroid adenoma was calculated using the formula for an ellipsoid (Volume = [4/3] π r1r2r3, where r1, r2, r3 are the lengths of the semiaxes in centimeters). Corrected calcium was derived using the following calculation: serum calcium (mg/dL) + 0.8 x (4 - serum albumin [g/dL]). PLR was calculated as the ratio of platelet count to lymphocyte count and NLR as the ratio of neutrophil count to lymphocyte count. Postoperative hypocalcemia was described as a serum calcium level of less than 8.5 mg/dL on the first biochemical test following parathyroidectomy.

The IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses. The normality assumption was assessed by using the Kolmogorov-Smirnov and Shapiro-Wilk's tests. Continuous variables were given as either mean standard deviation or median (interquartile range) depending on the distribution pattern. The Mann-Whitney U test was used to perform the comparisons between groups and the Spearman's correlation analysis was used to determine the correlations between continuous variables. The receiver operating characteristics (ROC) analysis was used to determine the area under the curve (AUC) and cut-off values. A p-value <0.05 was considered statistically significant.

Results

A total of 368 patients were included in our study. The basic clinical and demographic features of this population are presented in Table 1. The mean age of the patients was 53.1 ± 12.9, with a female-to-male ratio of approximately 5 to 1. The Spearman's correlation analysis demonstrated that NLR was significantly correlated with PTH and PLR ($p = 0.001$, $r = 0.173$; $p < 0.001$, $r = 0.517$, respectively), while PLR was significantly related to only NLR. A significant positive correlation between gland weight and volume, and Ca and PTH levels was shown (weight and Ca, $p = 0.001$, $r = 0.187$; weight and PTH, $p < 0.001$, $r = 0.370$; volume and Ca, $p < 0.001$, $r = 0.198$; volume and PTH, $p < 0.001$, $r = 0.324$), while there was a significant but very weak negative correlation between gland volume and weight, and P levels (weight and P, $p = 0.044$, $r = -0.119$; volume and P, $p = 0.009$, $r = -0.141$). A very strong correlation between gland weight and volume ($p < 0.001$, $r = 0.831$) was also demonstrated.

Table 1 Demographics and clinical characteristics of patients (n=368)

Characteristic	n (%)
Age (years), median (min-max)	54 (18-84)
Gender	
male	60 (16.3)
female	308 (83.7)
Gonadal Status	
menopausal	158 (52.5)
eugonadal	143 (47.5)
Preoperative Nephrolithiasis	
yes	47 (28.3)
no	119 (71.7)
Postoperative Hypocalcemia	
yes	81 (22.1)
no	286 (77.9)
median (25^{th}-75^{th} percentile)	
Ca (mg/dL)	10.7 (10.3-11.2)
P (mg/dL)	2.6 (2.3-3.0)
PTH (pg/mL)	194 (135-305)
Postoperative PTH (pg/mL)	29 (13-74)
25OH-D (ng/mL)	17 (11-25)
NLR	1.95 (1.52-2.69)
PLR	117.45 (90.93-148.02)
Macroscopic Characteristics of Adenoma	
weight (gr)	1.10 (0.50-2.36)
volume (cm^3)	5.86 (2.51-16.03)

Ca: calcium NLR: neutrophil lymphocyte ratio; P: phosphorus; PLR: platelet lymphocyte ratio; PTH: parathyroid hormone; 25OH-D: 25-hydroxy vitamin D

A significant relationship between postoperative hypocalcemia and age, preoperative Ca, PTH, and NLR was demonstrated ($p = 0.001$, $p = 0.014$, $p = 0.003$, and $p = 0.031$, respectively) by the Mann-Whitney U test (Table 2). NLR values of patients who developed postoperative hypocalcemia were significantly higher than patients without. ROC curve analysis was performed to estimate preoperative predictive levels of Ca, PTH, age, and NLR for postoperative hypocalcemia (Figure 1). The threshold Ca level that would distinguish between patients who developed postoperative hypocalcemia and those who did not was 10.3 with an AUC of 0.589 ($p = 0.02$), 351 for PTH with an AUC of 0.614 ($p < 0.01$), 51 for age with an AUC of 0.623 ($p < 0.01$), and 2.95 for NLR with an AUC of 0.579 ($p = 0.03$). Moreover, there was also a significant association between the preoperative nephrolithiasis and preoperative PLR, P, Ca x P, and 24 hr UCa levels ($p = 0.004$, $p = 0.005$, $p = 0.012$, and $p = 0.039$, respectively).

The independent risk factors for hypocalcemia were investigated by using a multivariate linear regression analysis (Table 3). After adjusting for the potential

contributors to postoperative hypocalcemia, i.e., age, parathyroid gland weight, preoperative Ca, PTH, PRL, and 25OH-D levels, the significance of the correlation between NLR and the postoperative hypocalcemia disappeared (p = 0.332). In this multivariate regression analysis, younger age, lower preoperative Ca, and higher PTH levels were shown as the only predictive risk factors for postoperative hypocalcemia (p = 0.022, p = 0.029, and p = 0.013, respectively).

Table 2 The comparison between the clinical characteristics and the early postoperative hypocalcemia in patients with primary hyperparathyroidism

	Postoperative Hypocalcemia		
	Yes¶	No¶	p*
Ca	10.7 (10.1-11.0)	10.8 (10.4-11.2)	**0.014**
P	2.7 (2.2-3.2)	2.6 (2.3-2.9)	0.422
Ca x P	27.8 (24.1-31.0)	27.8 (24.0-31.9)	0.844
PTH	227 (148-987)	187 (133-284)	**0.003**
NLR	2.0 (1.7-3.1)	1.9 (1.5-2.6)	**0.031**
PLR	127.6 (94.3-178.9)	115.7 (88.7-144.2)	0.051
24 hr UCa	392 (201-446)	312 (225-445)	0.764
Age	49.0 (36.5-59.0)	56.0 (45.0-63.0)	**0.001**
Gland weight	1.5 (0.5-2.5)	1.0 (0.5-2.2)	0.660
Gland volume	6.0 (2.5-16.2)	5.9 (2.4-16.5)	0.656

Ca, calcium; NLR, neutrophil lymphocyte ratio; P, phosphorus; PTH, parathyroid hormone; PLR, platelet lymphocyte ratio; 24 hr UCa, 24-hour urinary calcium Bold font indicates statistical significance. αData are expressed as mean ± standard deviation ¶Data are expressed as median (25th-75th percentile) *Evaluated by Mann-Whitney U-test

Table 3 Multiple logistic regression analyses of the adjusted factors, correlation with the early postoperative hypocalcemia in patients with primary hyperparathyroidism.

	OR	95% CI for OR	p
Age	0.963	0.993 - 0.994	0.022
Ca	0.558	0.331 – 0.941	0.029
PTH	1.001	1.000 - 1.002	0.013
NLR	1.232	0.808 – 1.878	0.332
PLR	1.006	0.997 – 1.015	0.190
25OH-D	1.000	0.964 – 1.037	0.995
Gland weight	1.000	1.000 – 1.000	0.329

Ca, calcium; CI, confidence interval; NLR, neutrophil lymphocyte ratio; OR, odds ratio; P, phosphorus; PTH, parathyroid hormone; PLR, platelet lymphocyte ratio; 25OH-D, 25-hydroxy vitamin D Bold font indicates statistical significance

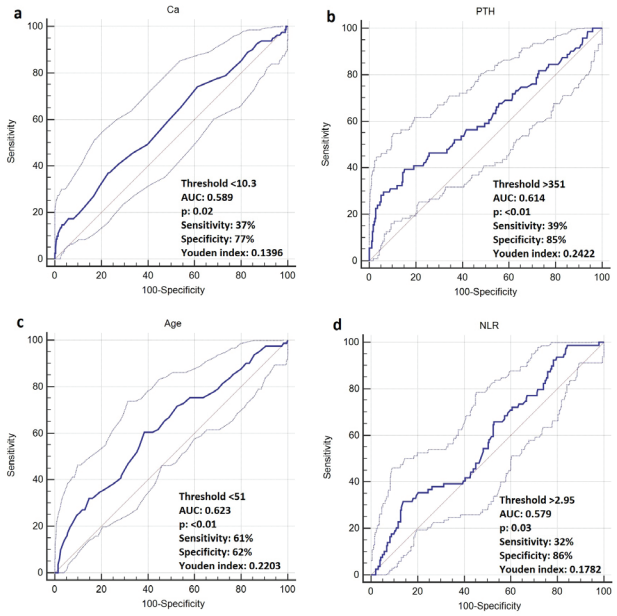

Figure 1:
Receiver operating characteristic curve analysis of preoperative
(a) Ca, (b) PTH, (c) age, and (d) NLR levels for predicting postoperative hypocalcemia.

Discussion

In our study, NLR levels were significantly higher in patients with PHPT who developed postoperative hypocalcemia compared to those who had normal postoperative Ca levels. On the other hand, after adjusting for other confounding factors, the results showed elevated NLR was not significantly a predictive risk factor for postoperative hypocalcemia. To date, this is the first study that investigated the correlation between hemogram-derived inflammatory markers and postoperative hypocalcemia in patients with PHPT. We also showed that younger age, lower serum preoperative Ca levels, and higher PTH levels were predictive risk factors for the development of postoperative hypocalcemia in patients with PHPT. A significant, but very weak correlation between NLR and PTH levels was shown in our analysis. Therefore, it can be stated that PTH may play a role as a confounding factor that causes elevated NLRs in patients with postoperative hypocalcemia compared to those without.

The predictive risk factors for postoperative hypocalcemia which were found in our study are newly discovered findings for the literature. Mittendorf et al. have reported that there was no significant association between any of the laboratory values or other clinical factors, and postoperative hypocalcemia in 162 patients with PHPT (4). In another study with similar sample size, the authors found no significant relationship between preoperative PTH, Ca, P, magnesium, albumin, blood urea nitrogen, thyroid stimulating hormone and vitamin D levels, and postoperative early and permanent hypocalcemia in patients with PHPT (9).

A recent study conducted by Liu et al. supports and contradicts some findings of this present study. In line with our findings, the authors found that the patients who were younger than 45 years had higher Ca decreases after parathyroidectomy than the older patients (19). Moreover, it was reported that the weight of the removed parathyroid gland predicted the amount of Ca drop postoperatively in patients with PHPT. The lesions heavier than 2g had a more significant Ca decrease following parathyroidectomy. In contrast with this finding, our results showed that the removed gland weight was not a predictive risk factor for postoperative hypocalcemia.

In our correlation analysis, we demonstrated a significant but very weak correlation between NLR and preoperative serum PTH levels. Our finding is consistent with the results that were presented by a study with a similar sample size (16). Toraman et al. have reported that NLR showed a significant and very weak correlation with serum PTH, vitamin D, and Ca levels in patients with elevated PTH. Similarly, Zeren et al. demonstrated a significant moderate correlation

between NLR and preoperative serum PTH levels in only 32 patients with PHPT (17). In line with this report, a significant medium correlation between NLR and preoperative serum PTH levels was shown by another study which included 37 patients with PHTP (18). The relatively small sample sizes in these two studies might be the main factors that augmented the correlation levels between these two parameters.

Conclusion

In conclusion, we found that NLR was significantly higher in patients with PHPT who developed postoperative hypocalcemia; however, our regression analysis did not find elevated NLR as a significant predictive risk factor for postoperative hypocalcemia. Moreover, the patients with nephrolithiasis had significantly higher PLR than those without any renal stones. To the best of our knowledge, this is the first study investigating the correlation between hemogram-derived inflammatory markers and clinical parameters, such as the development of postoperative hypocalcemia and preoperative nephrolithiasis, in patients with PHPT. Secondly, in this presented study, younger age, higher PTH, and lower preoperative serum Ca levels were shown as the predictive risk factors for postoperative hypocalcemia in patients with PHPT. We believe that our findings are of paramount importance to the literature on the management of primary hyperparathyroidism.

Conflict of Interest Statement
The authors declare no conflicts of interest.

Ethical Statement
Ethics approval was obtained from the Non-Invasive Clinical Research Ethics Committee of Kocaeli University (Date:25.10.2021, No: GOKAEK 2021/18.19 - 2021/305). The study was conducted in accordance with the principles set forth in the Declaration of Helsinki.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Data is available on request from the authors.

Authors Contributions
EG: Conceptualization; Formal analysis; Investigation; Validation; Visualization; Writing-original draft.

ÖZ: Data curation; Investigation; Methodology.

BYB: Data curation; Formal analysis; Investigation; Methodology.

AS: Supervision; Writing-review & editing.

BÇ: Supervision; Writing-review & editing.

ZC: Supervision; Writing-review & editing.

DK: Conceptualization; Investigation; Writing-original draft.

MS: Conceptualization; Investigation; Writing-original draft.

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ORIGINAL RESEARCH

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Evaluation of Hepatitis Serology Screening Frequency and Viral Reactivation in Patients Followed with Biological Therapy or Cytotoxic Chemotherapy

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Abstract

Objective
Our study aimed to evaluate the results of hepatitis B and C serology screening before biological therapy and chemotherapeutic treatments in internal medicine clinics (rheumatology, medical oncology, and gastroenterology) by comparing between departments and investigating the virus reactivation status.

Material and Method
The study included 1147 patients aged 18 and over who were admitted to the medical oncology, rheumatology, and gastroenterology departments between 2019 and 2021 and received cytotoxic chemotherapy and biological treatment. HBsAg, Anti-HBs, Anti-HBc, and Anti-HCV data were used to screen for hepatitis. The departments were compared and evaluated based on the frequency of screening and reactivation.

Results
Before undergoing chemotherapy or biological therapy, 77% of patients in oncology, 40% in rheumatology, and 43% in gastroenterology were fully screened for hepatitis. The rates of incomplete screening were 16%, 48%, and 52%, respectively, while 3%, 10%, and 4% were never screened. In total, reactivation was observed in twelve patients (1.0%), while no reactivation was observed in 1135 patients (99.0%). A statistically significant correlation was found between the departments and the presence of reactivation ($p<0.001$). Reactivation was detected in 1 oncology patient and 11 rheumatology patients, while no reactivation was seen in all gastroenterology patients.

Conclusion
Although complete screening for viral hepatitis was recommended by the guidelines, it was observed that it was not implemented in clinical practice. It is important to note the need to improve screening rates, especially in populations receiving chemotherapy or biological therapy, where the risk of reactivation is high. Raising awareness about HBV and reminder practices about hepatitis B and C serology screening before chemotherapy and biological therapies for clinical applications may help to increase screening rates.

Keywords: Biological therapy, chemotherapy, hepatitis B, hepatitis C, reactivation

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Introduction

Hepatitis B virus (HBV) is the cause of active fulminant hepatitis, chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). Turkey is located in an endemic region for hepatitis B virus. The prevalence of HBsAg positivity in Turkey is 4%, and anti-HBc IgG positivity is 30.6% (1). Even if the HBsAg test result of patients who have had HBV infection is negative, the virus continues its genetic structure as a carrier in the patient (2). The frequency of HBV reactivation increases as a result of immunosuppression (3).

The use of chemotherapeutic and immunosuppressive agents is increasing due to developments in the treatment of malignant and inflammatory diseases. Therefore, HBV reactivation is frequently observed in susceptible individuals. To prevent severe exacerbations that may be life-threatening, it is important to determine which patients will receive prophylactic antiviral treatment before initiating immunosuppressive treatment, in terms of HBV reactivation (4). Therefore, it is crucial to diagnose and treat HBV reactivation promptly. HBV reactivation can range from an asymptomatic stage to fulminant hepatitis (5).

The risk of HBV reactivation is classified according to the guidelines of the American Gastroenterological Association (AGA) and the American Association for the Study of Liver Diseases (AASLD). According to the AGA guidelines, the risk of reactivation is above 10% when using anthracycline derivatives and high-dose corticosteroids. The risk of reactivation when using cytokine, integrin, TNF-α, and tyrosine kinase inhibitors, as well as medium-dose corticosteroids, is between 1-10%, depending on the patient's HBV serology. The risk of reactivation when using low-dose or intra-articular corticosteroids and traditional immunosuppressive drugs such as azathioprine, 6-mercaptopurine, and methotrexate is less than 1% (6).

Immunosuppression caused by chemotherapy may lead to HBV reactivation, resulting in discontinuation of anti-cancer treatment and liver failure. To prevent this, guidelines recommend HBV screening in high-risk patients with HBV infection and the use of antiviral drugs as prophylaxis in cancer patients receiving chemotherapy (7, 8). Additional doses of vaccine or high doses of vaccine may be necessary to induce an immune response in these patients. Preemptive treatment is recommended for patients who test positive for HBsAg, regardless of their HBV DNA levels and genotype. Nucleoside analogues are potent agents used to treat patients with high viral load. It is recommended that patients who are seropositive for hepatitis B virus receive prophylactic antiviral treatment, even if they are positive for both anti-HBs and anti-HBc IgG. Patients who are positive for anti-HBc IgG should be monitored and treated similarly to those who are positive for HBsAg and have a high level of HBV DNA. To monitor patients with low HBV DNA and natural immunity, it is recommended to monitor both HBV DNA and alanine aminotransferase (ALT) levels every 1-3 months. If a patient is HBV DNA positive but HBsAg negative and Anti-HBc IgG positive, preemptive treatment may be necessary before immunosuppressive treatment. Treatment should be continued for at least 12 months after the end of immunosuppressive treatment (9). In cases of active liver disease related to hepatitis B, treatment should be administered following general hepatitis B treatment principles (10, 11). It is important to implement preventive medicine principles at an optimal level and direct individuals who have encountered hepatitis B to appropriate treatment, especially considering the obstacles in accessing healthcare services and patient follow-up, as outlined in the guidelines. The demand for antiviral treatment is rising due to the growing number of patients undergoing cytotoxic chemotherapy, the widespread use of organ transplantation, and the use of biological drugs to treat autoimmune diseases. Due to Turkey's location in the middle endemic region for HBV, patient screening is crucial. Studies conducted in our country have revealed deficiencies in viral hepatitis serology screening and follow-up (9, 12).

Hepatitis C virüs (HCV) is an RNA virus that can cause chronic liver disease, hepatocellular cancer (HCC) and cirrhosis. There are six genotypes of HCV, designated 1, 2, 3, 4, 5 and 6. The most common genotype in Turkey is 1b. HCV reactivation after immunosuppressive treatment is observed rarely. It has been observed that drug-induced hepatotoxicity occurs more frequently in chronic HCV patients receiving chemotherapeutic and immunosuppressive agents. Consequently, an increase of more than 1 log 10 IU/ml in HCV RNA level is indicative of HCV reactivation. In patients who do not have liver malignancy, do not have a recent history of blood transfusion, do not receive hepatotoxic drugs and do not have a history of systemic diseases other than HCV, at least a three-fold increase in ALT level may be considered as exacerbation (13, 14).

Our study aimed to evaluate the results of hepatitis B and C serology screening before biological therapy and chemotherapeutic treatments in internal medicine clinics (rheumatology, medical oncology, and gastroenterology) by comparing between departments

and investigating the virus reactivation status.

Material and Method

Patients aged 18 years and over who applied to the medical oncology, rheumatology and gastroenterology departments of the University Faculty of Medicine Hospital between January 2019 and January 2021 and received cytotoxic chemotherapy and biological treatment were included in the study. A total of 1147 patients received treatment in the rheumatology, gastroenterology, and medical oncology departments.

Inclusion criteria:

1. Patients over 18 years of age receiving cytotoxic chemotherapy and biological agent treatment

2. Being followed up in the departments of Rheumatology, Gastroenterology and Medical Oncology

3. Patients whose socio-demographic data, and clinical and laboratory findings before and after treatment were obtained.

Exclusion Criteria:

1. Those who have not completed at least 1 cycle of chemotherapy

2. Patients who do not take the biological treatment started to the patient at the planned dose and duration

3. Patients with positive markers of human immunodeficiency virus (HIV)

4. Patients with secondary liver disease such as haemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency severe cardiopulmonary disease, hepatocellular carcinoma causing chronic liver damage,

5. Patients whose treatment is terminated due to death due to primary disease during biological treatment or chemotherapy

6. Patients who were followed up in the COVID intensive care ward during treatment or within 6 months after treatment

HBsAg, Anti-HBs, Anti-HBc, and Anti-HCV data were used to screen for hepatitis. The frequency of screening was compared and evaluated in the rheumatology, gastroenterology, and medical oncology departments. The initiation status of prophylactic antiviral treatment and the antiviral agents (adefovir, entecavir, lamivudine, and tenofovir) given to patients before planned chemotherapy and biological treatment were also evaluated. The study evaluated the frequency of antiviral treatment based on the patients' HBsAg and Anti-HBc test results.

The recorded data included demographic characteristics, diagnosis, hepatitis B and C serology screening, and prophylactic antiviral treatment of patients who received cytotoxic chemotherapy in the medical oncology department, and biological treatment in the rheumatology and gastroenterology department. The study also evaluated cytotoxic chemotherapies and biological treatment administered according to the American Gastroenterological Association (AGA) guidelines. The guideline categorised the grouping as high, medium, or low risk (15).

In the rheumatology department, the study included various drugs such as abatacept, adalimumab, etanercept, golimumab, infliximab, sertolizumab, rituximab, secukinumab, tocilizumab, and ustekinumab. These drugs are cytokine and integrin inhibitors, TNF-α inhibitors, anti-CD20 monoclonal antibodies, interleukin 17 receptor inhibitors, interleukin 6 receptor inhibitors, and interleukin 12 and interleukin 23 inhibitors. The reactivation status of each patient was assessed based on their diagnosis and the biological treatment they received. Patients who received biological treatment (adalimumab, infliximab, and vedolizumab) in the gastroenterology department were recorded, along with information on prophylactic antiviral treatment. Patients were grouped by ulcerative colitis and Crohn's disease.

HBV reactivation is defined as a positive HBV DNA level in patients who had negative HBV DNA at baseline and an increase in HBV DNA of more than 2 log10 IU/mL in patients who had positive HBV DNA at baseline. The term 'reverse seroconversion' refers to the presence of HBsAg in patients who were previously HBsAg negative and anti-HBc positive (15, 16). Clinical and laboratory information of patients who developed reactivation were recorded.

The electrochemiluminescence immunoassay (ECLIA) method with Roche Diagnostic cobas E411 automatic immunoassay uniassay chemistry analyser was used to perform HBsAg, anti-HBc, anti-HBs, and anti-HCV tests (Elecsys, Diagnostic cobas E411, Roche, Sandhofer straße, Mannheim, Germany). The PCR (real-time polymerase chain reaction) method using COBAS (Roche Molecular Diagnostics) devices

was used to analyse HBV DNA. The biochemical parameters AST and ALT were studied using the AU 5800 series AU model biochemistry analyser. Normal values for AST and ALT are 0-35 IU/L.

Statistical Analysis

The data were analysed using IBM SPSS 23 software (IBM Inc., Chicago, IL, USA). Before statistical analysis, we checked for data entry errors and ensured that the parameters were within the expected range. Descriptive statistics of continuous variables were presented using mean and standard deviation, while categorical variables were presented using the number of people (n) and percentage (%) values. The relationships between categorical variables were analysed using chi-square test analysis. Shapiro-Wilk's normality test and Levene's test were used to check the homogeneity of variance in continuous variables. If normal distribution was not observed, three-level comparisons were performed using the Kruskal-Wallis H-test. Post-hoc tests were used to determine correlation. A significance level of $p<0.05$ was used for all analyses.

Results

The study included 1147 patients followed up in rheumatology, gastroenterology and medical oncology clinics. The mean age of the patients included in the study was 53.66±14.50 years. The mean age of the patients in the oncology department was 58.72±11.90 years, in the rheumatology department 46.15±14.76 years and in the gastroenterology department 47.31±15.08 years. There was a statistically significant difference between the mean age and the departments ($p<0.001$). Of the patients, 556 (48.5%) were male and 591 (51.5%) were female. Of the patients, 681 (59.4%) were followed up in oncology, 418 (36.4%) in rheumatology and 48 (4.2%) in gastroenterology (Table 1).

Before treatment, patients with oncological conditions were not screened for HBsAg (3.4%), Anti-HBs (3.7%), Anti-HBc (22%), or Anti-HCV (3.2%). Among patients with rheumatological conditions, 10.3% were not screened for HBsAg, 14.4% for anti-HBs, and 59.1% for anti-HBc tests before treatment. Conversely, 4.2% of gastroenterology patients had not undergone screening for HBsAg, 4.2% for anti-HBs, 56.3% for anti-HBc, and 2% for anti-HCV tests before treatment. A statistically significant relationship was detected between the departments and HBsAg, Anti-HBs, Anti-HBc, and Anti-HCV test groups ($p<0.001$). In six patients (2 with a diagnosis of oncology and 4 with a diagnosis of rheumatology), the presence of HCV RNA was investigated following a positive anti-HCV test. However, all six patients had negative results. (Table 2). Antiviral treatment was initiated before treatment in 60 (8.8%) patients in the oncology group, 23 (5.5%) in the rheumatology group, and 4 (8.4%) in the gastroenterology group (Table 3).

Reactivation of HBV was detected in 1 oncology patient and 11 rheumatology patients, while no reactivation was seen in all gastroenterology patients. In total, reactivation was observed in twelve patients (1.0%), while no reactivation was observed in 1135 patients (99.0%). A statistically significant correlation was found between the departments and the presence of reactivation ($p<0.001$) (Table 4). It was noted that 3 of the patients with reactivation did not receive antiviral treatment. In the study, 60 (8.8%) oncology, 23 (5.5%) rheumatology and 4 (8.4%) gastroenterology patients received antiviral treatment. It was found that entecavir treatment was preferred most frequently. When the frequency of antiviral treatment was evaluated

Table 1 Sociodemographic characteristics

	Oncology (n= 681)	Rheumatology (n=418)	Gastroenterology (n=48)	p
Age, years	58,72±11,90	46,15±14,76	47,31 ± 15,08	**<0,001***
Woman, (n, %)	311 (45,7)	256 (61,2)	24 (50,0)	**<0,001***
Common diagnosis (%)	1. Lung Ca (25.5%) 2. Breast Ca (17.3%)	1. SpA (51%) 2. RA (41.1%)	1.UC (58.3%) 2.CD (41.7%)	

*: Significant at 0.05 level according to paired Student's t-test,

Table 2 Distribution of hepatitis serology by departments

		Oncology (n= 681)	Rheumatology (n=418)	Gastroenterology (n=48)	
		n (%)			p
HBsAg	Negative	642 (94,3)	363 (86,8)	43 (89,6)	**<0,001***
	Positive	16 (2,3)	12 (2,9)	3 (6,3)	
	Not tested	23 (3,4)	43 (10,3)	2 (4,2)	
Anti HBs	Negative	450 (66,1)	239 (57,2)	31 (64,6)	**<0,001***
	Positive	206 (30,2)	119 (28,5)	15 (31,3)	
	Not tested	25 (3,7)	60 (14,4)	2 (4,2)	
Anti HBc	Negative	366 (53,7)	132 (31,6)	18 (37,5)	**<0,001***
	Positive	165 (24,2)	39 (9,3)	3 (6,3)	
	Not tested	150 (22,0)	247 (59,1)	27 (56,3)	
Anti HCV	Negative	657 (96,5)	369 (88,3)	46 (95,8)	**<0,001***
	Positive	2 (0,3)	4 (1,0)	0 (0,0)	
	Not tested	22 (3,2)	45 (10,8)	2 (4,2)	

*: Significant at 0.05 level according to paired Student's t-test, HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, Anti-HBc: Hepatitis B core antibody, Anti-HCV: Hepatitis C virus antibody

Table 3 Antiviral treatment status of patients according to departments

		Oncology	Rheumatology	Gastroenterology	
		n (%)			p
		60 (8,8)	**23(5,5)**	**4(8,4)**	
Antiviral Treatment	**Entecavir**	42 (6,2)	15 (3,6)	1 (2,1)	0,072
	Tenofovir	17 (2,5)	7 (1,7)	2 (4,2)	
	Lamuvidine	1 (0,1)	1 (0,2)	1 (2,1)	

*: Significant at 0.05 level according to paired Student's t-test,

according to HBsAg and Anti-HBc test results in the rheumatology department, it was seen that 19 patients in the anti-HBc positive patient group were given antiviral treatment. In the rheumatology department, 51 (43%) of the patients who received rituximab treatment, a high-risk drug, were not screened for anti-HBc. Of the 15 patients who tested positive for anti-HBc, 9 received antiviral treatment. Only 1 patient receiving rituximab showed reactivation. In the oncology group, 654 (57.0%) patients were in the low-risk group, while 16 (1.4%) and 11 (1.0%) were in the high and intermediate-risk groups, respectively.

Table 4 Reactivation status of patients according to departments

		Oncology	Rheumatology	Gastroenterology	p
		n (%)			
Reactivation	**Yes**	1 (0,1)	11 (2,6)	0 (0,0)	**<0,001***
	No	680 (99,9)	407 (97,4)	48 (100,0)	

*: Significant at 0.05 level according to paired Student's t-test,

Discussion

In our study, the frequency of hepatitis B and C serology screening before biological therapy and chemotherapy treatment in internal medicine (rheumatology, medical oncology and gastroenterology) clinics was found to be low, similar to the literature. Upon examination of the departments, we observed that viral hepatitis screening before chemotherapy was more common in the medical oncology department than in the rheumatology and gastroenterology departments. In rheumatology and gastroenterology departments, the AntiHBc test was performed less frequently on low and medium-risk patients due to their lower risk of reactivation. The increasing use of biological and chemotherapeutic treatments has led to a higher frequency of hepatitis B reactivation. Despite frequent updates to hepatitis B and C serology screening recommendations, our study shows that it has not been fully implemented in clinical practice.

In a retrospective study by Hwang et al, 1,787 (16.7%) of 10,729 newly diagnosed cancer patients receiving chemotherapy were screened for HBV serology (17). Engin et al. found that 47.8% of 445 patients receiving immunosuppressive treatment were not screened for hepatitis, 28.9% were incompletely screened (HBsAg or Anti-HBc IgG was not checked), and 23.3% were fully screened before receiving treatment (18). Bozkurt et al. conducted a study to determine the rate of HBV screening and reactivation frequency in patients receiving anti-TNF. The study retrospectively evaluated 644 patients using anti-TNF for different indications. Before treatment, hepatitis B indicators (HBsAg, Anti-HBc IgG, Anti-HBs) and viral load were analysed. Only 410 (63.7%) of the patients were screened for hepatitis B before treatment (19). The study found that before receiving chemotherapy in the oncology department, 77.7% of patients were fully screened for hepatitis B, 16.6% were incompletely screened, and 3.4% were not screened at all. In the rheumatology department, 40.9% of patients were fully screened for hepatitis, 48.8% were incompletely screened, and 10.3% were not screened at all. In the gastroenterology department, 43.8% of patients were fully screened for hepatitis, 52% were incompletely screened, and 4.2% were not screened at all. High rates of viral hepatitis screening before chemotherapy were observed in the medical oncology department. The study found that screening for viral hepatitis tests was more frequent in rheumatology and gastroenterology departments compared to the literature. The reason for incomplete screening in rheumatology and gastroenterology departments is that 72% of the biological treatments given in rheumatology and all of them in gastroenterology departments were classified as low-medium risk according to AGA guidelines. Therefore, it is believed that in patients at low to intermediate risk, HBsAg and Anti-HBs were tested without checking for the Anti-HBc total.

According to the AGA guideline classification of hepatitis reactivation, prophylactic antiviral treatment is not recommended if the patient is HBsAg-negative, Anti-HBc-positive, and in the low or medium-risk group. However, some studies do recommend prophylactic antiviral treatment. Risk factors for hepatitis reactivation include young age, male gender, and high ALT levels in patients before immunosuppressive treatment (20). In the clinical approach, elevated ALT and AST levels in patients who are planned to receive biological treatment other than rituximab (in the intermediate risk group according to AGA risk classification) indicate the need for prophylactic antiviral treatment. According to a study conducted by Bessone et al., a high baseline ALT level was found to be significant in terms of HBV reactivation (21). Conversely, in the study conducted by Cheng et al., no such association was found between ALT levels before treatment (22). There is still uncertainty regarding the evaluation of AST and ALT levels as a criterion for initiating prophylactic antiviral treatment before biological treatment. Our study found

no statistically significant difference between the group that received antiviral treatment before biological treatment and the group that did not receive antiviral treatment, both of which were in the intermediate risk group according to AGA risk classification. Regarding reactivation, refraining from initiating antiviral treatment before biological treatment did not show any association with AST and ALT values. Due to the limited number of patients experiencing reactivation, it is challenging to establish a correlation between AST and ALT values and reactivation. Therefore, a more extensive study is required in this area.

Reactivation of the HBV was observed in one patient in the oncology department and eleven patients in the rheumatology department. No viral reactivation was observed in the gastroenterology department. The patient in the oncology follow-up who experienced reactivation had received anthracycline-containing chemotherapy, and antiviral treatment was initiated before chemotherapy. Reactivation occurred in one out of 16 high-risk patients according to AGA guidelines in the oncology department. No viral reactivation was observed in the low and medium-risk groups. It was observed that 10 of the rheumatology patients with reactivation used etanercept, while one used rituximab treatment. The high incidence of reactivation in patients using etanercept treatment is not due to the drug being inherently more risky, but rather to the fact that it is more commonly used in patients who are at a higher risk of developing reactivation. In the case of hepatitis B carriers, anti-TNF therapy is recommended as a first-line treatment option, with etanercept being the preferred agent. Consequently, this treatment was selected more frequently. Two patients in the oncology department and four patients in the rheumatology department were found to have negative HCV RNA results, despite positive anti-HCV results. No evidence of HCV reactivation was observed in this group.

In their systematic review, Cholongitas et al. found that although reactivation was higher in patients receiving rituximab-containing combination therapy compared to those receiving rituximab-free combination therapy in the general population, the difference was not statistically significant. However, in HBsAg(-)/Anti-HBc(+) patients, reactivation was significantly higher in those receiving rituximab treatment (23). Koskinas et al. (24) found no significant difference between patients who received rituximab and those who did not. In our study, only one out of 117 patients who received rituximab treatment in the rheumatology department experienced reactivation. The patient had a positive HBsAg test, and as per the literature, none of the patients with a negative anti-HBc test who received rituximab treatment developed viral reactivation.

Although the retrospective nature of our study is a limitation, extremely valuable data were obtained. Prospective screening and follow-up programmes and studies including a large number of patients will be more enlightening in this regard. The limitations of our study include the fact that it included patients admitted between the specified dates, the insufficient number of patients with reactivation, the inability to follow up AST, ALT and reactivation for a longer period, and the insufficient number of patients in the high-risk group according to AGA risk assessment. Since the chemotherapy treatment initiated by patients in the oncology department is very diverse and includes different types of treatments, more comprehensive studies are needed because obtaining accurate data is limited.

Conclusion

In conclusion, although complete screening for viral hepatitis was recommended by the guidelines, it was observed that it was not implemented in clinical practice. Even in patients who were fully screened for hepatitis, prophylaxis or referral to vaccination was found to be incomplete. Failure to initiate prophylactic antiviral treatment results in viral reactivation. In patients with viral reactivation, treatment of the primary disease is delayed. This results in an increase in primary disease and hepatitis-related mortality. The organisation of joint educational meetings by the centres dealing with HBV education and treatment in cooperation with the centres applying chemotherapy and biological treatment and raising awareness about HBV through these programmes are among the recommended solutions.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study was approved by the ethics committee of Süleyman Demirel University (Ethics committee approval number (2022-4/56). The study was conducted according to the "Declaration of Helsinki".

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions

AK: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft

AD: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Supervision; Visualization; Writing-original draft; Writing-review & editing.

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ORIGINAL RESEARCH

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Fluvoxamine Administration Attenuates Lipopolysaccharide-Induced Pancreatic Damage

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Abstract

Objective
Certain types of bacteria contain lipopolysaccharide (LPS), which can cause widespread inflammation in the body, including the pancreas. Fluvoxamine (FLV), a selective serotonin reuptake inhibitor (SSRI) commonly prescribed for psychiatric disorders, has been shown to possess anti-inflammatory properties and may be beneficial in conditions involving tissue damage and inflammation. This study aims to evaluate the potential protective effects of FLV against experimentally induced pancreatic disease in rats using LPS.

Material and Method
In this experiment, a total of 32 Wistar albino male rats were randomly divided into four groups: control, LPS (5 mg/kg, intraperitoneally (i.p.)), LPS + FLV (50 mg/kg FLV, i.p.) and FLV. The rats were euthanatized 6 hours after the administration of LPS, and serum and pancreas tissue samples were collected during the necropsy for biochemical, histopathological, and immunohistochemical evaluations.

Results
According to the study findings, LPS lowered blood glucose levels. Histological examination showed that LPS caused edema, mild infiltration of inflammatory cells, increased vacuolization in the cells of the Langerhans islet, and severe hyperemia. Immunohistochemical investigations revealed a reduction in the expression of insulin and amylin. The biochemical, histopathological, and immunohistochemical outcomes were improved by FLV.

Conclusion
The results of this experimental rat model study indicated that LPS causes damage to the endocrine pancreas. However, FLV demonstrated significant ameliorative effects on the pancreas in rats with LPS-induced pancreatitis.

Keywords: Biochemistry, IHC, LPS, pancreas, pathology

Introduction

Lipopolysaccharide (LPS) is a compound found in bacterial cell membranes, commonly known as an endotoxin. These endotoxins are potentially harmful molecules that can trigger inflammation and immune responses in the body. LPS, specifically found in the cell walls of bacteria in the intestinal microbiota,

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can be released through various processes in the intestines, allowing it to enter the circulatory system and, potentially cause damage to various organs (1-8). The pancreas is an organ that produces digestive enzymes and hormones (9). When LPS enters the circulatory system, the systemic inflammation it causes can lead to pathological changes in the pancreas resulting in conditions such as pancreatitis (7,8). The hormones insulin, glucagon, and amylin which are secreted by the pancreas, provide critical information about pancreatic damage (10).

Fluvoxamine (FLV) is an antidepressant belonging to the selective serotonin reuptake inhibitor (SSRI) class. This medication influences neurotransmission in the central nervous system by regulating serotonin levels and, is commonly used to treat psychiatric conditions such as major depressive disorder, obsessive-compulsive disorder (OCD), panic disorder, and social anxiety disorder (11).

FLV works by preventing the reuptake of serotonin from nerve terminals, thereby increasing serotonin levels between nerve cells. This action allows the neurotransmitter to remain in synapses for a longer duration, communication between nerve cells. Serotonin is a crucial neurotransmitter that regulates mood, sleep, appetite, and overall behavior (11,12).

Recent research has indicated that FLV may possess anti-inflammatory and immunomodulatory properties potential and benefits in treating conditions associated with inflammatory processes (13).

LPS exerts its harmful effects on the pancreas primarily by inducing inflammation (7,8,14). This experimental rat model study aims to investigate the cellular-level effects of FLV on LPS-induced pancreatic pathology.

Material and Method

Animals and Study Design

All experiments conducted for this study adhered to the ARRIVE (Animal Research Reporting in Live Experiments) 2.0 guidelines for animal research.

Thirty-two Wistar Albino male rats were obtained from the Experimental Animals Laboratory of SDU and randomly divided into four groups.

Group 1 (Control, n=8): 0.5-1 ml physiological saline (PS) was administered intraperitoneally (i.p.) to the left inguinal regions of the rats, followed by 0.5 ml of PS to the right inguinal regions 30 minutes later.

Group 2 (LPS, n=8): After the i.p. administration of 0.5-1 ml PS to the left inguinal regions, 5 mg/kg of LPS in a volume of 0.5 ml was administered i.p. to the right inguinal regions 30 minutes later. The LPS, in solid form, was dissolved in PS (15).

Group 3 (LPS+ FLV, n=8): 50 mg/kg of FLV (16) dissolved in PS in a volume of 0.5-1 ml, was administered i.p. to the left inguinal regions. Thirty minutes later, 5 mg/kg of LPS in a volume of 0.5 ml was administered i.p. to the right inguinal regions.

Group 4 (FLV, n=8): 50 mg/kg FLV, dissolved in PS in a volume of 0.5-1 ml, was administered i.p. to the left inguinal regions. Thirty minutes later, 0.5 ml PS was administered i.p. to the right inguinal regions.

The experimental animals were sacrificed with 80–100 mg/kg of ketamine (Ketasol, Richter Pharma AG, Austria) and 8–10 mg/kg of xylazine (Xylasinbio%2, Bioveta, Czech Republic) six hours following the last drug administration. Serum glucose levels are measured using blood samples. All rats had their pancreatic tissue samples carefully removed, and they were fixed in a 10% formaldehyde solution for immunohistochemical and histopathological analyses.

Biochemical Analyses

Serum glucose levels were determined using a spectrophotometric method with a commercial kit (glucose GOD FS-1 2500 99 10 923, DiaSys, Holzheim, Germany) compatible with an autoanalyzer (Beckman Coulter AU5800, USA).

Histopathological Assessment

During necropsy, pancreatic tissue samples were collected and fixed in a 10% buffered formaldehyde solution. After two days of fixation, the tissues underwent standard processing with an automated tissue processing device. They were then embedded in paraffin wax, and sliced into 5µm sections using a rotary microtome (Leica Microsystems, Wetzlar, Germany). The sections were stained with hematoxylin-eosin (HE) and examined under a light microscope in a blinded manner. The pancreas was semi quantitatively scored for hyperemia, hemorrhage, edema, inflammation, degeneration, and necrosis on a scale of 0-3.

Immunohistochemical Analysis

Three consecutive sections of pancreatic tissue samples were immunostained for insulin (Anti-Insulin antibody [EPR17359] (ab181547)), amylin (Anti-Amylin/DAP antibody [EPR22556-138] (ab254259)), and glucagon (Anti-Glucagon antibody [EP3070] (ab92517)) following histopathological examination

to assess the expression of these markers. Immunostaining was performed using the streptavidin-biotin peroxidase technique according to the manufacturer's instructions. The secondary antibody used was the Mouse and Rabbit Specific HRP/DAB Detection IHC kit (ab64264), with diaminobenzidine (DAB) serving as the chromogen. Both primary and secondary antibodies were supplied by Abcam (Cambridge, UK). For negative controls, antibody dilution solutions were used in place of the primary antiserum step.

A specialized histopathologist from a different university, who was unaware of group assignments, evaluated each examination. Under X40 objective magnification, the percentage of cells positively immunostained for each marker was calculated in 10 different fields for each section across all groups. Image analysis was done using ImageJ software (version 1.48, National Institutes of Health, Bethesda MD). Microphotographs were generated using the Database Manual Cell Sens Life Science Imaging Software System (Olympus Co., Tokyo, Japan).

Statistical Analysis

The data obtained were subjected to statistical analysis using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Group comparisons were conducted using ANOVA, and variable assessments were performed with the Tukey test. Statistical significance was set at $p < 0.05$.

Results

When blood glucose levels were examined across the groups, it was observed that LPS administration significantly reduced blood glucose levels. Conversely, FLV applications were found to be effective in normalizing the levels. Blood glucose levels for each group are presented in Figure 1.

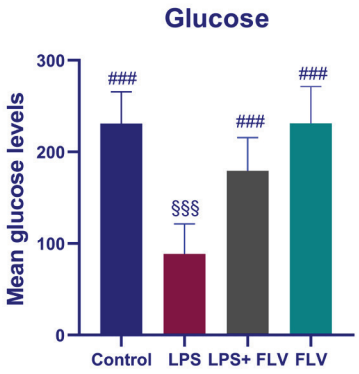
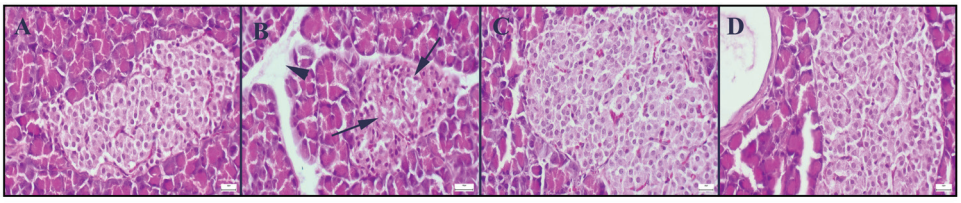
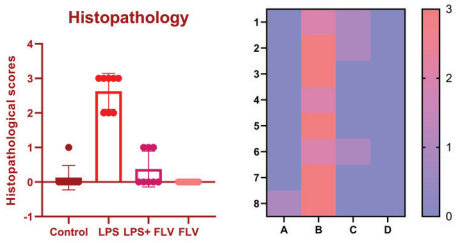


Figure 1:
Blood glucose levels (mg/dl) between the groups, differences between groups with different superscripts are statistically significant, p<0.001.(a) Ca, (b) PTH, (c) age, and (d) NLR levels for predicting postoperative hypocalcemia.



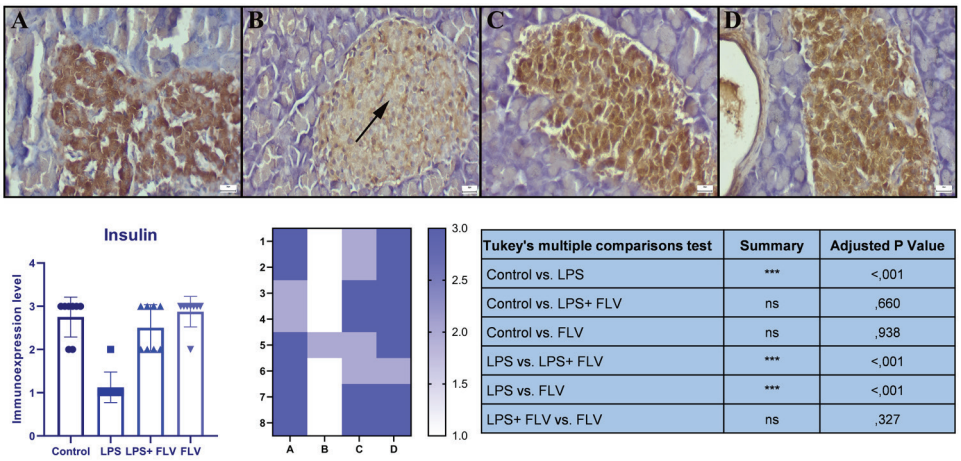


Tukey's multiple comparisons test	Summary	Adjusted P Value
Control vs. LPS	***	<,001
Control vs. LPS+ FLV	ns	,613
Control vs. FLV	ns	,926
LPS vs. LPS+ FLV	***	<,001
LPS vs. FLV	***	<,001
LPS+ FLV vs. FLV	ns	,274

Figure 2:
Representative histopathological images of the pancreas between the groups and statistical analysis results of histopathological scores. (A) Normal pancreatic histoarchitecture in a rat from the control group. (B) Marked edema (arrowhead) and numerous necrotic cells (arrows) in pancreatic Langerhans islets a rat belonging LPS group. (C) Almost normal histological appearance in pancreatic Langerhans islet cells in a rat form LPS+FLV group. (D) Normal pancreatic histology in a rat in FLV group, HE, Scale bars= 20µm.

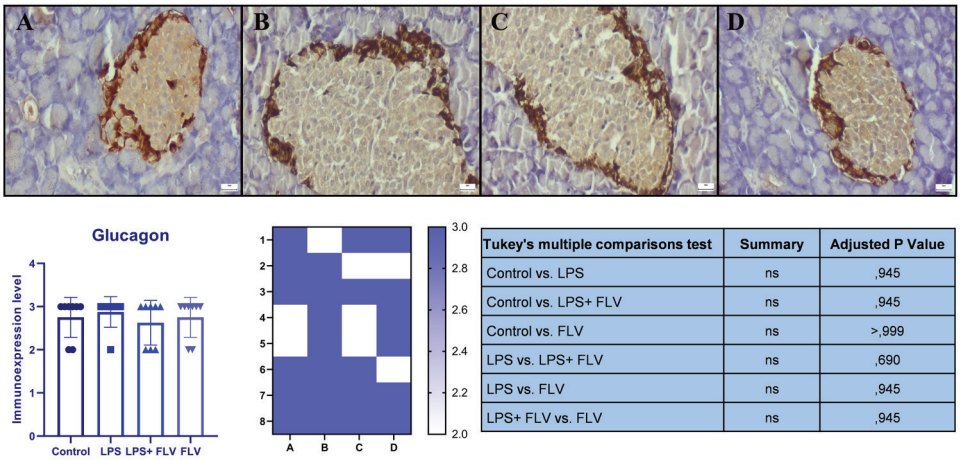
The pancreatic tissue in the control rats appeared normal. Histopathological analysis of the pancreas in the LPS group showed markedly elevated levels of endocrine cell vacuolization, edema, and moderate infiltrations of inflammatory cells, primarily neutrophils. Additionally, single-cell necrosis in the Langerhans islets was also noticed in the LPS group. The administration of FLV resulted in an improvement in these pathological findings. Microscopic examination of the pancreas in the FLV group showed no abnormalities (Fig. 2).

During the immunohistochemical analysis, glucagon-immunopositive cells were found at the periphery of the Langerhans islet, whereas amylin- and insulin-immunopositive cells were observed in the center region. Each of the three markers was located in the cytoplasm. The analysis indicated that LPS administration markedly decreased the expression of insulin and amylin, while there was no significant change in glucagon level. Additionally, in the LPS group, both insulin and amylin expressions showed a significant decrease compared to the control group



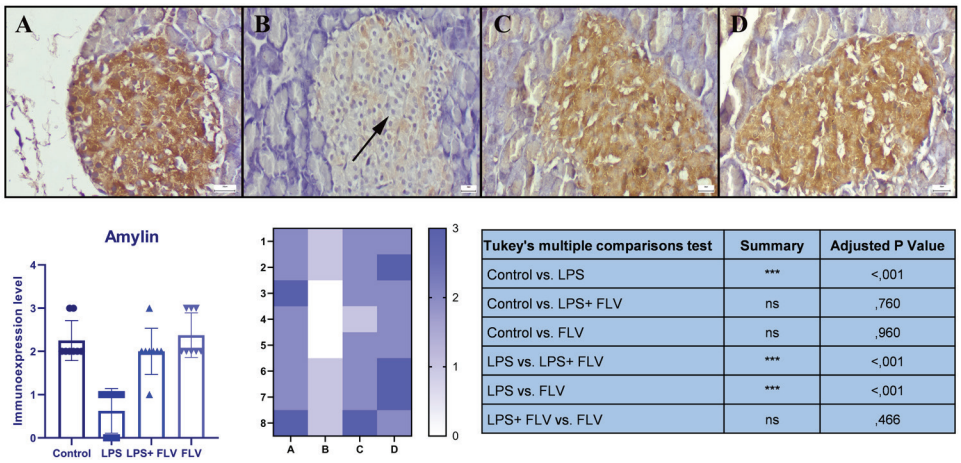
Tukey's multiple comparisons test	Summary	Adjusted P Value
Control vs. LPS	***	<,001
Control vs. LPS+ FLV	ns	,660
Control vs. FLV	ns	,938
LPS vs. LPS+ FLV	***	<,001
LPS vs. FLV	***	<,001
LPS+ FLV vs. FLV	ns	,327

Figure 3:
Insulin immunoexpressions in the endocrine islet of the pancreas among the groups and statistical analysis results of insulin IHC scores. (A) Significant expressions in the control group. (B) Decreased 7 expression (arrow) in the LPS group. (C) Markedly increased in expressions in the LPS+FLV group. (D) Normal significant expressions in all markers in the FLV group. Streptavidin biotin peroxidase method, scale bars=20µm.



Tukey's multiple comparisons test	Summary	Adjusted P Value
Control vs. LPS	ns	,945
Control vs. LPS+ FLV	ns	,945
Control vs. FLV	ns	>,999
LPS vs. LPS+ FLV	ns	,690
LPS vs. FLV	ns	,945
LPS+ FLV vs. FLV	ns	,945

Figure 4:
Glucagon immunoexpressions in the endocrine islet of the pancreas among the groups and statistical analysis results of glucagon IHC scores. Similar expressions at the peripheral area of the Langerhans islet in the (A) control group, (B) LPS group, (C) LPS+FLV group, and (D) FLV group. Streptavidin biotin peroxidase method, scale bars=20µm.



Tukey's multiple comparisons test	Summary	Adjusted P Value
Control vs. LPS	***	<,001
Control vs. LPS+ FLV	ns	,760
Control vs. FLV	ns	,960
LPS vs. LPS+ FLV	***	<,001
LPS vs. FLV	***	<,001
LPS+ FLV vs. FLV	ns	,466

Figure 5:
Amylin immunoexpressions in Langerhans islet of the pancreas in the groups and statistical analysis results of amylin IHC scores. (A) Marked expressions in the control group. (B) Decreased expression (arrow) in the LPS group. (C) Increased in expressions in the LPS+FLV group. (D) Marked expressions in the FLV group. Streptavidin biotin peroxidase method, scale bars=20µm.

($p < 0.001$ for both), but the decrease in glucagon expression was not statistically significant ($p > 0.05$). Following treatment with FLV in the LPS-FLV group, Amylin and insulin levels returned to normal. Likewise, insulin and amylin levels were significantly higher in the FLV group compared to the LPS group ($p < 0.001$). The glucagon expressions in the FLV-treated groups did not differ significantly from the other groups ($p > 0.05$ for all) (Fig. 3-5).

Discussion

In this study, the effects of FLV, an antidepressant belonging to the selective serotonin reuptake inhibitors (SSRI) class, were investigated for the first time against LPS-induced pancreatic damage. The impact of LPS on the pancreas was assessed, and the therapeutic effects of FLV were identified.

LPS is a molecule found in bacterial cell walls that can stimulate the immune system and initiate inflammatory responses. Excessive activation of LPS can contribute to inflammatory diseases and overstimulation of the immune system, leading to harmful effects on various tissues. The pancreas is particularly sensitive to LPS and is severely affected by its actions. The Langerhans islets are the most impacted part of the pancreas (7,8,17).

Blood glucose levels and overall metabolism are greatly influenced by the endocrine activity of the pancreatic islets, which produce glucagon, insulin, proinsulin, somatostatin, pancreatic polypeptide, amylin and C-peptide. Glucagon elevates blood glucose levels while insulin reduces them. Insulin secreted by the pancreas, is essential for the metabolism of proteins, fats, and carbohydrates. Since glucose is a key energy source for immune cells, there is a connection between glucose metabolism and immunological function (18,19).

Elevated blood glucose levels have been linked to immune cell malfunction and apoptosis through oxidative stress and inflammation. On the other hand, low blood glucose levels can weaken the immune system and make a person more vulnerable to diseases. According to the study, exposure to LPS raises blood glucose levels and decreases pancreatic insulin expression. It is thought that LPS damages the cells that secrete insulin, preventing its production (8). However, the decrease in blood glucose that occurs when exposed to LPS is complicated. As a defensive mechanism, immune cells may enhance the uptake of glucose, and hepatic gluconeogenesis inhibition may also impact glucose homeostasis. Because LPS inhibits hepatic glucose synthesis, severe endotoxic shock might impair the body's ability to maintain glucose homeostasis, resulting in hypoglycemia (8, 20–22). In this study, serum glucose levels in this study dropped during necropsy and six hours after LPS injection. This decrease is thought to be caused by hyperinsulinemia that occurs just after LPS delivery, which stresses the beta cells in the pancreas responsible for producing insulin. Long-term hyperinsulinemia may be linked to pancreatic alterations and malfunction of the beta cells.

The pancreas can be damaged due to various reasons, and one significant indicator of damage to the Langerhans is the impairment of insulin expression. Particularly in conditions that lead to inflammation, degeneration, and necrosis, the synthesis of insulin tends to decrease. The endocrine part of the pancreas, consisting of more delicate cells compared to the exocrine part, is particularly susceptible to damage. Therefore, damage is more likely to occur in the endocrine cells of the pancreas, with cells responsible for insulin synthesis being the most vulnerable among the endocrine cells (7-9). Similar findings were observed in this study, where LPS markedly decreased in insulin expressions in the Langerhans islet.

Amylin is a hormone secreted by the pancreas that typically works in conjunction with insulin to help regulate blood glucose levels. Pancreatic damage, especially in conditions affecting the Langerhans islets, can impact amylin levels. Cellular damage in the pancreas can lead to irregularities in amylin production. This condition can result from diseases such as pancreatitis, pancreatic tumours, or other inflammatory conditions. Pancreatic damage can hinder the normal secretion of amylin and other digestive enzymes, leading to disruptions in the digestive process. Therefore, conditions associated with pancreatic damage can cause changes in amylin levels, thereby affecting the regulation of blood glucose (23,24). It has been reported that amylin expression decreases in pancreatic injuries (7,8). The findings of this study demonstrate parallelism with the prominent findings in the literature regarding the effects of LPS on amylin expression.

Glucagon is a hormone released from the pancreas and typically has the opposite effect of insulin. In situations where insulin levels are low, glucagon is released, promoting the conversion of glycogen to glucose in the liver and increasing blood glucose levels. Pancreatic damage, especially in cases where Langerhans islets are affected, can influence glucagon levels. Cellular damage in the pancreas can lead to irregularities in glucagon production. This condition may result from diseases such as pancreatitis, pancreatic tumours, or other inflammatory conditions. Pancreatic damage can disrupt the normal regulation of glucagon, leading to disturbances in blood glucose control. Therefore, conditions associated with pancreatic damage can cause changes in glucagon levels and, consequently, difficulties in regulating blood glucose (25). It has been reported that glucagon expression are less affected or not affected at all in pancreatic damage compared to insulin (7,8). In this study, a slight increase was observed in the cells synthesizing glucagon, but this increase was statistically insignificant. This result further supports the idea that the cells producing glucagon are among those least affected by LPS

LPS, a molecule found in bacterial cell walls, can stimulate the immune system and initiate inflammatory responses. The pancreas is a critical organ in the body, playing a pivotal role in digestion and energy metabolism. Excessive activation of LPS can contribute to the occurrence of inflammatory diseases and other conditions affecting the immune system (7,8). The pancreas is particularly sensitive to LPS and is one of the organs significantly affected by its impact. In cases of pancreatic damage, structures within the pancreas, such as the Langerhans islets, may be influenced by the effects of LPS. This situation can arise as a result of inflammatory conditions like pancreatitis or bacterial infections. Pancreatic damage may be associated with increased inflammatory responses in pancreatic tissue induced by LPS (7,8,26).

The findings of the present study demonstrate that LPS causes damage in the pancreas, particularly in the cells of Langerhans islets, and FLV is effective in preventing this damage at the cellular level. It is believed to exert its effect through its anti-inflammatory properties. More research is required on this topic.

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Conflict of Interest Statement
There is no potential conflict of interest.

Ethical Approval
The experimental protocol and ethical requirements of the study were approved by the Suleyman Demirel University Animal Experimentation Local Ethics Committee, with approval 01.03.2024 date number 265.

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Availability of Data and Materials
Data is available on request from the authors.

Authors Contributions
ŞT: Conceptualization; Data curation; Formal analysis; Methodology; Validation; Visualization; Writing-original draft.

ÖÖ: Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing-review & editing.

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ORIGINAL RESEARCH

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An Essential Problem in Patients with Hereditary Angioedema: Irritable Bowel Syndrome

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Abstract

Objective

Hereditary angioedema (HAE) is characterized by attacks of subcutaneous and mucosal edema. HAE usually affects the skin or mucosal tissues of the upper respiratory and gastrointestinal tract. Irritable bowel syndrome (IBS) is one of the diseases in which the abdominal symptoms of HAE may be confused. In this study, we aimed to clarify the role of IBS in clinical presentation and diagnostic delay in HAE.

Material and Method

50 patients with HAE followed in our clinic between January 2013 and April 2023 were included in this study, and hospital records were retrospectively reviewed. Patients with HAE were divided into two groups, those with and without IBS, and evaluated according to Rome IV criteria for diagnosing IBS.

Results

The mean age of the study group was 40 ± 13 years, and 60% (n=30) were female. IBS was observed in 30% (n=15) of the patients, and 60% (n=9) had IBS before diagnosing HAE. The frequency of attacks and history of gastrointestinal tract medical/surgical history were more frequent in HAE patients with IBS (p<0.001, p=0.032, respectively). Abdominal symptoms before the diagnosis of HAE and persistent abdominal symptoms other than attacks after the diagnosis of HAE were more common in HAE patients with IBS (p<0.001, p<0.001, respectively). HAE patients with IBS had a more significant delay in diagnosing HAE (p=0.011).

Conclusion

Clinicians should keep HAE in mind in patients with suspected IBS or patients presenting with recurrent unexplained abdominal pain.

Keywords: Hereditary angioedema, irritable bowel syndrome, abdominal symptoms, frequent attacks, diagnostic delay.

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Introduction

Hereditary angioedema (HAE) is a rare and potentially life-threatening disease that is characterized by itchy swelling of the subcutaneous or submucosal tissues of the skin, extremities, genital organs, and the respiratory and gastrointestinal tracts (1,2). The prevalence of HAE is estimated to be between 1:50000 and 1:100000 (3). HAE can be divided into three types according to the C1 inhibitor (C1-INH) levels and function. Approximately 85% of the HAE cases are caused by C1-INH deficiency (HAE type I), and 15% are caused by C1-INH dysfunction (HAE type II). Patients with HAE who have normal C1-INH levels and function are said to have “HAE with normal C1-INH”(4). Several genetic mutations have been identified in patients with HAE, including mutations in the genes of Factor XII, angiopoietin-1, plasminogen, and kininogen-1 (5). Since HAE is an autosomal dominant disease, patients have a family history of angioedema. However, a family history may not always be present; approximately 25% of HAE cases are caused by de novo mutations (6). Irritable bowel syndrome (IBS) is one of the most common causes of abdominal pain (7). HAE is a rare cause of abdominal pain and can sometimes be misdiagnosed as IBS (8). Therefore, patients with suspected IBS need to be analyzed more thoroughly to prevent a delay in diagnosis and avoid confusion with episodes of HAE-associated abdominal pain. The relationship between HAE and IBS remains unclear. Thus, in this study, we aimed to determine the role of IBS in the clinical presentation and diagnostic delay of HAE.

Material and Method

Study design

This retrospective cohort study was conducted at the Necmettin Erbakan University. The ethics committee approved the study (No: 2023/4368; date of approval). To clinically diagnose IBS, any underlying organic disease should be excluded and the diagnostic criteria should be fulfilled. Data from patients who met the inclusion criteria (age ≥ 18 years and diagnosis of HAE) between January 2013 and April 2023 were collected from their medical records in the hospital database. Complete blood count, erythrocyte sedimentation rate, and stool examination for occult blood, leukocytes, and parasites (examined in three independently collected stool samples) were examined to exclude organic diseases. Again, gastrointestinal system endoscopy and abdominal ultrasonography were performed to exclude organic conditions. Patients with no pathological findings were included in the study. Patients with an underlying organic pathology, such as inflammatory bowel disease, colon cancer, and alarm symptoms, were excluded (Figure 1).

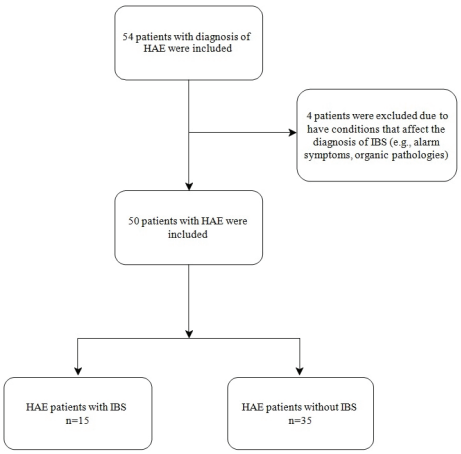

Figure 1:
Flow chart of the inclusion of the study population.
Abbreviations: HAE, hereditary angioedema; IBS, irritable bowel syndrome.

Data Collection

Patient data were obtained from their paper and electronic medical records. The diagnosis of IBS was confirmed using the Rome IV criterion that includes questions regarding the gastrointestinal tract symptoms. Patients with recurrent abdominal pain for an average of at least one day a week over the last 3 months and two or more of the following symptoms were diagnosed with IBS: Change in frequency of defecation, relief with defecation, and change in the stool form (9).

Statistical Analysis

Study data were analyzed with SPSS for Windows (version 22.0; IBM Corp., Armonk, NY, USA). We used the independent samples T-test to evaluate the continuous data. The chi-square ($\chi 2$) and Fisher’s exact tests were used to evaluate the categorical data. The continuous variables are expressed as mean ± standard deviation or median with interquartile range (IQR) and the categorical variables as numbers with percentages. $P < 0.05$ was statistically significant.

Results

Demographic Characteristics of the Patients with HAE

A total of 50 patients with HAE were included in the study. The mean age was 40 ± 13 years, and 60% (n = 30) of the patients were female. Type 1 HAE was present in 56% of the patients and type 2 HAE in 44%. The mean age at which HAE was diagnosed was 30

± 12 years, and the mean delay in making a correct diagnosis was 12 ± 10 years (Table 1). The patients with HAE were divided into two groups: those with IBS and those without. Patients with HAE who had IBS were predominantly female (73.3%), and the mean age was 43.4 ± 11 years. There was no significant difference in age and sex between the two groups (p = 0.259, p = 0.208, respectively) (Table 2).

Frequency of Abdominal Attacks and the Symptom Types

The median number of monthly attacks was 1 (IQR, 1–4), and the attacks were frequent in 28% of the patients. HAE-associated abdominal attacks were seen in 56% of the patients. The primary symptoms of the abdominal attacks were abdominal pain (72%), distension (64%), and nausea (60%). Diarrhoea (14%) and vomiting (20%) were not the predominant symptoms (Table 1).

Gastrointestinal System Findings Other Than an Abdominal Attack

IBS was observed in 30% of the patients, and IBS had been diagnosed before HAE in nine (60%) of the 15 patients with IBS. A medical/surgical history of the gastrointestinal tract was detected in 46% of the patients. A medical/surgical history related to the gastrointestinal tract and frequent attacks were more common in those with IBS than in those without IBS (p < 0.001, p = 0.032, respectively). Furthermore, those with IBS had more gastrointestinal symptoms before the diagnosis of HAE and persistent gastrointestinal symptoms other than abdominal pain after the diagnosis of HAE (p < 0.001, p < 0.001, respectively) (Table 2).

Diagnostic Delay and Misdiagnosis

There was a more significant delay in HAE diagnosis in those with IBS than in those without IBS (p = 0.011).

Symptoms Associated with IBS

Abdominal pain (n = 12) and distension (n = 9) were the most common symptoms of IBS encountered (Figure 2).

Table 1 Patients demographics and the characteristics of hereditary angioedema attacks.

Characteristics	Value
Age (years), mean ± SD	40 ± 13
Sex, n (%)	
Female	30 (60)
Male	20 (40)
Type, n (%)	
I	28 (56)
II	22 (44)
Diagnostic age (years), mean ± SD	30 ± 12
Diagnostic delay (years), mean ± SD	12 ± 10
Number of attacks (per month), median, IQR	1 (1–4)
Frequent attacks, n (%)	14 (28)
Abdominal attacks, n (%)	28 (56)
Abdominal pain	36 (72)
Distension	32 (64)
Nausea	30 (60)
Diarrhea	7 (14)
Vomiting	10 (20)

Abbreviations:IQR, interquartile range; SD, standard deviation.

Table 2 Gastrointestinal system findings other than abdominal attacks.

Variable	Patients with HAE and IBS	Patients with HAE and without IBS	P*
Total, n (%)	15 (30)	35 (70)	
Age (years), mean ± SD	43.4 ± 11	39.1 ± 14.8	0.259
Sex, n (%)			0.208
Female	11 (73.3)	19 (54.3)	
Male	4 (26.7)	16 (45.7)	
Gastrointestinal tract-related medical/surgical history	14 (61)	9 (39)	**<0.001**
Frequent attacks	9 (64)	5 (36)	**0.030**
Gastrointestinal tract symptoms before the diagnosis of HAE	18 (60)	12 (40)	**<0.001**
Persistent gastrointestinal tract symptoms other than attacks after the diagnosis of HAE	17 (61)	11 (39)	**<0.001**
**** Delay in diagnosing HAE, (years)**	18 ± 7.3	10.3 ± 8	**0.011**

* Chi Square test (data were shown as number and percentages).
** Independent samples T-test (data are shown as mean with standard deviation).
Abbreviations: HAE, hereditary angioedema; IBS, irritable bowel syndrome; SD, standard deviation

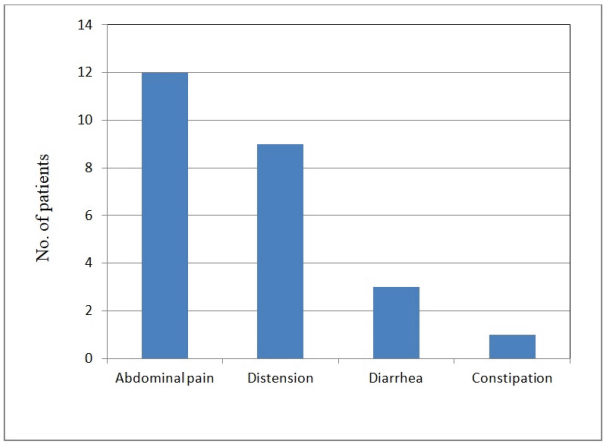

Figure 2:
Symptoms of IBS in patients with hereditary angioedema.

Discussion

Abdominal symptoms are characteristic of HAE. We determined that the most common symptom of patients with HAE was abdominal pain, and 56% of them presented with abdominal attacks. A gastrointestinal tract-related medical/surgical history, frequent attacks, and delay in HAE diagnosis were more common in patients with HAE and IBS. Additionally, the most common symptom encountered in patients with HAE and IBS was abdominal pain.

Abdominal symptoms are the most common findings after diffuse skin edema, especially of the extremities, in HAE. The lips, tongue, eyelids, and genitals may also be affected (10). Similarly, abdominal attacks were observed in most of our study patients. HAE can present with cramping abdominal pain, nausea, or vomiting. The abdominal pain can be severe and acute or recurrent, chronic, or of moderate severity (11). In a previous study, abdominal pain was the most common symptom during abdominal attacks (12). In another study, distension and crampy abdominal pain were the most common symptoms during an abdominal attack (13). Similarly, in this study, abdominal pain and distension were the most common symptoms during abdominal attacks. Diagnosing HAE is usually difficult if there are no skin symptoms; approximately 49% of the patients present with only abdominal pain(13). Abdominal symptoms may precede the skin manifestation for several years; such patients are more likely to be referred to another physician(14). Similar to this study, in a previous study, approximately 70% of patients with HAE had abdominal symptoms, and the mean delay between the onset of symptoms and

diagnosis was 14 years (12). An overlooked cause of abdominal pain is HAE (15). IBS is one of the diseases in which the HAE-related abdominal symptoms are associated with an alternative diagnosis, such as acute abdominal pain, appendicitis, pancreatitis, biliary colic, cholecystitis, nephrolithiasis, choledocholithiasis, and pyelonephritis (14). Functional gastrointestinal disorders represent a group of chronic unexplained bowel syndromes, and IBS is the most well-known (16). IBS is characterized by abdominal pain and changing bowel habits, with a prevalence of 7–10% in the general population (17). In another study, the prevalence of IBS was 11% (7). In this study, IBS was diagnosed in 30% of the patients with HAE, which is higher than that in the general population. In a study that included patients with familial Mediterranean fever (FMF), 18% had IBS, of which 86.3% had IBS before being diagnosed with FMF (18). Similarly, in this study, most patients had IBS before being diagnosed with HAE. Abdominal pain can be seen in both IBS and HAE; therefore, the delay in diagnosing HAE can be attributed to the diagnosis of IBS. In this study, the delay in diagnosing HAE was also longer in patients with IBS than in those without IBS. Visceral hypersensitivity, abnormal gastrointestinal motility, and psychological disturbances are involved in the pathogenesis of IBS. However, recently, low-grade intestinal inflammation, increased intestinal permeability, and immune activation have also been identified as underlying mechanisms causing IBS (16). Bradykinin is the primary mediator responsible for vascular endothelial inflammation in HAE. Bradykinin receptor-1 (BR-1) is absent in the vascular endothelium under normal physiological conditions. BR-1 is expressed in the vascular endothelium in response to inflammatory stimuli, such as interleukin (IL)-1β and TNF-α, via activation of nuclear factor kappa B (NF-κB) (19). IBS hurts the quality of life and work productivity. It is associated with increased psychological distress, and mental comorbidities such as major depression, and generalized anxiety disorder (20, 21). In this study, frequent attacks and persistent gastrointestinal symptoms other than abdominal attacks were more common in patients with HAE and IBS than in those without IBS. Thus, vascular inflammation and psychogenic factors in IBS may affect the quality of life and work productivity. Patients with IBS have a high rate of exposure to unnecessary surgeries due to abdominal symptoms. In one study, two-thirds of the patients with IBS had seen a doctor within the past 12 months, and 40% of them used medication to relieve their symptoms (22). Similarly, in our study, a gastrointestinal tract-related medical/surgical history was seen more commonly in patients with HAE and IBS. Although abdominal pain is one of the most common symptoms of IBS, bloating, a feeling of incomplete emptying, diarrhea, straining, and constipation may also occur (23). In our study, abdominal pain, and distension were the most common symptoms of IBS.

This study had several limitations. First, it was conducted at a single center and was retrospective. Because HAE is a rare disease, the number of patients included in the study was small. Despite these limitations, the study can guide further larger-scale multicenter studies.

Conclusion

Our study determined the characteristics of IBS seen in HAE. IBS is a diagnosis of exclusion and should be considered after all other causes have been excluded. Clinicians should keep HAE in mind in patients with suspected IBS or those who present with recurrent unexplained abdominal pain. An early diagnosis can lead to prompt treatment and relief of symptoms. Our findings highlight the importance of the association between HAE and IBS for future prospective studies.

Conflict of Interest Statement

It should be stated that there is no conflict of interest: The authors have no conflicts of interest to declare.

Ethical Approval

The study was approved by Necmettin Erbakan University Noninterventional Clinical Research Ethical Committee (Decision no: 2023/4368, Date: 02.06.2023). This article does not contain any studies with human or animal subjects.

Consent to Participate and Publish

The authors declared that getting consent from the patients was unnecessary because the study was a retrospective data analysis.

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Availability of Data and Materials

Authors can confirm that all relevant data are included in the article and/or its supplementary information files.

Authors Contributions

MK: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

FÇ, ŞA: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing-review & editing.

FSA: Investigation; Validation; Writing-original draft.

RE, MEG: Formal analysis; Investigation; Visualization; Writing-original draft.

EY, TÖ: Funding acquisition; Resources; Supervision; Writing-review & editing.

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ORIGINAL RESEARCH

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Evaluation of Patients Diagnosed with Spondylodiscitis

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Abstract

Objective

Spondylodiscitis is an infectious disease that affects the vertebral body, intervertebral disc, and/or adjacent paraspinal tissue, and it is a significant cause of morbidity, especially in older individuals. This study aims to evaluate cases of spondylodiscitis followed at Suleyman Demirel University Hospital.

Material and Method

Between January 2017 and December 2021, the medical records and electronic files of patients who began antimicrobial treatment with a diagnosis of spondylodiscitis at Suleyman Demirel University Hospital were retrospectively evaluated.

Results

A total of 33 patients were included in the study, consisting of 17 females and 16 males. The average age of the patients was 56.0 ± 13.6 years. Twenty patients (60.6%) were hospitalized, while 13 patients (39.4%) were followed as outpatients. Spinal surgery due to discopathy was performed in 9 cases (27.3%), and 4 of these patients had a history of recurrent surgical interventions. The most commonly affected region was the lumbar vertebrae (44.1%). The lumbosacral region (20.6%) and thoracolumbar region (14.7%) followed as the second and third most affected areas, respectively. Brucellosis complications were present in 14 cases (42.4%) of spondylodiscitis. Pyogenic microorganisms and tuberculosis were responsible for the remaining 11 (33,3%), and 2 (6%) patients respectively. In 11 patients (33.3.%), the causative microorganism was identified in tissue/abscess/blood cultures as methicillin-sensitive *Staphylococcus aureus* (3), methicillin-resistant coagulase-negative Staphylococcus (1), methicillin-resistant S. aureus (1), methicillin-sensitive coagulase-negative *Staphylococcus* (1), *Klebsiella pneumonia* (2), *Enterococcus faecalis* (2), *Acinetobacter spp.* (1), *Escherichia coli* (1). Staphylococcus aureus (12%) was the most common pathogen among pyogenic microorganisms. In one case, the identified pathogen was *Mycobacterium tuberculosis*. One of the patients was considered to have tuberculosis spondylodiscitis based on histopathological evaluation.

Conclusion

The fact that nearly half of spondylodiscitis cases observed in our hospital were complicated by brucellosis indicates the importance of evaluating patients presenting with back pain for brucellosis. Collaborative training programs with surgical specialities should be periodically repeated to prevent cases of spondylodiscitis that develop after spinal surgeries.

Keywords: Spondylodiscitis, brucellosis, *Staphylococcus aureus, Mycobacterium tuberculosis*

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Introduction

Spondylodiscitis is a serious and potentially debilitating infection affecting the vertebral body, intervertebral disc, and/or adjacent paraspinal tissue. This condition typically arises from the spread of infectious agents through the bloodstream or by direct extension from nearby infected tissues. The clinical presentation of spondylodiscitis can vary widely but commonly includes back pain that is often localized and may worsen with movement. Patients may also experience fever, chills, night sweats, and neurological symptoms such as radiculopathy or weakness if the infection extends to involve the spinal cord or nerve roots (1).

Spondylodiscitis is more commonly observed in individuals over the age of fifty and is more prevalent among males. It accounts for 5% of all osteomyelitis cases (2, 3). The aging population, use of intravascular devices, spinal implants, renal replacement therapy, diabetes, infective endocarditis, corticosteroid usage, and increased use of immunosuppressive therapies as well as increased access to health services and diagnostic methods have led to a rise in the number of cases diagnosed over the years (4).

Treatment of spondylodiscitis often requires a multidisciplinary approach involving infectious disease specialists, orthopedic surgeons, and neurosurgeons. Antibiotic therapy is the cornerstone of treatment and is usually administered intravenously for an extended duration, often ranging from 6 weeks to several months depending on the severity of the infection and the identified pathogen. In some cases, surgical intervention may be necessary for drainage of abscesses, debridement of infected tissues, or stabilization of the spine (5, 6).

Clinicians need to understand spondylodiscitis more thoroughly, and early detection and thorough assessment are crucial for improving patient outcomes and reducing complications. This study evaluated patients diagnosed with spondylodiscitis who were monitored and treated at our hospital's Department of Infectious Diseases and Clinical Microbiology.

Material and Method

The printed and electronic medical records of patients who began antimicrobial therapy due to a diagnosis of spondylodiscitis between January 2017 and December 2021 at Suleyman Demirel University were evaluated with the retrospective cross-sectional method.

Inclusion criteria:

1. Spondylodiscitis cases due to brucellosis, tuberculosis and pyogenic microorganisms

2. Cases with clinical and imaging findings of spondylodiscitis but no microbiological agent could be demonstrated and had clinical and laboratory improvement with antimicrobial therapy

3. Cases who had spondylodiscitis due to spinal surgery

Exclusion criteria

1. Cases under 18 years old

2. Cases with clinical and imaging findings of spondylodiscitis but no microbiological agent could be demonstrated and no response to antimicrobial therapy

Demographic characteristics, comorbid diseases, symptoms, duration of symptoms, history of hospitalization, history and dates of spinal surgery, microbiological examination results, imaging findings, and administered treatments were recorded. The diagnosis of vertebral osteomyelitis was established based on the presence of vertebral osteomyelitis findings on computed tomography or magnetic resonance imaging in patients with acute or chronic back pain, the detection of microbial growth in blood or tissue samples, or the histological presence of acute or chronic inflammation in vertebral tissue, or serological support for brucellosis diagnosis (7, 8).

“Blood cultures were processed with an automated microbial detection system (BacT/ALERT 3D, bioMérieux, France). Identification and antibiotic susceptibility tests of microorganisms were performed using an automated testing system (BD Phoenix, Becton Dickinson, USA). The Brucellacapt test (Vircell, Granada, Spain) was used to detect specific antibodies against Brucella infection. For the isolation and antimicrobial susceptibility test of Mycobacterium tuberculosis, M960 system (Becton Dickinson Microbiology System, Sparks, NV, USA)”.

For the diagnosis of implant-associated vertebral infection, one of the following criteria was utilized (7):

a) Clinical evidence of delayed wound healing, sinus tract formation, fistula formation, or purulent discharge at the implant site, with at least one positive finding of the 'probe to implant test.'
b) Histological evidence of inflammation at the implant site.

c) Microbiological evidence of significant growth (≥50 CFU/mL in two or more tissue samples or sonication fluid).

The diagnostic criteria for brucellosis, indicating that microbial growth in blood or tissue culture, or titers of 1/160 and above in the brucella capture test, are considered significant. Cases with lower titers are diagnosed through titer monitoring, considering clinical and epidemiological factors such as the history of consuming unpasteurized dairy products or engaging in animal husbandry (9-11).

Clinical response was categorized into three groups (12):

Complete response: Complete resolution of pain symptoms and normalization of acute phase parameters.

Partial response: Reduction of pain symptoms and decrease in acute phase parameters compared to baseline.

Non-response: Persistence of pain symptoms without improvement in acute phase parameters.

Statistical Analysis

Statistical analysis was performed by IBM SPSS Statistics 21.0. Statistical analysis included frequency and percentage for categorical variables, mean and standard deviation for continuous variables if distribution was appropriate, and median (minimum-maximum) values if distribution was not appropriate.

Results

A total of 33 patients were included in the study, comprising 17 females and 16 males. The mean age of the patients was 56.0 ± 13.6 years. Twenty patients (60.6%) were hospitalized, while 13 patients (39.4%) were followed up on an outpatient basis. The median duration of hospitalization for inpatients was 15 days (min 3, max 110), with a mean of 37.5 ± 27.6 days. Thirteen patients (39.4%) were referred to the neurosurgery department, 10 (30.3%) to the infectious diseases and clinical microbiology department, 5 (15.5%) to the physical therapy and rehabilitation department, and 5 (15.5%) to the rheumatology outpatient clinic. Eighteen patients (54.5%) had one or more comorbid diseases. Patients did not have a history of endocarditis or intravenous drug use; one patient was undergoing

Table 1 Complaints and comorbid diseases of patients followed with the diagnosis of spondylodiscitis at presentation.

Complaints	**n**	**%**
Back pain	26	57.8
Walking difficulty	8	17.8
Lower back pain	6	13.3
Fever	3	6.7
Neck pain	1	2.2
Pain in the hip and legs	1	2.2
Comorbidity		
Diabetes mellitus	8	24.2
Rheumatoid arthritis	6	18.2
Coronary artery disease	2	6.1
Chronic kidney failure	1	3.0
Heart failure	1	3.0
Duration of Complaint		
< 1 month	9	27.2
1-12 months	12	36.4
>12 months	12	36.4

hemodialysis treatment. Fifteen patients (55.4%) had a diagnosis of disc herniation. Spinal surgery due to trauma or discopathy before diagnosis was performed in 9 cases (27.3%), with 4 of these patients having a history of repeated surgical interventions. One patient had an implant-associated vertebral infection. The median duration of symptoms for patients was 70 days (min 3, max 7000), with the most common complaint on presentation being lower back pain, observed in 48.5% of cases. The presenting complaints of patients are shown in Table 1. At the time of diagnosis, the mean sedimentation rate was found to be 55.2 ± 33.2 mm/h (with a median value of 49, min: 3, max: 120), and the mean CRP level was 82.0 ± 76.3 mg/L (with a median value of 61, min: 3, max: 120). The most frequently affected region was the lumbar vertebrae, in 15 cases (44.1%). The lumbosacral (7; 20.6%) and thoracolumbar (5; 14.7%) regions ranked second and third, respectively. Brucellosis complications accounted for 14 cases (42.4%) of spondylodiscitis. Pyogenic microorganisms and tuberculosis were responsible for the remaining 11 (33,3%) and 2 (6%) patients respectively. No microbiological or serological evidence of the causative microorganism was obtained in seven patients. Tissue or abscess culture was performed in 16 out of 33 patients (48.5%) (Table 2). Among these, 11 patients (39.4%) had a total of 12 pyogenic microorganisms isolated, causing the infection. In 14 patients diagnosed with brucellosis-related spondylodiscitis, tissue/abscess culture was performed in 3 cases, with no growth detected in blood or tissue cultures. *Staphylococcus aureus* (12%) was the most common pathogen among pyogenic microorganisms. *Mycobacterium tuberculosis* was isolated as the causative agent in one case. In another case, a preliminary diagnosis of tuberculosis-related spondylodiscitis was made based on cytological examination of tissue samples, and a partial response to anti-tuberculosis treatment was observed. The clinical response to treatment based on the causative agent, surgical history, and duration of symptoms is shown in Table 3.

Discussion

In patients experiencing newly developed or aggravated back or neck pain accompanied by fever, undergoing hemodialysis, with recent bacteremia, endocarditis, intravenous drug use, elevated sedimentation rate and/or CRP levels, or presenting with new neurological deficits, suspicion of spondylodiscitis should arise (5). The incidence of spondylodiscitis increases with age, and it was reported to occur approximately twice as often in males (13). In this study, the mean age of spondylodiscitis cases was 56.0 ± 13.6 years, with a nearly equal distribution between females and

Table 2 Microorganisms Isolated in Patients Diagnosed with Spondylodiscitis

Causative Agents	Blood n	Tissue n	Blood and tissue n
Staphylococcus aureus	1	3	0
MSSA	1	2	0
MRSA	0	1	0
Coagulase-Negative Staphylococcus	1	1	0
MRCoNS	0	1	0
MSCoNS	1	0	0
Klebsiella pneumonia (ESBL +)	0	0	2
Enterococcus faecalis*	1	1	0
Acinetobacter spp.*	0	1	0
Escherichia coli (ESBL-)	0	0	1
Mycobacterium tuberculosis	0	1	0
TOTAL	3	7	3

*In one case, two causative agents were isolated. MSSA: Methicillin-Sensitive *Staphylococcus aureus*
MRCoNS: Methicillin-Resistant Coagulase-Negative *Staphylococcus* MRSA: Methicillin-Resistant S. aureus
MSCoNS: Methicillin-Sensitive Coagulase-Negative *Staphylococcus* ESBL: Extended-spectrum beta-lactamases

Table 3 Clinical Response to Treatment in Patients Diagnosed with Spondylodiscitis

	Full response (n)	Partial response (n)	No response (n)	Lost to follow-up (n)
Brucellosis (n=14)	5	6	1	2
Tuberculosis (n=2)	-	2*	0	0
Cases infected with pyogenic microorganisms (n=11)	5	4	0	2
Before diagnosis				
Disc herniation (n=13)	2	7	3	1
Vertebral surgery (n=9)	3	4	0	2
Invasive intervention/surgery for treatment				
Present (n=11)	4	6	-	1
Absent (n=22)	7	8	4	3
Duration of Symptoms				
<1 month (n=9)	5	3	0	1
1-12 months (n=12)	4	5	3	0
>12 months (n=12)	2	6	1	3

*One of these patients was considered to have tuberculosis spondylodiscitis based on histopathological evaluation. *Mycobacterium tuberculosis* was isolated as the causative agent in another case.

males. This could be attributed to approximately one-third of cases being associated with spinal surgery performed due to discopathy, and 42.4% being related to brucellosis. Prolonged stays in patients requiring hospitalization pose a significant burden for both patients and the healthcare system in the long term (14). The average duration of hospitalization among the cases included in our study was 37.5 ± 27.6 days. Among our cases, 69.7% had sought care at a clinic other than the infectious diseases department, with the neurosurgery clinic being the most common. This could be attributed to previous spinal surgeries or the common occurrence of discopathy.

In patients diagnosed with spondylodiscitis, the most common clinical symptom was localized pain in the infected disc area, which worsens with physical activity (5). The pain can persist and intensify over weeks or even months. In a study evaluating patients with spontaneous pyogenic vertebral osteomyelitis, the average duration of symptoms was found to be 48 ± 40 days (15). In our study, complaint duration was more than one month in 67.7% of cases. The higher incidence of involvement of the lumbar vertebrae explains the most common complaints being low back pain and/or walking difficulty. In a study conducted at a tertiary hospital in our country, Hatipoğlu et al. reported the most common complaints at presentation as low back pain (100%) and walking difficulty (40.9%) (16). Similarly, in our study, lower back pain was reported in 78.7% of cases, and walking difficulty in 24.2% of cases. In studies by Hamidi et al. and Kaya et al., low back pain was reported as the most frequent symptom in 90.2% and 90.1% of cases, respectively (17,18). Fever is not a common complaint in spondylodiscitis cases; in our series, only three cases reported high fever (Table 1).

In studies conducted in our country, the most affected site among patients with spondylodiscitis was reported to be the lumbar vertebrae, ranging from 60% to 86.3% (16-20). Farzan et al. noted in their recent spondylodiscitis studies that the lumbar region was the most commonly affected area (21). In our study, the most frequently affected region was the lumbar vertebrae, accounting for 44.1% (n: 15 cases) of cases. Spondylodiscitis, which can be seen as a musculoskeletal complication of brucellosis, usually involves the lumbar vertebrae. The predominance of disc herniation in this anatomical region in the

remaining cases in our study likely contributed to the diagnosis of discopathy and subsequent spinal surgery, which played a role in identifying involvement in this anatomical area.

In most patients, the infection is monomicrobial, with *Staphylococcus aureus* being the most common pathogen in over 50% of cases in developed countries according to the literature (4). In a study conducted in France, staphylococci were identified as the causative agent in 53% of spondylodiscitis cases (22). Other responsible microorganisms are streptococci, enterococci, coagulase-negative staphylococci, *Pseudomonas aeruginosa*, *Candida* spp., *Mycobacterium tuberculosis*, and *Brucella* spp. (1,4, 23). Gentile et al. analyzed 1756 patients and reported *Staphylococcus* spp., *M. tuberculosis*, and other bacteria as the causative agents in 40.3%, 30.9%, and 28.3% of cases, respectively (24). Among 212 patients with chronic kidney failure and spondylodiscitis, the most common organism found was *S. aureus* (18). Various studies conducted in our country have reported *Brucella* spp. as the causative agent for spondylodiscitis in proportions ranging from 19% to 42.6% (Table 4), (16-20). In our study, *Brucella* spp. was the most common agent, accounting for 42.2% of cases, followed by *S. aureus* at 12%. According to our findings, the incidence of brucellosis-related spondylodiscitis in our country is at the upper limit of the rates reported in studies. In regions where brucellosis is endemic, it is the most common cause of spondylodiscitis, accounting for approximately 50% of cases (25, 26). The province where our study was conducted is known as a highly endemic region for brucellosis, with an incidence of 24.2 per 100,000 individuals (27). The gold standard for diagnosis is the isolation of bacteria from sterile tissues and/or fluids. However, due to the slow growth and low isolation rate of Brucella spp., exposure history and serological methods are also used for diagnosis. Inoculation of tissue or bone biopsy samples into blood culture systems can significantly increase the isolation rate (28). Since the number of patients from whom bone or tissue samples could be obtained was limited in our study, culture positivity was not demonstrated in cases of brucellosis.

The diagnosis of spondylodiscitis can often be delayed by several months, initially misdiagnosed, and may progress to a degenerative process (5). Delayed diagnosis and consequently delayed treatment can lead to high morbidity. It can result in complications such as epidural or subdural abscess, meningitis, paraspinal abscess, compression of the spinal cord or nerve roots, empyema, or neurological symptoms. In the long term, residual neurological deficits, chronic back pain, and depression may occur (14, 15). In this study, complaint duration was more than one month in approximately three-quarters of cases and lasted longer than one year in more than one-third of cases. The rate for complete resolution of symptoms was higher in cases with a complaint duration of less than one month. However, due to the limited number of cases, statistical analysis could not be performed.

The data in this study should be interpreted in light of its limitations. Our study is completed in a single center and having a low number of cases, as well as the inability to isolate the microorganism in blood/tissue culture in patients diagnosed with brucellosis, limits the generalizability of our findings.

Conclusion

The fact that nearly half of the spondylodiscitis cases followed in our hospital are complications of brucellosis indicates the need for evaluation of brucellosis in patients presenting with back pain. “Pathogens such as *Brucella* spp. and M. tuberculosis are gaining importance again in today's world of increased

Table 4 Causes of Spondylodiscitis in Some Studies Conducted in Our Country

Study (Reference No.)	Pyogenic	Brucellosis	Tuberculosis
Hatipoğlu et al. (16)	12	8	2
Turunç et al. (20)	30	32	13
Mete et al. (19)	44	24	32
Hamidi et al. (17)	37	20	46
Kaya et al. (18)	153	138	52

interregional human mobility, and a multidisciplinary approach is required in consultation with microbiology, radiology and pathology departments in case of suspected spondylodiscitis." As the departments of physical therapy and rehabilitation and neurosurgery are the most likely places where patients with complaints of back pain may seek assistance, awareness should be increased among physicians in these specialities. To prevent cases of spondylodiscitis from developing after spinal surgeries, training programs should be periodically repeated in collaboration with surgical departments.

Conflict of Interest Statement
There are no conflicts of interest.

Ethical Approval
The study was approved by the Ethics Committee of Suleyman Demirel University Faculty of Medicine at a meeting on June 22, 2023, with decision number 10/127. The research was conducted by the Helsinki Declaration.

Consent to Participate and Publish
As the research was conducted retrospectively, there was no requirement for informed consent.

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Availability of Data and Materials
Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Authors Contributions
OÜ: Conceptualization; Formal analysis; Data curation; investigation; Methodology; Writing-original draft

MY: Conceptualization; Data curation; Writing; Investigation

GRY: Conceptualization; Formal analysis; Data curation; investigation; Methodology; Writing-review & editing

FZA : Supervision; Writing-review & editing

OK : Supervision; Writing-review & editing

ENT: Supervision; Writing-review & editing

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ORIGINAL RESEARCH

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Psychiatric Emergencies in Perinatal Women: A Retrospective Analysis

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Abstract

Objective

The perinatal period represents a critical juncture in a woman's life marked by profound emotional, social, and physical changes. During this phase, there is a propensity for the exacerbation of pre-existing psychiatric symptoms or the emergence of new ones. Notably, there is often an uptick in psychiatric emergencies and presentations to emergency psychiat-ric departments among women in the perinatal period. This study aimed to retrospectively evaluate women accessing emergency psychiatric departments during pregnancy and the postpartum period, focusing on their presenting complaints, diagnoses, clinical trajectory, and factors influencing the decision for inpatient treatment.

Material and Method

A retrospective review was conducted on the records of 11,419 women aged 18 to 45 who sought care at the Psychiatric Emergency Department of Bakirkoy Prof. Dr. Mazhar Osman Research and Training Hospital between July 2015 and July 2016.

Results

Among them, the records of 163 women who were either pregnant or within one year postpartum were analyzed. Of the women accessing services during the perinatal period, 46% were pregnant, while 54% were in the postpartum phase. Additionally, 38.7% of these women presented to the psychiatric department for the first time. Distress and anxiety emerged as the most common reasons for seeking help. Interestingly, no significant differences were observed between the pregnancy and postpartum periods regarding presenting complaints and clinical progression. However, the incidence of psychotic disorders was notably higher during the postpartum period compared to pregnancy. Through logistic regression analysis involving pregnancy status, presenting complaints, and diagnoses, it was determined that the nature of the presenting complaint significantly influenced the decision for inpatient treatment. Notably, scepticism, agitation, and suicidal ideation were identified as the most prevalent complaints among women who required inpatient care.

Conclusion

Mental health challenges during the perinatal period not only jeopardize the well-being of the woman but also impact the health of the infant. Detecting and addressing emergent psychiatric issues during this phase are pivotal for timely intervention and preventive measures.

Keywords: Pregnancy, postpartum, perinatal psychiatry, emergency psychiatry

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Introduction

The perinatal period is recognized as a pivotal phase in a woman's life, characterized by notable emotional, social, and physical changes (1). Variability in experiences during this period is observed based on individual social contexts and cultural backgrounds. (2). Mental disorders in the perinatal period are acknowledged by the World Health Organization (WHO) as a significant public health concern, with data indicating that at least one in 10 women encounter severe mental health issues during pregnancy or within a year postpartum (3). Guidance from the American College of Obstetricians and Gynecologists (ACOG) Committee recommends mental disorder screening for women at least once during both pregnancy and the postpartum period (4).

During the perinatal period, there is an elevated risk of psychiatric disorders (5). Depression and anxiety are prevalent mental health concerns during this phase, with perinatal depression ranging from 4% to 19% in prevalence and anxiety disorders affecting over 15% of women (6–8). Studies tracking the course of mood disorders in this period indicate relapses in 23% of women diagnosed with bipolar disorder during pregnancy and 52% postpartum (9).

Although the prevalence of pregnancy in patients with psychotic disorders is lower compared to other conditions, an acute psychotic episode arising during pregnancy is deemed a psychiatric and obstetric emergency (10–12)

Many women perceive negative emotions as a natural aspect of the perinatal process, believing they can manage these symptoms independently (13). Despite the heightened risk of mental disorders compared to the general population, research indicates that even within standard healthcare systems, diagnosis rates and access to treatment remain around 50% (14). It's understood that perinatal mental disorders can negatively impact both maternal and infant health, potentially affecting the long-term emotional, cognitive, and social development of the child (15,16).

Moreover, only 10-15% of women diagnosed with a mental disorder or seeking treatment receive adequate care (13,16). For women in the perinatal period not undergoing regular monitoring and treatment, there may be an increased likelihood of experiencing emergency psychiatric conditions and visits to the emergency department.

Psychiatric emergencies, as per the definition by the American Psychiatric Association, encompass disturbances in thought, behaviour, mood, and social interactions necessitating immediate intervention by the patient, family, or community (17). Assessing and managing psychiatric emergencies during pregnancy necessitates collaborative efforts among emergency physicians, psychiatrists, and obstetricians. Establishing a comprehensive support system during this phase involves evaluating the health status of both the woman and the baby (18). Accurately identifying and treating life-threatening mental disorders in the perinatal period is crucial for mitigating maternal mortality rates and addressing this significant public health concern (19,20).

Our study aimed to retrospectively describe the complaints, diagnoses and clinical course of pregnant and postpartum women admitted to the emergency psychiatry service, while also exploring the factors influencing decisions for inpatient treatment during the perinatal period. In this period of many changes and role transitions in women's lives, it is important that psychiatric complaints can be intervened quickly and effectively. Our study aims to contribute to clinicians by identifying the important points in the management of psychiatric disorders in the perinatal period by defining the emergencies in women who need psychiatric support in the perinatal period and the situations requiring inpatient treatment.

Material and Method

This study was conducted following approval from the Ethics Committee of Bakirkoy Prof. Dr. Mazhar Osman Research and Training Hospital Hospital, with a decision dated 07.02.2017 and numbered 627. The study period was determined as between March 2017 and June 2017.

The hospital files of women admitted to the Psychiatry Emergency Department of a Hospital, the largest psychiatric hospital in Turkey, between July 2015 and July 2016 were included in the study. During this period, 11,419 women between the ages of 18 and 45 years were admitted to the emergency psychiatry service of our hospital.

A retrospective analysis of the medical records of 11,419 women revealed that 163 women were admitted to the psychiatric emergency department during pregnancy or within a year of giving birth.

The socio-demographic characteristics, admission complaints, previous psychiatric disorders and treatment histories, psychiatric evaluations, diagnoses

and treatment methods performed at the time of admission were extracted and recorded from the patient's files. In cases where patients reported more than one complaint, the first and most important complaint was prioritized for analysis.

Statistical Analysis

Socio-demographic characteristics, presenting complaints, psychiatric evaluations, diagnoses, and treatment modalities were extracted and recorded from the patients' files. In cases where patients reported multiple complaints, the first and most significant complaint was prioritized for analysis.

Data analysis was conducted using SAS Studio 3.71 software. Descriptive statistics, including mean and standard deviation for continuous variables, and frequency (n) and percentages (%) for categorical variables, were calculated. The Shapiro-Wilk test was employed to assess compliance with normal distribution. Group comparisons were conducted using the Mann-Whitney U-Test for two groups. The distribution of categorical variables between groups was assessed using the Chi-Square test or Fisher's Exact Test. Post hoc evaluation was performed using the Bonferroni test if a significant difference was detected. Binary logistic regression analysis was employed to identify factors predicting the decision for hospitalization. Results were deemed statistically significant if the p-value was less than 0.05.

Results

Between July 2015 and 2016, Bakirkoy Prof. Dr. Mazhar Osman Research and Training Hospital Hospital Psychiatry Emergency Department admitted a total of 11,419 women, of whom 163 were in the perinatal period. Among these perinatal cases, 46% were preg-

Table 1 Socio-Demographic Characteristics of Women in Perinatal Period Admitted to the Psychiatric Emergency Department

	Pregnancy period		Postpartum Period		
	n/Mean	%/SD	n/Mean	%/SD	p
Age	29.79	5.50	29.91	4.83	0.889
Week	17.73	9.77	14.83	12.49	0.069
Smoking					
No	40	53.3%	55	62.5%	0.386
Yes	7	9.3%	9	10.2%	
Unknown	28	37.3%	24	27.3%	
Usage of PAS & Alcohol					
No	42	56%	60	68.2%	0.272
Yes	4	5.3%	3	3.4%	
Unknown	25	28.4%	29	53.7%	
History of Suicidal Attempt					
No	27	36%	33	37.5%	0.972
Yes	11	14.7	12	13.6%	
Unknown	37	49.3%	43	48.9%	
History of Psychiatric Hospitalization					
No	57	76%	61	69.3%	0.368
Yes	13	17.3%	23	26.1%	
Unknown	5	6.7%	4	4.5%	

PAS: Psychoactive substance

nant, and 54% were in the postpartum phase. Notably, eight women had multiple admissions during this period. The mean age of these admitted women was 28.85±5.13 years. Additionally, 38.7% of the women sought care at the psychiatry department for the first time. Socio-demographic characteristics of women in the perinatal period admitted to the psychiatric emergency department are shown in Table 1.

Regarding complaints of women admitted to the psychiatric emergency department during pregnancy and the postpartum period, distress and anxiety emerged as the most prevalent reasons for admission (26.7% and 26.14% respectively). No significant difference was observed between the pregnancy and postpartum periods concerning admission complaints ($p>0.05$). However, a statistically significant difference was noted between the two groups regarding admission diagnoses ($p<0.05$). Further post-hoc analyses revealed a significantly higher prevalence of psychotic disorder diagnoses during the postpartum period, as depicted in Table 2.

Upon analyzing the clinical characteristics of women deemed appropriate for hospitalization, it was observed that both the diagnosed condition and the

Table 2 Clinical Characteristics of Women in Perinatal Period Admitted to the Psychiatric Emergency Department

	Pregnancy period		Postpartum Period		p
	n/Mean	%/SD	n/Mean	%/SD	
Admission Complaints					
Distress & Anxiety	26.67% (20)		26.14%(23)		0.543
Nervousness & Agitation	14.67% (11)		12.50% (11)		
Insomnia	18.7% (14)		7,95% (7)		
Suicidal Thought/Attempt	10.67% (8)		9.09% (8)		
Unhappiness & Crying	5.3% (4)		13.64% (12)		
Somatic complaints	6,7%(5)		9.1%(8)		
Suspiciousness	5.3%(3)		9.1%(8)		
Manic/hypomanic symptoms	4%(3)		2.3%(2)		
Other	8%(6)		10.2%(9)		
Diagnosis					
No Diagnosis	32% (24)		19.3%(17)		0.022*
Bipolar Disorder	22.67% (17)		12.50% (11)		
Depressive Disorder	12% (9)		21,6% (19)		
Anxiety Disorder	10.67% (8)		9.1% (8)		
Psychotic Disorder	4% (3)		18.2% (16)		
Adjunct Disorder	6,7%(5)		4.5%(4)		
Other	12%(9)		14.8%(13)		
Clinical Outcomes					
Outpatient control was recommended by giving psychoeducation	55.7% (39)		41.2%(35)		0.155
A prescription was given, control visit was recommended	25.7% (18)		29.4% (25)		
Hospitalized	18.6% (13)		29.4% (25)		

presenting complaint significantly differed ($p<0.05$), as illustrated in Table 3.

Binary logistic regression analysis was conducted to assess factors predicting the decision for hospitalization. Pregnancy status, admission complaint, and admission diagnosis were included as variables in the model. The analysis revealed that the admission complaint significantly predicted the decision for hospitalization, as depicted in Table 4. The distribution of admission complaints by hospitalization decision is shown in Figure 1.

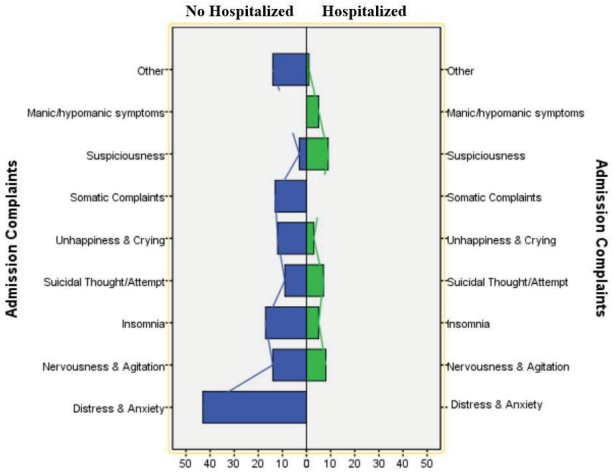

Figure 1:
Admission Complaints by Hospitalization Decision

Table 3 Clinical Characteristics of Women Hospitalized in The Perinatal Period

	No Hospitalized		Hospitalized		p
	n/Mean	%/SD	n/Mean	%/SD	
Age	29.86	5.163	29.84	5.097	0.882
Pregnancy Status					
Pregnancy	62	49.6%	13	34.2%	0.069
Postpartum	63	50.4%	25	65.8%	
Admission complaints					
Distress & Anxiety	43	34.4%	0	0%	
Nervousness & Agitation	14	11.2%	8	21.1%	
Insomnia	17	13.6%	5	13.2%	
Suicidal Thought/Attempt	9	7.2%	7	18.4%	
Unhappiness & Crying	12	9.6%	3	7.9%	<0.001*
Somatic complaints	13	10.4%	0	0%	
Suspiciousness	3	2.4%	9	23.7%	
Manic/hypomanic symptoms	0	0%	5	13.2%	
Other	14	11.2%	1	2.6%	
Diagnosis					
No Diagnosis	41	32.8%	0	0%	
Bipolar Disorder	12	9.6%	16	42.1%	
Depressive Disorder	20	16%	8	21.1%	
Anxiety Disorder	16	12.8%	0	0%	<0.001*
Psychotic Disorder	6	4.8%	13	34.2%	
Adjunct Disorder	9	7.2%	0	0%	
Other	21	16.8%	1	2.6%	

Table 4 Logistic regression Analysis of Hospitalization Decision

		B	S.E.	Wald	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Step 1[a]	Admission complaints	.184	.071	6.739	.009	1.201	1.046	1.380
	Diagnosis	.000	.094	.000	1.000	1.000	.832	1.202
	Pregnancy status	-.581	.398	2.128	.145	.559	.256	1.221
	Constant	-1.718	.544	9.981	.002	.179		
Step 2[a]	Admission complaints	.184	.070	6.787	.009	1.201	1.047	1.379
	Pregnancy status	-.581	.394	2.169	.141	.559	.258	1.212
	Constant	-1.718	.403	18.137	.000	.179		
Step 3[a]	Admission complaints	.190	.070	7.360	.007	1.209	1.054	1.386
	Constant	-1.987	.368	29.095	.000	.137		

Variable(s) entered on step 1: Admission complaints Diagnosis, Pregnancy status.
Nagelkerke R2 Step 1 =.087 Step 2= .087 Step 3 =.068

Discussion

In our study, the objective was to examine the sociodemographic characteristics, complaints, diagnoses, and clinical course of women in the perinatal period who sought assistance from the psychiatric emergency department, as well as to analyze the clinical characteristics of women who were recommended for inpatient treatment. It was observed that anxiety and distress were the prevailing reasons for seeking care at the emergency psychiatric department during both pregnancy and the postpartum period.

Upon reviewing admission diagnoses during pregnancy and the postpartum period, a significantly higher incidence of psychotic disorder diagnosis was noted in the postpartum phase compared to the pregnancy period. Additionally, it was established that the complaints voiced by women presenting to the psychiatric emergency department were predictive of their inclination towards inpatient treatment. Notably, scepticism, agitation, and suicidal thoughts emerged as the most common complaints among those recommended for inpatient care. Regarding reasons for presenting to the psychiatric emergency department, it was evident that distress and anxiety were the leading causes during both pregnancy and the postpartum period. Furthermore, insomnia was prevalent, accounting for 18.7% of cases during pregnancy, while reports of unhappiness were documented in 13.64% of cases during the postpartum period.

Distress is defined as a notably adverse emotional state characterized by persistent arousal and impaired functioning (21,22). Within the perinatal context, distress is also delineated as the emotional response of women to the transitional process into motherhood, encompassing changes in their bodies, societal roles, and social circumstances (23). Given the relevant literature, anxiety, depression, and stress appear as the most common mental distress conditions in studies on perinatal mental health (24,25). In our study, anxiety & distress emerged as the predominant complaint leading to emergency psychiatric admission during both pregnancy and the postpartum period, aligning with findings from existing literature.

The second most common complaint during pregnancy was identified as insomnia, accounting for 18.7% of cases. It is well-documented that insomnia is more prevalent during pregnancy compared to the general population. In a meta-analysis conducted by Sedov and colleagues, they reported a prevalence of 38.2% for insomnia during pregnancy (26). Biological changes such as increased body temperature, nasal congestion, and frequent urination during pregnancy are cited as factors that may disrupt sleep patterns (27). Given that anxiety symptoms during pregnancy can contribute to sleep disturbances, it is advisable to screen women experiencing insomnia for signs of stress and anxiety (28).

In our study, upon examining the diagnoses of admission to the emergency department, it was

noted that a certain number of women who sought care during both periods did not receive a specific diagnosis. Additionally, when comparing admission diagnoses between pregnancy and the postpartum period, a significantly higher prevalence of psychotic disorder diagnosis was observed in the postpartum phase. This finding aligns with existing literature, which indicates that the rate of antepartum psychosis is lower than the rate of postpartum psychosis (29). The increased risk of admission diagnoses of psychotic disorder in the postpartum period compared to pregnancy in our study may be attributed to several factors. Firstly, the protective effect of high estrogen levels during pregnancy is known to mitigate the risk of psychotic symptoms. However, the rapid decline in estrogen levels postpartum removes this protective effect, potentially increasing vulnerability to psychotic episodes. Additionally, the combination of factors such as insomnia, which is common during the postpartum period, and the profound psychological impact of transitioning to motherhood may exacerbate existing vulnerabilities or precipitate psychotic symptoms in susceptible individuals. Moreover, the availability of high levels of medical care and social support during pregnancy may serve as protective factors, whereas the sudden reduction in support systems postpartum may contribute to increased stress and exacerbation of underlying psychiatric conditions. Taken together, these factors likely contribute to the higher prevalence of psychotic disorder diagnoses in the postpartum period observed in our study compared to the pregnancy period (30).

When assessing the factors influencing the decision to undergo inpatient treatment during the perinatal period, our analysis reveals that admission complaints serve as a significant predictor. Specifically, when examining the frequency of complaints among women who were recommended for hospitalization, scepticism, agitation, and suicidal thoughts emerge as the predominant factors, respectively. Complaints of scepticism and agitation frequently co-occur with severe mental illnesses (31,32). Conditions like postpartum psychosis and mood disorders often manifest with symptoms such as irritable mood, severe behavioural disturbances, and disordered thinking. Delusional beliefs regarding the baby can elevate the risk of infanticide and physical aggression towards the infant. Furthermore, in depressive disorders, where the risk of suicide is heightened, the presence of psychotic symptoms or feelings of hopelessness may pose a risk of harm to the baby as well (33). With the enhancement of obstetric care protocols globally, there have been notable reductions in maternal mortality rates attributed to general medical conditions. Nevertheless, maternal mental health emerges as a significant factor in maternal and infant mortality (34). It is crucial to consider the option of inpatient treatment for high-risk complaints closely linked to the health of both the mother and the baby, such as scepticism, agitation, and suicidal thoughts/attempts.

The analysis in terms of smoking, alcohol, and psychoactive substance (PAS) use revealed that 9.33% of pregnant women smoked, while 5.33% used PAS. The most commonly used PAS was identified as synthetic cannabinoids, accounting for 60% of cases. Comparatively, in the study by Gressier et al., the prevalence of smoking during pregnancy was reported as 37.5% (35). Additionally, the prevalence of PAS use during pregnancy was found to range between 10% and 15%, with cannabis being the most commonly used PAS (36). In our study, the rates of smoking and PAS use during pregnancy were lower than those reported in the literature. However, it is estimated that 44% of pregnant women who use PAS do not seek healthcare services. Therefore, the rates of smoking and PAS use during pregnancy may be higher than those detected in our study (37). It is speculated that the low rates of smoking and PAS use observed in our study may be attributed to limited healthcare service utilization or may be related to the retrospective nature of the study and potential data loss.

Our study aimed to explore the factors influencing the decision for inpatient treatment in the perinatal period and to compare clinical features between pregnancy and the postpartum period. Specifically, we sought to identify differences in clinical course and diagnosis related to psychiatric symptoms in women during these periods, to develop more effective approaches for managing and treating psychiatric complaints in this critical timeframe. By diagnosing urgent mental health concerns and situations requiring inpatient treatment early on, it becomes feasible to implement timely preventive measures using protective approaches, thus safeguarding the mental health of both the mother and the baby.

Despite its contributions, our study has several limitations, including its retrospective nature, lack of follow-up, and potential data loss. Our study is valuable in that it examines women presenting to psychiatric emergency services during pregnancy and the postpartum period, an important group that few studies have focused on. This study provides valuable information for the identification, management and prevention of situations that lead to acute psychiatric crises requiring emergency intervention. Strengths of the study include the identification of differences

between pregnancy and the postpartum period, and the identification of complaints and psychiatric disorders that may require inpatient treatment and consisting of data from the largest psychiatric hospital in our country.

Future longitudinal studies could examine in more detail how psychiatric symptoms and disorders in women in the perinatal period change over time. In addition, comparisons of perinatal psychiatric conditions in different societies may help to understand the role of cultural factors and to develop culture-specific intervention strategies. Such research can help to develop more effective health policies and clinical practices for the health of women and infants in the perinatal period.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
This study was conducted following approval from the Ethics Committee of Bakirkoy Prof. Dr. Mazhar Osman Research and Training Hospital, with a decision dated 07.02.2017 and numbered 627. This study was conducted by the principles of the "Helsinki Declaration".

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Availability of Data and Materials
Data is available on request from the authors.

Authors Contributions
KŞM: Conceptualization; Project administration; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Resources; Writing-original draft, Writing-review & editing

AİÜ: Data curation; Formal analysis; Investigation; Resources; Visualization; Writing-review & editing

PÇA: Conceptualization; Project administration; Investigation; Methodology; Writing-review & editing.

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ORIGINAL RESEARCH

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Exploring Internalized Stigma, Self-Esteem, and Symptom Severity in Depression: A Comparative Study of Active and Remitted Phases

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Abstract

Objective

Internalized stigma, which refers to the internalization of negative attitudes and beliefs towards persons with mental illness, significantly impacts their self-perception and overall well-being. This research examines the correlations among internalized stigma, the severity of symptoms, and self-esteem in individuals diagnosed with major depressive disorder (MDD), specifically comparing those currently experiencing active depression with those who are in remission.

Material and Method

Participants were selected from a psychiatric outpatient unit based on their diagnosis of MDD. Participants provided sociodemographic information and completed assessments measuring the severity of depression, level of anxiety, self-esteem, and internalized stigma.

Results

Participants experiencing active depression exhibited elevated levels of depression severity, anxiety severity, and internalized stigma, while also reporting diminished self-esteem in comparison to those who were in a state of remission. Strong positive relationships were observed between the severity of depression and internalized stigma where self-esteem was negatively correlated with the stigma. The results of the regression analysis showed that there was a significant relationship between the severity of depression, self-esteem, and internalized stigma in the group of individuals with active MDD.

Conclusion

This study underscores the impact of depression severity and self-esteem on internalized stigma in individuals with MDD. The findings indicate the need to implement comprehensive treatment techniques that address psychological and social variables like self-esteem and internalized stigma in addition to symptom management. Future studies should investigate the long-term connections and assess the efficacy of interventions in reducing the obstacles caused by stigma in the process of recovering from depression.

Keywords: Anxiety, depression, internalized stigma, self-esteem, symptom, remission

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Introduction

Internalized stigma, sometimes referred to as self-stigma, is a kind of stigma that manifests alongside other forms such as personal (1), public stigma (attitudes towards others with mental illnesses) (2), perceived stigma (perceived attitudes of others towards mental illness), enacted stigma (experienced stigma), and treatment stigma (negative attitudes and beliefs about receiving treatment) (3). If a person agrees with stigmatizing beliefs and acts, they then proceed to internalize the stigma, which has a long-lasting and deep impact on them (4). An individual's preexisting social identity, which is determined by their positions within the community such as being a son, brother, sister, friend, employee, or possible lover, is gradually substituted with a diminished and stigmatized perception of oneself (5).

The presence of stigma related to mental diseases has been identified as a significant obstacle to maintaining treatment for depression (6) and may lead to reduced self-esteem (7) where negative thoughts may become a barrier to recovery (8). Studies have reported that higher depression symptoms predicted higher self-stigma, suggesting that those with higher depression hold more stigmatized views of themselves (9). Individuals who experience depression are often stigmatized as being unable to be cured, lacking strength, and having difficulty communicating (3). Therefore, individuals who experience depression may internalize stigmatizing judgments that make them feel unlovable, imperfect, and inadequate (10). Upon examining the literature, some studies found a significant relationship between depressive symptoms and internalized stigma among depressive disorder patients (6,10,11), anxiety and psychotic disorders (6), somatoform pain disorder patients (12), bipolar disorder patients (6,13) and the general public (9).

In addition, individuals may attribute responsibility to themselves and experience feelings of guilt for lacking the resilience to overcome their condition or feel a sense of humiliation over their sickness. Ultimately, it results in a substantial decline in one's self-esteem, to be more precise (3,14). Self-esteem is the personal assessment of one's ideas and emotions. Self-esteem may be seen as a cognitive framework that serves as a mechanism by which external information can impact mood and behaviour, either in a good or negative manner. Numerous studies have highlighted low self-esteem as an important risk factor for depression, where the link between self-esteem and depression is bidirectional, with self-esteem having a higher impact as a risk factor for depression (the vulnerability model) compared to depression's impact on self-esteem (the scar model) (15). Self-stigma is found associated both with harming self-esteem (16) and is negatively correlated with self-esteem in numerous studies which is in line with one of the definitions that conceptualize internalized stigma as “the loss of self-esteem and self-efficacy that occurs when people internalize the public stigma” (17).

Over the past two decades, the concept of internalized stigma has received significant scholarly attention. This is reflected in the substantial increase in both qualitative and quantitative research on the topic, highlighting its growing importance. Despite this wealth of research, there remain inconsistent findings regarding the relationships between sociodemographic factors, diagnostic categories, symptom severity, and internalized stigma (18). Considering the potential associations between internalized stigma, self-esteem, and depression, the previous research emphasized the importance and the need for cross-cultural studies and they acknowledged the present relationship may vary according to the clinical diagnosis and different phases of the illnesses (3,5,6,18). This study aims to address these inconsistencies by examining these associations across different diagnostic groups and sociodemographic settings. Accordingly, the primary goal of this research was to compare the internalized stigma, self-esteem, and symptom severity between individuals experiencing active phases of depression and those in remission, providing insights into how these constructs vary across different stages of the disorder. Additionally, the research sought to identify associations between internalized stigma, self-esteem, and symptom severity, illuminating the intricate interactions between these elements in the context of active depression. We hypothesize that individuals with active depression have higher levels of internalized stigma and lower levels of self-esteem compared to remitted depression patients. Moreover, there would be significant associations between symptom severity, self-esteem and internalized stigma. We acknowledge that by explaining the dynamics of internalized stigma, self-esteem, and symptom severity, this study may contribute to the creation of targeted therapies aimed at reducing the burden of depression and improving the well-being of affected persons.

Material and Method

Participants and Procedure

The patient cohort was drawn from individuals seeking assistance at the psychiatric outpatient unit of Celal Bayar University Hospital between January 2012 and March 2012, specifically selected if they met

the diagnostic criteria for MDD through DSM-IV-TR structured clinical interviews. The inclusion criteria for patients were: (i) to be between 18 and 65 years old, (ii) to have a diagnosis of MDD (iii) to not have any alteration in treatment regimen within the preceding month before the study. The exclusion criteria were: (i) Presence of any comorbid psychiatric disorders other than MDD, and (ii) the presence of psychotic symptoms, mental retardation, Substance Use Disorder /Alcohol Use Disorder, and neurocognitive disorder which may affect the responses of the participants, and (iii) presence of current hospitalization. Initially, 100 patients were recruited; however, 27 individuals were excluded due to the presence of psychiatric comorbidities other than MDD. Consequently, the patient group was divided into 2 subgroups including active MDD patients (n=50) and patients who are in remission (n=33). At the time of the study, all patients were undergoing regular antidepressant treatment.

Sociodemographic Form

The participants' demographic characteristics (e.g., age, education, disease duration, treatment duration, suicide attempt) were documented with the sociodemographic form prepared by the researchers.

Hamilton Depression Rating Scale (HDRS)

The Hamilton Depression Scale (HDRS) was developed to assess symptom severity in depression. The scale was revised by the same researcher in 1967 and given its final form with some modifications. In this study, we used the last modified version which includes 17 items (e.g. depressed mood, feelings of guilt, suicide, agitation) with a score from 0 to 4 or 0 to 2, depending on the severity. The scores are then summed up to obtain a total score, which can range from 0 to 53, with higher scores indicating more severe depression. The validity and reliability study for the Turkish population was carried out by Akdemir et al. (19) and the internal consistency coefficient was found to be .76.

Hamilton Anxiety Rating Scale (HARS)

The Hamilton Anxiety Rating Scale (HARS) consists of 14 items about somatic and psychological symptoms, including anxious mood, depressed mood, tension, insomnia, somatic symptoms, problems in the intellectual, sensory, cardiovascular, respiratory gastrointestinal, genitourinary, or autonomic systems, and the behaviour observed at interview (fidgety, restless, etc.). Each item is scored on a scale from 0 (not present) to 4 (very severe), with a total score range of 0-56. A total score <17 indicates mild anxiety whereas scores >25 or higher refer to moderate and severe anxiety. Yazıcı et al. (20) conducted the validity and reliability research among the Turkish population and the Cronbach alpha value was found to be .72.

Rosenberg Self-esteem Scale (RSES)

The Rosenberg Self-esteem Scale (RSES) was developed to evaluate an individual's self-esteem. The 4-point Likert-type scale consists of 10 items. The high scores obtained from the Rosenberg Self-Esteem Scale indicate low self-esteem. The responses to the items in this scale receive score values in the range of 0-6. In interpreting the scores; those scoring 0-1 are considered to have "high" self-esteem, those scoring 2-4 are considered "moderate," and those scoring 5-6 are considered to have "low" self-esteem (21). Cronbach Alpha coefficient for reliability was found to be .81.

Internalized Stigma of Mental Illness Scale (ISMI)

The Internalized Stigma of Mental Illness Scale (ISMI) is a self-report measure that includes 29 items within the framework of five subscales titled alienation, confirmation of stereotypes, perceived discrimination, social withdrawal, and resistance to stigma. The scale assesses people's subjective stigmatization experiences. The items are rated on a four-point Likert scale which ranges between strongly disagree (1) and strongly agree (4). For our research purposes, we only utilized the overall score of the ISMI scale in the analyses. The overall ISMI score is calculated by summation of the subscale scores ranging from 4 to 116. Higher ISMI scores indicate that the person's internalized stigma is more negative and severe. Turkish validity and reliability study was performed by Ersoy et al. (22) and Cronbach's alpha was found .93.

Statistical Analysis

All analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 16.0 (IBM Corp., Armonk, NY). The normality of distribution was checked by skewness kurtosis and visual plots. To examine differences in sociodemographic variables and applied scales between MDD and remission MDD groups, chi-square tests and independent samples t-tests were performed. Pearson bivariate correlations were utilized to analyze the relationship between variables including HDRS, HARS, RSES, and ISMI in the active MDD group. Subsequently, a multiple linear regression analysis was run to identify potential associations between ISMI and related variables in the active MDD group. Cohen's f2 was calculated to define the effect size within the regression model. According to Cohen's guidelines, f2 values of ≥ .02, ≥ .15, and ≥ .35 represent small, medium, and large effect sizes, respectively. The level of statistical significance (p) was set at <.05.

Results

Characteristics of the Participants

The sociodemographic features of individuals with MDD and those in remission from MDD are shown in Table 1. In the active MDD group, mean age, disease duration, and treatment duration were comparable to those in the MDD remission group. Both groups had similar educational backgrounds and gender distributions. Marital status also showed no significant difference between the two groups. However, there was a significant difference in the place of residence, with a higher proportion of individuals with active MDD residing in the city center compared to those in remission from MDD. Psychiatric history in the family, keeping mental disorders secret, experiencing

Table 1 Sociodemographic features of the groups

	Group						Statistics
	MDD (n = 50)			MDD remission (n = 33)			
	M	SD	n (%)	M	SD	n (%)	
Age	39.66	11.98		44.64	11.14		t(81) = -1.82, p = .072
Disease duration (months)	66.14	51.28		82.12	70.99		t(81) = -.921, p = .360
Treatment duration (months)	21.38	28.72		33.88	40.53		t(81) = -1.64, p = .104
Education							
Primary			32 (64%)			23 (70%)	χ2(2) = .508, p = .913
High			11 (22%)			7 (21%)	
University			7 (14%)			3 (9%)	
Gender							χ2(1) = .825, p = .364
Male			8 (16%)			3 (10%)	
Female			42 (84%)			30 (90%)	
Marital status							
Married			36 (72%)			26 (78%)	χ2(2) = 5.10, p = .164
In relationship			11 (22%)			2 (6%)	
Single			3 (6%)			5 (16%)	
Psychiatric history in family							
Present			21 (42%)			11 (33%)	χ2(1) = .63, p = .427
Not present			29 (58%)			22 (67%)	
Keeping mental disorder secret							χ2(1) = 1.319, p = .250
Yes			23 (46%)			11 (33%)	
No			27 (54%)			22 (67%)	
Exposure to discrimination							
Yes			11 (22%)			4 (12%)	χ2(1) = 1.310, p = .252
No			39 (78%)			29 (87%)	
Suicide attempt							
Yes			7 (14%)			2 (6%)	χ2(1) = 1.296, p = .255
No			43 (86%)			31 (94%)	

M: mean; SD: standard deviation

discrimination, sharing mental disorders, and reporting suicide attempts did not differ significantly between the groups. Table 2 compares individuals with active MDD to those in remission from MDD across several measures. In the active MDD group, the HDRS score was significantly higher than in the remission group. Similarly, for the HARS, the MDD group had significantly higher scores compared to the remission group, however, for both groups the anxiety severity was negligible. Additionally, the RSES scores were markedly higher in the active MDD group compared to the remission group which showed that the active group has less self-esteem relative to remission group. Similarly, the ISMI showed higher scores in the MDD group compared to the remission group indicating active group has more internalized stigma.

The associations between HDRS, HARS, RSES, and ISMI

The correlations among the main variables are illustrated in Table 3. According to the results of bivariate correlations, there was a positive correlation

Table 2 The comparison of mean values between groups

	Group						
	MDD (n = 50)			MDD remission (n = 33)			Statistics
	M	SD	n (%)	M	SD	n (%)	
HDRS	19.84	5.14		7.12	3.53		t(81) = 12.40, p < .001
HARS	7.42	5.33		2.82	2.05		t(81) = 4.72, p < .001
RSES	3.60	1.60		1.45	1.41		t(81) = 6.24, p < .001
ISMI	69.46	14.47		50.52	11.14		t(81) = 6.36, p < .001

Notes: HDRS: Hamilton Depression Scale, HARS: Hamilton Anxiety Scale, RSES: Rosenberg Self Esteem Scale, RSQ: Rosenberg Self-Esteem Questionnaire, ISMI: Internalized Stigma of Mental Illness Scale

Table 3 Correlational coefficients between HDRS, HARS, RSES and ISMI in the MDD group

Variable	1	2	3	4	5	6	7
1. Age	-	.17	-.32*	.09	-.01	-.14	-.13
2. Gender		-	.23	.02	.13	-.02	.10
3. Education			-	-.09	-.05	.06	-.23
4. HDRS				-	.49*	.17	.30*
5. HARS					-	.07	.19
6. RSES						-	.56**
7. ISMI							-

Notes: HDRS: Hamilton Depression Scale, HARS: Hamilton Anxiety Scale, RSES: Rosenberg Self Esteem Scale, RSQ: Rosenberg Self-Esteem Questionnaire, ISMI: Internalized Stigma of Mental Illness Scale
*p < .05, **p < .01

Table 4 The results of multiple linear regression analysis

Independent variables	Standardized βeta	t	p	R^2
HDRS	.365	3.129	.016	.53
RSES	.566	5.506	<.001	

Notes: Dependent variable: ISMI: Internalized Stigma of Mental Illness Scale; HDRS: Hamilton Depression Scale, RSES: Rosenberg Self Esteem Scale

between HDRS, RSES, and ISMI. However, there were no significant relationships found between age, gender, education, and HARS variables with ISMI. We executed multiple linear regression with the enter method to explore whether HDRS and RSES factors, which had significant associations in correlational analyses, were associated with the ISMI variable. In regression analysis, we included only a group of individuals which was referred to as an active patient group. The regression results revealed that both HDRS and RSES were associated with the ISMI ($F(2, 47) = 33.11$, $p < .001$) accounting for 53% of the variance which indicates a large effect size according to Cohen's guidelines. Coefficients are shown in Table 4.

Discussion

The study investigated the depression and anxiety symptom severity, self-esteem, and internalized stigma in patients with MDD, comparing individuals in active depression with those in remission. Additionally, we examined the associations between internalized stigma, symptom severity and self-esteem among individuals who have active depressive symptoms. Our results demonstrated that the active MDD group exhibited significantly higher scores on measures of depression severity, anxiety severity, and internalized stigma, along with lower self-esteem compared to the remission group. Moreover, our research revealed noteworthy associations between internalized stigma, self-esteem and the severity of depressive symptoms; that is, individuals with lower self-esteem and more pronounced depressive symptoms experienced a greater degree of internalized stigma.

Internalized stigma has become a significant focus of research, with a notable increase in related literature. Despite the extensive data, there are still conflicting findings in various diagnostic and sociodemographic contexts, such as different phases of mental disorders (23,24). Considering the need in this field, our study compared MDD patients who were in two distinct stages of the illness, and the results indicated that the patients who suffer from active depressive symptomatology bear higher internalized stigma when compared to the remission group. This finding corroborates the previous metanalysis findings that demonstrated mental disorder severity as a prominent risk factor in internalized stigma (3,5). Moreover, the studies including only depression samples demonstrated similar results that depression symptom severity poses a risk factor in internalized stigma (10,11,25). Although the anxiety scale was used to exclude its comorbid presence with depression in our study, we have included it in further analysis to examine the relationship. Our results showed no significant associations between anxiety and internalized stigma. In the literature, anxiety symptom severity was found to be positively correlated with internalized stigma among patients with anxiety disorders (5,26). This null finding could be attributed to the milder symptoms (<17 in HARS) of our sample which did not exceed the threshold to negatively affect the internalized stigma.

The sociodemographic variables including age, gender, and education were not related to the internalized stigma in our sample. Previous studies showed inconsistent findings and yielded mostly non-significant associations. In one systematic review, which explored the relationship between internalized stigma and socio-demographic characteristics, no consistent or strong correlation was found between internalized stigma and socio-demographic characteristics such as age, gender, education, employment, marital status, income, or ethnicity. In more detail, among the included studies in the review, 31 (81.6%) out of 38 studies reported no significant outcomes on gender and internalized stigma. Out of 35 age studies and 27 education studies, 24 (68.6%) and 22 (81.5%) reported non-significant results (17). These data suggest that the Turkish depression population also faces internalized stigma similarly regardless of socio-demographic factors.

While the prevailing body of research has linked self-stigma to diminished self-esteem, Livingston and Boyd's (17) investigation put forth the hypothesis that self-stigma could be predicted by individuals with mental illness who exhibited low self-esteem. One potential rationale for the association between low self-esteem and self-stigmatization is heightened vulnerability to stigmatizing concepts, additionally; low self-esteem is also considered to be a comorbidity with depression (27). Previous studies acknowledged self-esteem as a protective factor for internalized stigma. Particularly the researchers focused on solely depression samples and found out that higher self-esteem plays a noticeable role in decreasing self-stigma attitudes (28–30). Therefore, our study supports the earlier findings which again presented self-esteem's vital role in internalized stigma.

Study limitations: Although the research yielded valuable insights, it is imperative to acknowledge several limitations. Causal conclusions cannot be drawn from the cross-sectional design, and the findings may be difficult to generalize due to the relatively small sample size. Moreover, response bias may be introduced by the use of self-report measures, and the findings may not apply to the broader population of individuals with depression due to the exclusion of those with comorbid psychiatric conditions. Additionally, we did not include a control group in our study which may distort our perspective in reference scores of the healthy population.

Notwithstanding these constraints, the research enhances our comprehension of the intricate dynamics that exist among internalized stigma, severity of symptoms, and self-esteem in the context of depression. By incorporating participants in both the active depression and remission phases, significant insights can be gained regarding the varying effects of internalized stigma at distinct stages of the illness. Furthermore, our research conducted a comparative analysis of sociodemographic attributes (such as age, gender, education, and marital status) and psychosocial factors (including familial psychiatric history, secrecy regarding mental illness, encounters with discrimination, disclosure of mental disorder, and suicide attempts) between groups with active and remitted MDD. These variables were previously recognized as potential mediators in the development of internalized stigma. The absence of any discernible difference in these comparisons enhanced our ability to interpret our findings related to symptom severity, self-esteem and internalized stigma measurements. In active MDD patients, our research emphasizes the significance of two critical determinants of internalized stigma: depressive symptoms and self-esteem. This primary finding is consistent with one of the most recent systematic reviews, which identifies elevated self-esteem as a protective factor against internalized stigma and increased severity of depressive symptoms as a risk factor (3). The results emphasize the necessity of developing all-encompassing treatment strategies that tackle psychological and social determinants of depression in addition to alleviating symptoms. While the notion of stigma has persisted for several decades, curiosity and attention regarding its underlying causes, impact on mental health, and potential remedies have only emerged in recent times (24). Self-esteem and internalized stigma may be addressed through cognitive-behavioural techniques, peer support programs, and psychoeducation that seek to dispel negative beliefs and foster resilience (17). To mitigate internalized stigma and offer assistance and empowerment to individuals with mental illness, educational interventions that enhance their coping mechanisms and stigma management capabilities could be quite useful in clinical practice. Future research should explore longitudinal associations between internalized stigma, symptom severity, and self-esteem, and evaluate the effectiveness of interventions aimed at reducing stigma-related barriers to recovery in individuals with depression.

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Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
In our study, written consent was obtained from all the cases participating in our study, in accordance with the Declaration of Helsinki. Ethics Committee permission was obtained from Celal Bayar University Medical Faculty Clinical Research Ethics Committee with the decision dated 04.01.2012 and numbered 001.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Data is available on request from the authors.

Authors Contributions
PUA: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing-original draft.

EOT: Conceptualization; Project administration; Supervision; Validation; Writing-review & editing.

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ORIGINAL RESEARCH

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Perceived Stress in Medical Education: Relationship with Empathy and Stigmatisation

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Abstract

Objective

Medical students have been shown to report high levels of perceived stress. Perceived stress leads to a loss of empathy and negatively affects attitudes and behaviours towards patients. This study aimed to investigate the perceived stress levels and empathy skills of medical students and their relationship with their attitudes to mental illness.

Material and Method

A cross-sectional study was conducted in Türkiye between March 2024 and April 2024 using an online survey. A total of 544 medical students attending university in the academic year 2023-2024 completed the questionnaire, which included the sociodemographic data form, the perceived medical school stress scale, the empathy scale, and the beliefs towards mental illness scale. Participants were asked whether they had received psychiatry training, whether they had been diagnosed with a mental illness, and whether they would disclose if they were diagnosed with a mental illness.

Results

By gender, the mean Perceived Medical School Stress Scale score of females was statistically significantly higher than that of males (p=0.035). Perceived Medical School Stress Scale scores did not differ by training year, whereas Beliefs Towards Mental Illness Scale Weak Social and Interpersonal Skills sub-dimension scores did (p=0.643; and p=0.027, respectively). The Empathy Scale score of students who received psychiatry training was statistically significantly higher than that of students who did not receive a placement (p=0.003). A low significant negative correlation was found between the Perceived Medical School Stress and Empathy Scale scores (rho=-0.098; p=0.005).

Conclusion

In our study, the perceived stress of medical students during their training differs according to gender, and its relationship with empathy skills is demonstrated. Individualised interventions to prevent and alleviate stress should be developed for students who need support coping with difficulties during their training.

Keywords: Empathy, medical students, stigma, stress

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Introduction

Medical education is a difficult process that continues for years. Stress arising from medical education is a topic that has been investigated all over the world (1-3). Stress awareness in medical education is also growing in Turkey (4, 5). Research has indicated that medical students exhibit elevated levels of anxiety, depression, stress and symptoms of burnout compared to other students, the general population, and their peers (1, 2, 6, 7). A recent prospective study indicated that the stress levels see a notable increase throughout their first year of medical education (8). The elevated degree of stress encountered by medical students is mostly attributed to distinct stressors inherent to medical school. These factors include a rigorous curriculum, excessive knowledge, academic rivalry, high-performance standards, grade-related stress, feelings of inadequacy, and dread of errors (1). In addition, witnessing diseases, disabilities, and deaths are also considered emotional stress factors (9). Perceived intense stress is associated with decreased school performance of students and negative mental health outcomes including burnout (10-12).

According to reports, individuals who possess strong empathy skills can readily experience the emotions of others, effectively utilize problem-solving abilities, enhance their awareness of social dynamics, approach situations without bias, demonstrate a willingness to assist others and maintain a balanced approach in interpersonal relationships (13). Various studies have shown that the adequacy of empathy skills of physicians has a positive effect on the health outcomes of patients (14-16).

Perceived medical school stress has been shown to cause a loss of empathy and negatively affect students' attitudes toward patients (10, 12). The quality of patient care is significantly impacted by high levels of stress (17). A review of studies suggests that empathy may also be a potential predictor of stigmatization (18). The presence of stigmatization of mental illness has also been documented in university populations, more specifically in studies related to health sciences (19-21). In a study examining medical students' attitudes toward disclosure of mental illness, the majority of participants reported that they would not disclose a diagnosis of mental illness (22). In the case of mental health problems, negative attitudes towards psychiatric disorders have been reported to delay necessary treatment (23). Various practices in medical education have been shown to reduce the stigma of mental illness through direct contact with patients (24, 25). Also by implementing technologies like simulated reality in education, it has been shown that stigmatization towards patients with psychotic experiences decreased and empathy increased in medical students who experienced positive psychotic symptoms (26).

It is especially important to know the level of stress perceived by medical students during their education, to be aware of their empathy skills, and to understand their beliefs about mental illnesses, as they will shape the future of society as healthcare professionals in the future. The objective of this study is to quantify the level of stress experienced by medical school students and investigate how it correlates with their empathy abilities and attitudes towards mental diseases. We hypothesized that perceived medical school stress would be related to empathy and that levels of empathy would affect attitudes toward mental illness. In terms of methods to be developed to manage stress during medical education, our study will contribute to the literature.

Material and Method

Study Design

A cross-sectional study was conducted between 05.03.2024 and 06.04.2024 during the 2023-2024 academic year was continuing. A total of 544 medical students studying at different universities in various locations in Turkey who agreed to participate in the study participated in the study. Participants were asked to complete four stages of the questionnaire delivered through the Google Forms online platform, which took approximately 10 minutes. The first stage included items about general demographic information, educational information, and information about the presence of chronic diseases in themselves or their families. Additional sections of the study encompassed the Perceived Medical School Stress Scale (PMSS-TR), the Empathy Scale (ES), and the Beliefs towards Mental Illness Scale (BMI), all of which underwent validity and reliability evaluations specific to the Turkish context. As it was mandatory to answer every question before proceeding to the next one, all 544 medical faculty students who participated in the study completed the questionnaire and were then analyzed. Once the questionnaire was finished, the link became invalid, allowing individuals to only complete the form once. The poll was conducted in a manner that ensured the participants' identities remained unknown and the information they provided was kept private. The poll invitation was distributed through WhatsApp student groups, social networks, and email. The investigation employed the snowball sampling technique. Participants were instructed to distribute

the questionnaire to a maximum number of individuals. Before commencing the survey, every participant was required to familiarize themselves with the objective of the study and thereafter provide informed consent. Participants were notified that their involvement in the study was entirely optional. Participants were not compensated for their involvement in the study.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: being a medical school student in Turkey in the 2023-2024 academic year, being over 18 years of age, agreeing to participate in the study, and signing the consent form. Those who were not medical school students, who did not give consent for participation in the study, and who did not fill out the questionnaire questions properly were excluded from the study.

Data Collection Tools

General and Sociodemographic Information

Participants were asked about their mental health diagnosis and whether they had a family history of chronic illness. Individuals with a mental health diagnosis were asked about their willingness to disclose this information. Participants were asked about years of training and whether they had received psychiatry training. Age was recorded based on self-report, while gender was recorded as either 'male' or 'female'.

Evaluation of Medical School Stress

The Perceived Medical School Stress Scale (PMSS-TR), which was specifically designed for use in medical faculties, was used to measure the stress of medical students due to studying in medical faculty (27). The scale focuses on a wide range of stressors including economic concerns, social isolation, workload, and competition. It consists of 13 items and higher scores indicate higher levels of stress and anxiety. The Turkish scale has been tested for validity and reliability and Cronbach's alpha is 0.81 (28).

Evaluation of Beliefs about Mental Illness

In our study, the Beliefs Towards Mental Illness Scale (BMI), a self-assessment scale developed to determine positive and negative beliefs towards individuals with mental illness in different cultures, was used. The scale consists of 21 items and is a six-point Likert-type scale. Each item is scored between 0-5. The scale consists of statements including negative beliefs about mental illness. The scale has three sub-dimensions: dangerousness (the belief that individuals with mental illness are dangerous), weak social and interpersonal skills (the belief that individuals with mental illness are weak in social and interpersonal relationships), and helplessness (the belief mental illness is incurable). The maximum score of 150 points can be obtained from the scale in total, while the minimum score is 0. High scores obtained from the sub-dimensions and in total indicate negative beliefs (29). The Turkish validity and reliability study was conducted. The Cronbach alpha coefficient of the scale is 0.82, and the subscale Cronbach alpha values are between 0.69-0.80. The scale and subscales showed an acceptable level of internal consistency (30).

Evaluation of Empathic Skills

The Empathy Scale (ES) was developed within the scope of the Empathisation Systemisation theory (31). The Turkish validity and reliability study was performed and internal consistency was found to be 0.84 (32). It consists of 40 items to measure empathy and 20 distractor items. The answers to the questions consist of 4 options with ‘strongly agree’ and ‘strongly disagree’ at both ends. Only the 40 questions evaluating empathy are taken into consideration in scoring. Among the answers given to these questions, 2 points are given to the most empathic response, 1 point to the second empathic response, and 0 points to the 2 least empathic responses. In total, the maximum score that can be obtained from the scale is 80. Some questions are reverse-scored. For some of the answers, ‘strongly agree’ and in others ‘strongly disagree’ express an empathic response. In our study, the short form of the scale consisting of 22 items selected by factor analysis method from 40 empathy questions was used (33).

Statistical Analysis

The data analysis was conducted using the SPSS 24.0 (Statistical Package for the Social Sciences, Version 24.0) software. The data were presented as number and percentage distributions for categorical variables, and as mean, standard deviation, median, lowest value, and maximum value for continuous variables. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Given the absence of the normal distribution, statistical analyses were conducted using non-parametric tests, namely the Mann-Whitney U test and the Kruskal-Wallis test. The relationship between the scales and subscales was analyzed using the Spearman correlation test. The degree of correlation between variables was measured with the Spearman correlation coefficient (r).

Results

A total of 544 students, 330 female and 214 male, with a mean age of 21.94±4.22 years, participated in the

study. 24.6% (n=134) of the participants were in their first year of training. 74.1% (n=403) had completed their psychiatry internship. A total of 77.9% of the research group, consisting of 544 people, reported that they would disclose a mental health diagnosis if they had a mental disorder. While 21% of participants had been diagnosed with at least one mental illness, 13.8% (n=75) were currently receiving treatment. 41.5% of the participants had a family member who suffered from a chronic illness. Sociodemographics and some descriptive characteristics of the research group are shown in Table 1.

The mean score of the PMSS-TR was 34±7.42, and the median score was 36 (min=13-max=56); the mean score of the ES was 23.24±8.11, the median score was 23 (min=3-max=43), and the mean score of the BMI-Total was 47.57±14.10, the median score was 48 (min=0-max=91). The mean score of the Dangerousness BMI Subscale was 13.62±3.89, with a median score of 14 (min=0-max=25); the mean score of the Weak Social and Interpersonal Skills BMI Subscale was 19.65±7.53, with a median score of 20 (min=0-max=45); and the mean score of the Helplessness BMI Subscale was 14.30±5.01, with a median score of 14 (min=0-max=30) (Table 2).

The results showing the relationship between some socio-demographic and descriptive characteristics of the research group and the scores on the Beliefs Towards Mental Illness Scale and the Empathy Scale are presented in Table 3. The PMSS-TR and ES scores of females were statistically significantly higher than those of males (p=0.035, p=0.043, respectively), and the BMI total score of males was statistically significantly higher than that of females (p=0.021). The BMI Helplessness sub-dimension scores showed no significant difference (p=0.582) between genders. When analyzing the groups, it was found that the mean scores of the BMI Weak Social and Interpersonal Skills sub-dimension were statistically significantly higher for students in their final year of education compared to students in their first and second years of education (p=0.004; p=0.005). The mean ES scores of students who completed psychiatry training were statistically significantly higher than those who did not (p=0.003). The BMI Weak Social and Interpersonal Skills sub-dimension score of students who did not complete psychiatry training was statistically significantly higher than those who did (p=0.047). The ES score was significantly higher among those who said they would disclose if they had a mental illness (p=0.005). The mean BMI total score was statistically significantly lower among students with a diagnosis of

Table 1 Demographic and descriptive characteristics of the study group.

Variables (n)	**n (%)**	
Age	Mean±SE (year)	21,94±4,22
Sex (544)	Female Male	330 (60.7) 214 (39.3)
Year of training	Year 1 Year 2 Year 3 Year 4 Year 5 Year 6	134 (24.6) 51 (9.4) 85 (15.6) 75 (13.8) 129 (23.7) 70 (12.9)
Psychiatry training	Yes No	141 (25.9) 403 (74.1)
Disclose a mental health diagnosis	Yes No	424 (77.9) 120 (22.1)
Mental illness	Yes No	144 (26.5) 400 (73.5)
Receiving medical treatment (144)	Yes No	75 (13.8) 69 (12.7)
Family history of chronic illness	Yes No	226 (41.5) 318 (58.5)

Table 2 Descriptive characteristics of perceived medical school stress, empathy, and beliefs towards mental illness scale of the study group

		n	Median (min-max)	Mean±SD
PMSS-TR		544	36 (13-56)	34.67±7.42
ES		544	23 (3-43)	23.24±8.11
BMI	**Dangerousness**	544	14 (0-25)	13.62±3.89
	Weak Social and Interpersonal Skills	544	20 (0-45)	19.65±7.53
	Helplessness	544	14 (0-30)	14.30±5.01
	Total	544	48 (0-91)	47.57±14.10

BMI: Beliefs towards Mental Illness Scale; ES: Empathy Scale; PMSS-TR: Perceived Medical School Stress Scale

Table 3 Association between socio-demographic and descriptive characteristics of the study group and scores on the Perceived Medical School Stress, Empathy Scale, and Beliefs towards Mental Illness Scale.

Variables (n) Median (min-max)		PMSS-TR		ES		BMI Dangerousness		Weak Social and Interpersonal Skills		Helplessness		Total	
		Median (min-max)	p	Median (min-max)	p	Median (min-max)	p	Median (min-max)	p	Median (min-max)	p	Median (min-max)	p
Sex (544)	Female (330) Male (214)	35.15 (13-56) 33.84 (13-52)	**0.035**	24 (3-43) 22 (3-41)	**0.043**	13 (0-23) 14 (0-25)	**0.002**	19 (0-41) 21 (3-45)	**0.017**	14 (0-27) 14 (0-30)	0.582	47 (0-88) 50 (4-91)	**0.021**
Year of training	Year 1 (134) Year 2 (51) Year 3 (85) Year 4 (75) Year 5 (129) Year 6 (70)	37 (15-49) 35 (13-52) 36 (13-47) 35 (13-48) 36 (13-56) 37 (13-52)	0.643	21 (5-41) 23 (3-39) 22 (4-41) 23 (3-42) 24 (3-43) 24 (7-41)	0.056	14 (4-25) 14 (2-23) 14 (5-22) 14 (4-21) 14 (4-22) 13 (0-24)	0.163	22 (3-45) 23 (3-41) 20 (2-44) 19 (2-34) 19 (3-43) 17 (0-40)	**0.027**	13.50 (3-30) 15 (3-25) 14 (1-26) 14 (5-27) 15 (0-27) 14 (0-24)	0.890	49 (16-81) 52 (14-88) 47 (13-91) 48 (11-82) 48 (11-84) 46 (0-84)	0.310
Psychiatry training	Yes (141) No (403)	36 (13-56) 36 (13-52)	0.656	26 (7-43) 22 (3-42)	**0.003**	13 (0-24) 14 (0-25)	0.174	19 (3-43) 21 (0-45)	0.047	15 (0-27) 14 (0-30)	0.309	46 (4-84) 48 (0-91)	0.274
Disclose a mental health diagnosis	Yes (424) No (120)	36 (13-56) 36 (13-49)	0.847	23 (3-43) 21 (3-40)	**0.005**	14 (0-24) 14 (5-25)	0.107	20 (0-44) 21 (3-45)	0.146	14 (0-30) 15 (3-27)	0.100	47.50 (0-91) 48.50 (14-84)	0.078
Mental illness	Yes (144) No (400)	33 (13-52) 36 (23-56)	**0.004**	23.50 (3-39) 23 (3-43)	0.379	12 (4-21) 14 (0-25)	**<0,001**	15 (2-32) 21 (0-45)	**<0,001**	15 (0-25) 14 (0-30)	0.394	41 (11-73) 49 (0-91)	**<0,001**
Receiving psychotropic medication (144)	Yes (75) No (69)	32 (13-52) 36 (20-52)	**0.027**	24 (3-39) 22 (5-41)	0.154	12 (0-20) 13 (0-22)	**0.023**	14 (2-40) 20 (0-44)	**<0,001**	15 (0-25) 15 (0-30)	0.0454	41 (4-84) 48 (0-91)	0.005
Family history of chronic illness	Yes (226) No (318)	36 (13-56) 36 (13-52)	0.405	24 (3-43) 22 (3-41)	**0.044**	13 (2-25) 14 (0-24)	**0.042**	19 (2-45) 21 (0-44)	**0.021**	13.50 (1-30) 14 (0-26)	0.252	44 (16-84) 49 (0-91)	**0.024**

BMI: Beliefs towards Mental Illness Scale; ES: Empathy Scale; PMSS-TR: Perceived Medical School Stress Scale

mental illness than among those without a diagnosis (p=<0.001). The mean BMI total score of students without a family history of a disease requiring ongoing treatment was statistically significantly higher than the mean BMI total score of students with a family history of a disease (p=0.024). The ES score of those with at least one family history of chronic disease was statistically significantly higher than that of those without (p=0.044).

Table 4 Correlation between Perceived Medical School Stress, Empathy Scale and Beliefs towards Mental Illness Scale

		PMSS-TR	ES	BMI			
				Total	Dangerousness	Weak Social and Interpersonal Skills	Helplessness
PMSS-TR		-	-0.098*	-0.042	-0.054	-0.037	-0.020
ES		-0.098*	-	-0.069	-0.004	-0.120**	-0.010
BMI	**Total**	-0.042	-0.069	-	0.825**	0.918**	0.793**
	Dangerousness	-0.054	-0.004	0.825**	-	0.682**	0.520**
	Weak Social and Interpersonal Skills	-0.037	-0.120**	0.918**	0.682**	-	0.549**
	Helplessness	-0.120**	-0.010	0.793**	0.520**	0.549**	-

BMI: Beliefs towards Mental Illness Scale; ES: Empathy Scale; PMSS-TR: Perceived Medical School Stress Scale
**Indicates statistically significant difference (p<0.01).
*Indicates statistically significant difference (p<0.05).

There was a low level of significant negative correlation between the PMSS-TR score and the ES score (r=-0.098; p=0.022). There was a low level of significant negative correlation between the ES score and the BMI Weak Social and Interpersonal Skills subscale (r=-0.120; p=0.005). The relationship between the PMSS, the ES, and the BMI scores is shown in Table 4.

Discussion

In this study, we aimed to quantify the stress level perceived by medical students. We examined the relationship between stress levels, empathy, and attitudes towards mental illness. Our results show that stress differs according to gender and that there is a relationship between stress and empathy. Training in psychiatry was found to increase empathy. Perceived stress in medical school is an important measure of vulnerability but can be reduced by early intervention.

Perceived stress in medical school has also been found to be an indicator of psychological stress after graduation (6). An investigation utilizing the PMSS-German version reported that the stress score of medical students in Germany was 37.2±8.3 and that perceived medical school stress was high (34). Our study's students had an average PMSS-TR score of 34.67±7.42. The mean score for the PMSS was 36.4±8.4 in a Polish study (35). The stress score of students in Norway was 30.7±7.6 (6). These results suggest that various factors, such as differences in working conditions, the structure of the educational program, the intensity of the curriculum, the assessment and evaluation system, social facilities, and the working conditions of doctors, may contribute to the stress levels perceived by students. The financial status and economic well-being of students may also have influenced the results. Larger, multi-center, prospective studies are needed to clarify the factors that lead students to perceive high levels of stress.

The study, which was conducted to determine the level of psychological distress in medical students and to investigate the factors predicting psychological distress, showed that students in the fourth year showed a considerable decrease in psychological suffering. It has been shown that females have higher stress levels than male students throughout the education period (36). A study including 421 medical school students revealed that females exhibited a higher stress level (37). In a study conducted in Germany, it was shown that there was no difference in stress levels between male and female students (34). In our study, it was found that females perceived stress at a higher level than male students. The stress level did not differ according to the training year. It was found that the stress level of those who had a mental illness was low. It is possible that receiving pharmacotherapy or psychotherapy related to the diagnosis is the reason for the difference in stress levels in these students.

Although the majority of medical students accepted that they needed health care, many reported that they sought services outside their educational institution, consulted their peers, or gave up seeking care altogether because of fears of confidentiality and stigma (2). Research indicates that medical students possess an understanding of the stress they encounter, although they display hesitancy in acknowledging their mental health issues and actively pursuing assistance from trained professionals (38, 39). They have been shown to face unique barriers to care and problems related to stigma (40). In our study, 20% of students reported that they would not disclose if they had a mental illness. Hence, it is imperative to ascertain the stress encountered by medical students and the determinants that impact it, to formulate preventive measures.

There is evidence that there is a positive correlation between medical students' empathy scores and communication scores in clinical skills (41). The results of our study align with a comprehensive review that found higher levels of empathy among female medical students compared to males. Whether empathy is an inherent and unchanging characteristic of one's personality or a dynamic and adaptable skill with cognitive and emotional components is a subject of ongoing debate (42). In our study, it was found that those who received training in psychiatry had better empathic skills. Those who had a family history of mental illness had higher empathy scores. It was found that empathy did not differ according to the training year. Longitudinal studies with large samples are needed to follow the development of empathy during medical training.

Evidence suggests that education can effectively diminish negative attitudes, perceptions, and beliefs about mental illness. Attending courses on mental illness has been shown to have a positive effect on beliefs (43,44). Various curricula used in psychiatric training have been shown to reduce stigma towards patients with mental illness through education and direct contact with patients (45,46). Attitudes towards people with mental illness have been shown to change positively in those who have attended courses on how to deal with people with mental illness (47). A study of 458 medical students reported that final-year students had more positive attitudes towards mental illness (48). Another study, which aimed to evaluate the effect of psychiatry training on medical students' attitudes toward psychiatric patients, showed that students' positive beliefs about mental illness increased with years of training (49). Similarly, a study of medical students in Turkey found that final training-year students had more positive attitudes towards people with mental illness than first-year students (50). It has been observed that education about mental illness and knowledge that treatment is available reduces the belief that these individuals are dangerous and should be avoided and the belief of helplessness associated with being diagnosed with the illness (51,52). A study has shown that among university students, medical students who have received psychiatric training have more positive attitudes towards mental illness (53). In a study assessing stigma towards patients with mental illness among medical students, the presence of a relative with mental illness was found to have a significant effect on stigma levels (54). In our study, it was observed that those who received psychiatry training had more positive attitudes towards mental illness, but no statistically significant difference was found. As medical students will be directly or indirectly involved in caring for people with mental illness after graduation, it is important to know their attitudes and awareness of mental disorders.

Although psychological distress in medical students reflects the difficulties of training, it is also thought to be related to stigma. Empathy leads to positive attitudes towards people with mental illness and then influences individual behavioural motivations to support these individuals (55). In a study of nurses working in a psychiatric ward, empathy was shown to reduce limitations in relationships with people with mental disorders (56). A study of 558 dental students found that empathic skills were better in fourth and fifth-year students at the start of clinical placements (57). Studies have found that levels of empathy and social distance influence beliefs about mental illness and that lack of empathic skills explains negative beliefs about mental illness (58,59). In a study of 536 university students, attitudes towards mental illness were found to be influenced by demographic factors, faculty, and year of study, and having a relative with mental illness was associated with positive attitudes (60). Our study found that those who disclosed a mental illness had higher levels of empathy. Students with a diagnosis of mental illness were shown to have more positive attitudes towards mental illness. Those with a family history of chronic illness were not found to have more positive attitudes towards mental illness. This implies that personal experiences may enhance empathy, but this does not necessarily result in more favourable attitudes toward mental illness. In our study, it was also found that the level of empathy did not differ according to the year of education. In addition to the individual's educational attainment, the community's view of mental illness in the environment in which each student grows up, the presence of mental illness

in themselves, and access to mental health services may influence attitudes towards mental illness and empathy.

The study was restricted to medical students enrolled at Turkish universities during the academic year 2023-2024. The data cannot be generalized due to its cross-sectional nature. Longitudinal studies evaluating the change in perceived stress levels over time in medical school are needed.

Conclusion

This study shows that among medical students, women have higher stress levels and better empathy skills. Empathy skills were found to decrease as perceived stress in medical school increased. As empathy skills decreased, attitudes towards mental illness were found to be negative. As expected, students who had been treated for mental disorders and had a family history of chronic illness tended to have more understanding and positive attitudes toward mental illness. Students who received psychiatry training during their education were found to have better empathy skills.

This study contributed to the assessment of the level of stress experienced by medical students during their education and to the understanding of the relationship between educational stress and empathic skills and attitudes toward mental illness. Various interventions such as student counselling, promotion of positive thinking, and awareness training are recommended to manage stress during medical training. Periodic evaluation of patient-physician communication aptitude may assist in mitigating the adverse effects of stress on empathy. There is limited literature comparing medical students in different years of training. Prospective studies comparing consecutive years of training will help to understand the effect of training on empathy and attitudes toward mental illness.

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Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study was conducted according to the Declaration of Helsinki and approved by the Süleyman Demirel University Clinical Research Ethics Committee (decision dated 29.12.2023 and numbered 17/371).

Consent to Participate and Publish
Participants were informed of the purpose of the study and then gave informed consent for participation and publication.

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Availability of Data and Materials
Data available on request from the authors.

Authors Contributions
GBY: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing-original draft.

BN: Conceptualization; Formal analysis; Investigation; Methodology; Validation; Writing-review & editing.

Gİ: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

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CASE REPORT

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Catamenial Hemoptysis: A Case Report and Literature Review

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Abstract

Thoracic endometriosis is a rare form of endometriosis. It is divided into pleural and pulmonary forms, and pleural endometriosis is more common. Our patient was a 33-year-old patient who had been complaining of hemoptysis due to a menstrual cycle for 4 months and had no comorbidities. Computed tomography of the thorax during menstruation when the patient complained of hemoptysis showed a ground-glass density in the upper lobe of the right lung, which was significantly reduced on computed tomography after the end of menstruation.

Keywords: Catamenial, endometriosis, hemoptysis, menstrual cycle

Introduction

Endometrial tissue growth outside the endometrium is called endometriosis and is characterized by symptoms such as infertility, dysmenorrhea, pelvic pain, and menorrhagia (1). Although endometriosis can affect up to 15% of women of reproductive age, thoracic endometriosis syndrome (TES) is a very rare condition. TES presents clinically as catamenial pneumothorax (CP), catamenial hemothorax, catamenial hemoptysis (CH), and parenchymal nodules (2). TES has two forms; pleural and pulmonary. The pleural form presents as CP, catamenial hemothorax, and chest pain, whereas the pulmonary form presents as CH and parenchymal nodules(3). The pleural form is more common. Pulmonary endometriosis was first described by Schwarz in 1938 (1). The most common symptom of TES is CP, while the most common symptom is chest pain (3). Different theories have been proposed regarding the presence of endometrial tissues in the thorax. Some of these theories include celiomic metaplasia, i.e., the transformation of the pleural epithelium into the endometrium, while others include lymphatic and hematogenous microembolization (2,4). Here, we describe a young patient with CH who was diagnosed with computed tomography (CT) scans taken during and after menstruation. There are not many studies on this subject in the literature. For this reason, we compiled 32 articles presenting patients with CH and presented them with our case (Table 1).

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Table 1 Studies included in the review and patient characteristics

PUBLICATION	PATIENT AGE	SYMPTOM	CT FINDING	BIOGRAPHY	TREATMENT
Latters et al / 1956 (18)	34	Hemoptysis	Right middle lobe ground-glass nodule	Medical abortion	Segmentectomy
Lindenberg et al / 1975 (19)	43	Hemoptysis	Right upper lobe ground-glass nodule	Caesarean section	Oophorectomy
Suginami et al / 1985 (20)	25	Hemoptysis	Right lung ground-glass nodule	Medical abortion	Lobectomy
Karpel et al / 1985 (21)	31	Hemoptysis	Right middle lobe nodule	Normal	Birth
Elliot et al / 1985 (22)	30	Hemoptysis	Right lung nodule	Medical abortion	Danazol
Hertzanu et al / 1987 (23)	32	Hemoptysis	Right lower lobe nodule	Medical abortion	Progesterone
Lawrence et al / 1988 (24)	34	Hemoptysis	Left lower lobe nodule	Medical abortion	Birth
Bateman et al / 1990 (25)	33	Hemoptysis	Normal	Medical abortion	Danazol
Guidry et al / 1990 (26)	30	Hemoptysis	Bilateral density increase	Medical abortion	Progesterone
Kristiansen et al / 1993 (27)	24	Hemoptysis	Right middle lobe ground-glass nodule	Normal	Lobectomy
Joseph et al / 1994 (28)	30	Hemoptysis	Pleural effusion	Laparatomy	Danazol
Kuo et al / 1996 (29)	31	Hemoptysis	Right middle lobe ground-glass nodule	Normal	Danazol
Huang et al / 2013 (30)	29	Hemoptysis	Left upper lobe ground-glass nodule	Medical abortion	Lobectomy
Yisa et al / 2004 (31)	36	Hemoptysis	Right upper lobe nodule	Laparascopy	İmplanon
Cassina et al / 1997 (32)	26	Hemoptysis	Right upper lobe nodule	Normal	Wedge resection
Chatra et al / 2012 (3)	34	Hemoptysis	Right upper lobe ground-glass nodule	Over kisti	Oral contraceptive
Chen et al / 2020 (33)	18	Hemoptysis	Right upper lobe ground-glass nodule	Normal	Segmentectomy
Burdon et al / 2001 (34)	37	Hemoptysis	Normal	Medical abortion	Lobectomy
Nakashima et al / 2011 (35)	22	Hemoptysis	Right middle lobe ground-glass nodule	Normal	Lobectomy
Tong et al / 2019 (1)	29	Hemoptysis	Right lower lobe ground-glass nodule	Laparoscopy	Wedge resection
Wood et al / 1993 (36)	32	Hemoptysis	Right upper lobe ground-glass nodule	Mol hidatiform	Segmentectomy
Matsubara et al / 1997 (37)	19	Hemoptysis	Left lower lobe ground-glass nodule	Medical abortion	GNRH agonist
Fujimoto et al / 2017 (38)	20	Hemoptysis	Right lower lobe ground-glass nodule	Medical abortion	Segmentectomy
Gill et al / 2003 (39)	28	Hemoptysis	Left upper lobe ground-glass nodule	Laparascopy	GNRH agonist
Lu et al / 2006 (13)	17	Hemoptysis	Left lower lobe ground-glass nodule	Medical abortion	Wedge resection
Suwatanapongched et al / 2015 (40)	38	Hemoptysis	Right lower lobe ground-glass nodule	Caesarean section	Danazol
Furuya et al / 2017 (8)	21	Hemoptysis	Right middle lobe ground-glass nodule	Medical abortion	Wedge resection
Aboujaoude et al / 2021 (41)	34	Hemoptysis	Right upper lobe nodule	Laparatomy	GNRH agonist
Park et al / 2006 (42)	31	Hemoptysis	Right upper lobe nodule	Caesarean section	Wedge resection
Shin et al / 2014 (6)	34	Hemoptysis	Left lower lobe ground-glass nodule	Normal	Bronchial artery embolization
Yao et al / 2023 (5)	19	Hemoptysis	Right middle lobe ground-glass nodule	Normal	Lobectomy
Kim et al / 2020 (7)	26	Hemoptysis	Right lower lobe ground-glass nodule	Normal	GNRH agonist

Case Report

A 33-year-old woman presented with hemoptysis for 4 months. Her complaints coincided with the menstrual bleeding period. Before the first episode of hemoptysis, she complained of hemoptysis with flu-like symptoms and consulted the pulmonology department. Pneumonia treatment was initiated after a ground-glass nodule was observed in the upper lobe of the right lung on thorax CT (Figure 1A). Despite pneumonia treatment, the patient presented with recurrent hemoptysis during the next menstrual bleeding. Her physical examination was normal, and she had a 13-year pack-year smoking history. She underwent ovarian cyst excision approximately 6 months ago, and no pathology was detected in current blood tests, urine tests, and respiratory tract cultures. The patient's family history included only

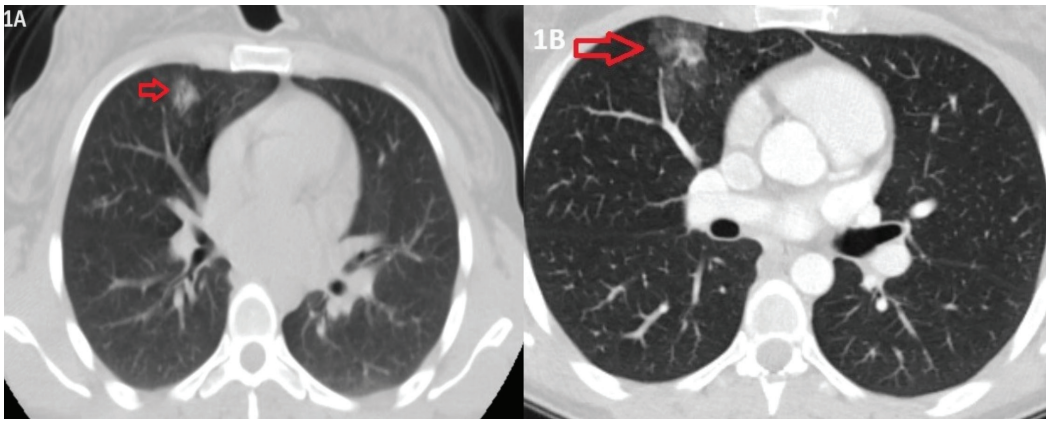

Figure 1A, 1B:
Thoracic CT images taken during different menstrual periods

cardiologic diseases, and there was no psychiatric disorder. Thorax CT repeated during the menstrual period showed the same findings (Figure 1B). Thorax CT performed on the 14th day outside the menstrual period showed that the nodule in the upper lobe of the right lung had disappeared, and the patient was diagnosed as TES clinically and radiologically (Figure 2). Medical, interventional, and surgical treatment options for the treatment of CH were shared with the patient. However, the patient preferred bronchial artery embolization (BAE), so she was referred to the relevant unit.

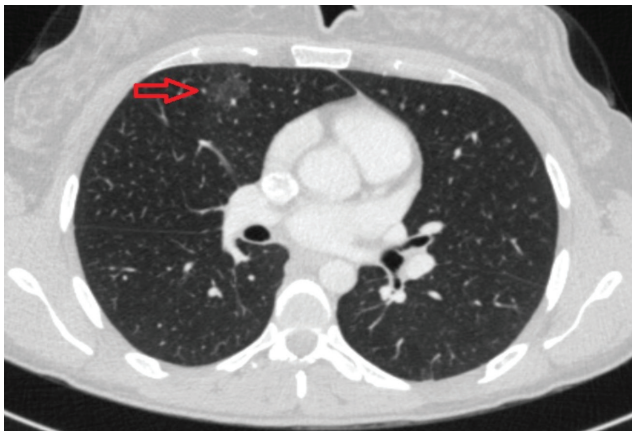

Figure 2:
Thoracic CT image taken 14 days after menstruation

Discussion

Patients with TES often present with clinical findings such as recurrent chest pain, dyspnea, hemoptysis, pneumothorax, and hemothorax, and most of them are not initially diagnosed with TES. In patients presenting with recurrent hemoptysis, diseases such as tuberculosis, pneumonia, and bronchiectasis are usually initially investigated. Thorax CT findings include pneumothorax and high-density nodules (5). The theory of vascular or lymphatic microembolization may explain TES. Trauma to the uterine tissue predisposes to microembolization. Most of these patients have an obstetric and gynecologic history, which can cause uterine trauma. In a Korean study including 19 patients with catamenial hemoptysis, it was reported that 16 patients had such a history(6). Our patient also had a gynecological history. Our patient had CH, which is the pulmonary form of TES. The diagnosis of CH is usually made clinically and by excluding other causes, whereas the diagnosis of surgical patients can be made by histopathological demonstration of endometrial tissues. The clinical finding is periodic hemoptysis simultaneously with menstruation. In the report by Kim et al. 8 of 19 patients were diagnosed histopathologically and 11 were diagnosed clinically (7). Nodules can be seen on X-ray. These nodules are endometrial nodules formed as a result of the implantation of endometrial tissue into the lung parenchyma. Thoracic CT is useful for detecting ground-glass nodules and excluding other causes. In CT follow-up, the size of the nodules may change according to the menstrual cycle (6). In this patient, it was observed that the size of the nodule decreased on CT after the menstrual bleeding ended. While thoracic endometriosis is most commonly observed on the right side, there is no opinion proving this (8). In a study of 110 patients by Channabasavaiah et al., 85% of the lesions were on the right side, whereas in our patient, they were also on the right side (9). Since most pathologic lesions are located in the parenchyma in the distal bronchi, and intrabronchial lesions are usually absent, the role of bronchoscopy is limited in diagnosis (6,10). In the analysis study by Kim et al., no

intrabronchial lesion was found in 84% of patients who underwent bronchoscopy during hemoptysis attacks (7). However, Wang et al. reported that it was useful to perform bronchoscopy within the first two days after the onset of the menstrual cycle (11).

There are no guidelines for CH treatment. Patients presenting with hemoptysis usually start drugs such as transamin. Hormonal therapy is considered the first treatment option for CH. Oral contraceptives, progesterone derivatives, danazol, and gonadotropin-releasing hormone (GnRH) agonists are used in medical treatment (2). Surgical treatment is also performed due to failure of medical treatment and possible side effects. Operative techniques include wedge resection, lobectomy, pneumonectomy, and segmentectomy, and wedge resection gives better results compared to others (12). Preoperative marking can be performed with the help of CT and bronchoscopy, so the part to be resected lung can be determined more accurately. For example, Furuya et al. performed CT-guided marking with fluorescein sodium and resection of the 4th segment of the right lung (8). Lu et al. performed preoperative CT-guided wire marking(13). According to the literature, spontaneous regression is rarely observed in patients who do not receive any treatment (14).

Shin et al. preferred BAE as a different method in the treatment of CH. BAE is generally used as an alternative to surgery for hemoptysis due to causes such as lung cancer, bronchiectasis, and tuberculosis (6). The procedure was first performed in 1973, and many publications have emphasized its efficacy. However, this procedure may have rare complications, such as postembolism syndrome, stenosis, tracheoesophageal fistula, spinal cord injury, transient chest pain, and an esophageal ulcer (6,15). Kervancioglu et al. reported no recurrence for 3 months after BAE in a patient with CH(16). Katoh et al. did not find any pathology in the bronchial angiography of patients with pulmonary endometriosis (17). Shin et al. found a small nodular spotting on bronchial angiography and followed the patient for 5 months without recurrence (6).

There are no guidelines for the diagnosis and treatment of thoracic endometriosis have been published. It requires early diagnosis and treatment due to pneumothorax, hemothorax, and hemoptysis. The most effective method for diagnosing the disease is to determine whether the hemoptysis coincides with the menstrual cycle as a result of good anamnesis and then to perform consecutive thoracic CT scans in periods with and without menstrual bleeding. Thus, early diagnosis and treatment will improve the patient's standard of living and enable treatment without increasing costs.

Conflict of Interest Statement
There is no conflict of interest, personal or financial.

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Availability of Data and Materials
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Authors Contributions
HEY: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

HEC: Investigation; Validation; Formal analysis; Writing-original draft.

SEA: Investigation; Validation; Formal analysis; Writing-original draft.

RY: Data curation; Formal analysis; Invetigation; Validation; Writing- review & editing.

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REVIEW

Med J SDU / SDÜ Tıp Fak Derg ▸ 2024:31(3):277-287 doi: 10.17343/sdutfd.1498527

Effects of School-Based Interventions Implemented by Nurses for Children Aged 3-6 Years: A Systematic Review of Experimental Evidence

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Abstract

Objective

The 3-6 age period, which includes the pre-school, is when the child acquires essential habits, develops skills, and socializes. This systematic review was planned to examine the available evidence on the effectiveness of school-based interventions implemented by nurses and administered to preschool children.

Material and Method

The systematic review used a search to identify studies published between 2015 and 2024 from PubMed, Medline, Cochrane Library, ProQuest, Science Direct, and Web of Science databases.

Results

When the findings were examined, fifteen studies, including six randomized controlled trials and nine quasi-experimental studies, met the inclusion criteria. In the studies conducted, it was determined that the duration of the interventions applied only to children was between 2 and 16 sessions, the intervention periods of the studies that included parents along with children were between 8 and 30 sessions, and only 4 studies used theory or models. It was determined that the programs applied by nurses to children between the ages of 3-6 in the school environment provided children with knowledge and skills and had positive effects on the development of their physical, social, and emotional health.

Conclusion

Nurses are responsible for increasing children's knowledge and skills in schools and promoting healthy lifestyles. Nurses must collaborate with parents to ensure that children's health education at home and school complement each other. The results of the studies included in the systematic review should be cautiously interpreted due to the limited number of studies and small sample size. To obtain the best evidence on the effectiveness of interventions, randomised controlled trials aiming to improve social and emotional competencies are needed to evaluate comprehensive, high-quality, and long-term effects.

Keywords: Child, nursing, pre-school, school-based intervention

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Introduction

Children constitute a large proportion of the world's population (1). Protection, development, and maintenance of children's health, who constitute a significant portion of the world population, are among the primary objectives. Children's cognitive, social, emotional, and physical development progresses rapidly, especially in the first six years. Children whose development is supported with awareness in this period contribute to forming healthy generations. In addition, children supported in the desired quality show more development in their future lives. It is known that preschool education creates positive opportunities for children in terms of learning and development. In addition, preschool education institutions have an essential place in protecting and improving the health of young children (2,3). A review of the literature reveals that school-based programs support the cognitive, social, emotional, and physical development of preschool children and increase their well-being (4-7). It was determined that the studies were conducted by professionals such as teachers, psychiatrists, psychologists, social workers, and nurses (8).

The nursing profession encompasses care to protect and promote the health and well-being of individuals of all ages, parents, groups, and communities in all settings and to heal in case of illness (9). Nurses have a vital position to fulfil their roles as researchers, educators, and advocates as part of health promotion activities in schools, hospitals, and all areas where health services are provided. In schools, nurses can carry out interventions to support child development by addressing health holistically (10). In this period, nurses need to implement health-promoting nursing interventions to prepare the child for life in the best way (11). When the literature was examined, no study was found that analyzed experimental and quasi-experimental studies evaluating the effect of school-based interventions implemented by nurse researchers for preschool children. Our systematic review results are thought to shed light on creating nurse-led programs to meet the health needs of preschool children in schools.

The purpose of this systematic review was to evaluate the available data regarding the efficacy of nurse-led school-based treatments for preschoolers. As a result, responses to the following queries were requested:

1. What are the characteristics of the interventions nurses apply to preschool children in the school environment?

2. Which outcomes were measured in the interventions applied by nurses to preschool children in the school environment?

Material and Method

Study Design

The methodology for this study was a systematic review. The PROSPERO database has the study protocol registered (CRD42023467297). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were adhered to in this systematic study (12).

Eligibility Criteria for the Study

At the beginning of this study, we established the protocol according to the PICOS (Population, Intervention, Comparison, Outcomes and Study Design) approach. The PICOS approach formed the basis of the inclusion criteria in this study.

Inclusion Criteria

-Population: Studies in which the sample comprises healthy children aged 3-6 years or parents with children.

-Intervention: Activities carried out by nurses in the school environment with face-to-face education methods to children or children and their parents through different communication methods.

-Comparison: Studies with or without a control group

-Outcome: Social, emotional, and physical outcomes for children.

-Study type: Quasi-experimental studies and randomized controlled trials (RCTs)

Exclusion Criteria

Interventions for children with physical, mental, social, or psychological diagnoses.

Descriptive, cross-sectional, case-control, cohort studies, discontinuous time series, qualitative studies, feasibility studies, cost-effectiveness studies, study protocols, conference proceedings, or abstracts.

Search Methods

Two researchers independently analyzed research articles published in six databases between January 01, 2015, and July 31, 2024: PubMed, Medline, Cochrane Library, ProQuest, Science Direct, and

Web of Science. Additional records were identified through manual searching. The literature search used a systematic search strategy based on research questions in line with medical subject headings terms and synonymous combinations with topics across all items using Boolean ('AND' and 'OR') operators for each database. The reviews were analyzed from the identified databases using the following search strategy.

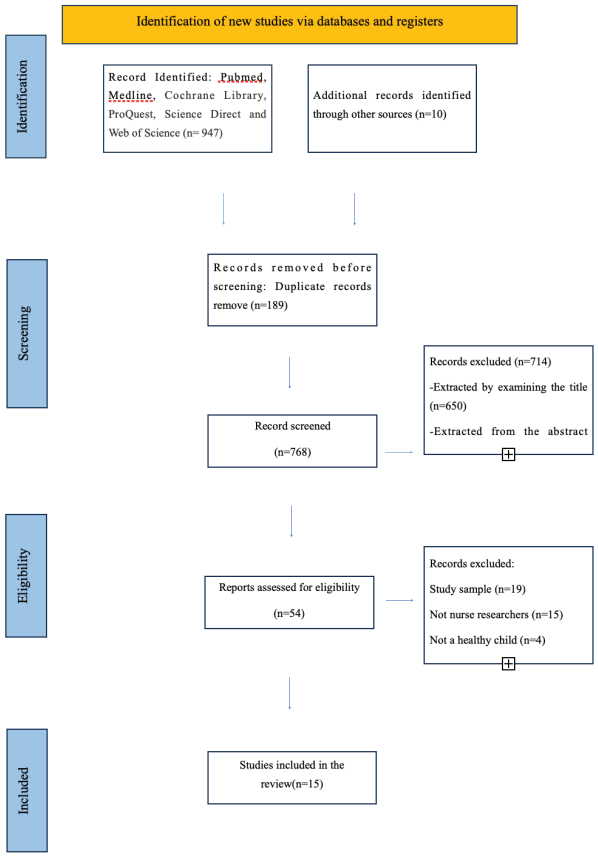

Figure 1:
The Flow diagram of the studies included in the review aligns with the PRISMA

(Child OR children OR kindergarten OR preschool OR pre-school OR nursery) AND (nursing OR 'school nurse' OR 'pediatric nursing') AND ('school based' OR 'school-based' OR 'school healthy') AND (intervention OR program OR programme OR training) AND ('randomis(z)ed Controlled Trial' OR 'controlled clinical trial' OR 'quasi-experimental'). Databases were searched using the English language.

EndNote X9, a reference management program, was used to save the studies obtained from scanning databases to eliminate duplications. The flow chart created in line with the PRISMA 2020 writing guide in the search strategy is given in Fig. 1

Study Selection and Data Extraction

All search results were imported into Endnote X9, a reference management software for data management. Titles and abstracts were assessed against the inclusion criteria, and two researchers discussed potential ambiguities. All data retrieved and classified as relevant or useful were obtained in full text and thoroughly assessed by two researchers to determine relevance. Inconsistencies were resolved through discussion and consensus between the two researchers.

Quality Assessment

The listed studies' methodological quality was evaluated separately by two researchers. The methodological quality of the studies was evaluated using the critical assessment instruments developed by the Joanna Briggs Institute (JBI) (13,14). JBI quality evaluation instruments were used to examine the studies' selection, performance, detection, and reduction of biases. The 13-item JBI is used in randomized controlled research. There are four possible responses to a question: "Yes," "No," "Unclear" (if the inquiry does not provide facts about a certain topic), and "Not applicable (NA)" (if the question is not answered). There are four possible scores for each question: one for "Yes," zero for "No," zero for "Unclear," and zero for "Not applicable." The overall result might range from 0 to 13 (13). JBI for quasi-experimental studies consists of 9 questions. Each question is scored as 'Yes' (1 point), 'No' (0 point), 'Unclear' (0 point), or 'Not applicable' (0 point). The total score ranged from 0 to 9 points (14). The high scores obtained from both tools indicate that the research is of methodological quality (13,14). Research with a substantial bias score of less than or equal to 50% of the items under examination were deemed to have low methodological quality. Nahcivan and Seckinli adapted the JBI critical evaluation instruments for experimental and quasi-experimental designs' Turkish validity and reliability for use in quality assessment (15).

Results

Characteristics of Studies

A total of 15 studies, including six RCTs (16-21) and nine quasi-experimental studies were included in the study (22-30). The studies were published between 2015 and 2024 and were conducted in the following countries: Turkey, Malawi, China, Egypt, Brazil, Hong Kong, and Spain. The general characteristics of the included studies are summarised in Table 1.

Risk of Bias within Studies

Table 2 and Table 3 list the studies that were evaluated using the JBI Critical Appraisal Checklist for RCTs and quasi-experimental designs.

Table 1 Main characteristics of the studies included in the systematic review (n = 15)

Author/ Year/ Country	Study Design	Sample Characteristics	Intervention	Control Group Intervention	Intervention Duration	Instruments	Primary Outcome	Theory/ Model
Bıyıkoglu Alkan et al., 2023/ Turkey	Randomized Controlled Trial T0: Before the start of the intervention T1: After intervention	(N= 65) (IG: 32; CG:33) Children Age: 5-6	Personel Hygiene Program	Standart School Curriculum	5 Sessions	Health Education Scale for Preschool Children (T0 T1) Control List for Children's Oral and Dental Health. (T0 T1)	After the intervention, a significant increase was observed in the scale scores of the intervention group for hand washing and oral dental health compared to the control group.	Bandura's Social Cognitive Theory
Altundağ and Körükçü, 2023/ Turkey	Quasi-Experimental Design T0: Before the start of the intervention T1: After intervention	(N=72) (IG: 36; CG: 36) Children Age: 5-6	Risk Reduction Education to Prevent Home Accidents	Standard School Curriculum	5 Sessions	A Determination of Home Environment Risks Form (T0 T1)	While the difference between the education health score averages of the entry and control groups was not found to be significant (p>.05), the difference between the groups after the education was found to be significantly significant (p<.05).	Theory or Model not used.
Mbakaya et al., 2023/ Malawi	Quasi-Experimental Design T0: Before the start of the intervention T1:After intervention T2: 3 months after completion of the intervention	(N=53) Children Age: 3-6	Hand Hygiene Program	-	16 Sessions	Handwashing Knowledge Scale (T0 T1 T2) Observational Checklist (T0 T1 T2)	A statistically significant difference was determined between hand hygiene knowledge scores and 5-step hand washing technique scores (p< .05).	Theory or Model not used.
Çıtak Tunç and Yavaş, 2022/ Turkey	Quasi-Experimental Design T0: Before the start of the intervention T1: After intervention T2: 4 weeks after completion of the intervention	(N=72) (IG: 40; CG: 32) Children Age: 3-6	Body Safety Training Program	Only Body Safety Training	7 Sessions	What If Situations Test (WIST). (T0 T1) (T2 only to the intervention group)	At the end of the program, it was determined that there was no statistically significant difference between the two groups (p > .05).	Theory or Model not used.
Kemer and İşler Dalgıç, 2022/ Turkey	Randomized Controlled Trial T0: Before the start of the intervention T1: After intervention	(N=87) (IG: 44; CG:43) Children Age: 5-6	Sexual Abuse Prevention Training Program	Standard School Curriculum	8 Sessions	Body Recognition and Body Safety Information Form (T0 T1)	It was determined that there was a statistically significant increase in the ability of children in the intervention group to recognize private parts of the body (p< .05). It was determined that the levels of noticing appropriate/inappropriate touching increased in the pre-test and post-test of the intervention and control groups, but there was no statistically significant difference between the two groups (p> .05). It was determined that the rate of knowing body protection skills was higher in the intervention group (p< .05).	Theory or Model not used.
Zhang et al., 2021/ China	Randomized Controlled Trial T0: Before the start of the intervention T1: 2 months after the start of the intervention T2:4 months after completion of the intervention T3: 6 months after completion of the intervention	N= 582 Children and Parent (IG: 289; CG: 293) Children Age: 3-4	Hand Hygiene Education Program (for children) Health Education Program (provided seminar, group interview, and WeChat via for parent)	Standard Hand Hygiene Curriculum	8 Sessions (for children) Eight weeks (for parents)	Hand Hygiene Behaviors of Children and Parents (T0 T1 T2 T3-for children) (T0 T1-for parents) Knowledge Level Questionnaire on Prevention of Communicable Diseases (T0 T1- for parents) School Attendance Form(T0 T3) Doctor's Diagnosis Laboratory Test Results	It was determined that families in the intervention group had better knowledge about hand hygiene and infection than families in the control group. It was determined that the number of absences due to infection was lower in children in the intervention group than in children in the control group.	Theory or Model not used.

Table 1 continued Main characteristics of the studies included in the systematic review (n = 15)

Author/ Year/ Country	Study Design	Sample Characteristics	Intervention	Control Group Intervention	Intervention Duration	Instruments	Primary Outcome	Theory/ Model
Akkaya and Sezici, 2021/ Turkey	Randomized Controlled Trial T0: Before the start of the intervention T1:After intervention	N: 100 (IG: 50; CG:50) Children Age: 4-6	Toothbrushing Program	Standard School Curriculum	15 Sessions	Toothbrushing Protocol (T0 T1) Plaque Index Evaluation Form (T0 T1)	Statistically significant improvements in tooth brushing and plaque control were found in children in the intervention group compared to children in the control group (p< .05).	Theory or Model not used.
Aboelmagd et al., 2019/ Egypt	Quasi-Experimental Design T0: Before the start of the intervention T1:After intervention	N: 100 (IG1:50 IG2:50) Children Age: 3-6	Education Program on Sexual Harassment Prevention	Both groups received the same training.	4 Sessions	Questionnaire on children's information on sexual harassment	It was determined that the education provided in schools located in two regions with different sociocultural levels was effective in increasing the knowledge and practices of preschool children regarding sexual harassment (p< .05).	Theory or Model not used.
Costa et al., 2019/ Brazil	Quasi-Experimental Design T0: Before the start of the intervention T1:After intervention	N: 39 Children age: 3-4	Nasal Hygiene Behavior Development Program	-	2 Sessions	With the observation of healthy behavior (T0 T1)	It was determined that there was a statistically significant difference in healthy nasal hygiene behaviors after the program (p< .05).	Theory or Model not used.
Suen and Cheung, 2019/ Hong Kong	Quasi-Experimental Design T0: Before the start of the intervention T1:After the intervention	N: 39 (IG:15; CG: 24) Children Age: 5-6	Hand Hygiene Program	Standard School Curriculum	4 Sessions	Hand Hygiene Knowledge Questionnaire for Children (T0) Use of Hand Scanner for Assessing the Coverage of Hand Sanitizer (T1)	After the application, it was determined that the intervention group had a higher level of knowledge about hand hygiene than the control group (p<.05). Significant improvements were observed in hand hygiene performance in the left palm and back of the hand, and in the right palm in the intervention group (p<.05).	Theory or Model not used.
Bermejo Martins et al., 2019/ Spain	Randomized Controlled Trial T0 = Before the start of the intervention T1 = After the intervention T2 = seven months after completion of the intervention	N: 37 (IG: 19; CG: 18) Children Age: 5-6	Social and Emotional Development Program (CRECES)	Standard School Curriculum	8 Sessions	Test Peabody-Iı Children (T0) Test Perceval V.2.0/ Child (T0 T1 T2) PKBS-Iı Scale/ Caregiver (T0 T1 T2) Chıp-Ce/Pe Questionnaire Child/ Caregiver (T0 T1 T2) Semi-StructuredInterview/ Caregiver (T1) Semi-Structured Interview/Caregiver And Children (T1)	It was determined that there were positive effects on the emotional perception and resilience levels of children in the intervention group (p<.05).	Model of Social and Emotional Competence Development
Ayyıldız and Cimete, 2019/ Turkey	Quasi-Experimental Design T0: Before the start of the intervention T1:After intervention T2:3 months after completion of the intervention	N: 67 Children and Parent (IG: 36; CG: 31) Children Age: 5-6	Social Skills Development Program (for children) A booklet containing positive and negative communication examples, violent behaviors, influencing factors, and preventive approaches was given (for Parents)	Standard School Curriculum	30 Sessions	Parental Attitude Scale (T0) Social Skills Assessment Scale (SSAS) (T0 T1 T2) Chart to Monitor Verbal and Behavioral Violence in Children (for six months) Parent Interview Form (T1)	It was determined that the increase in social skills scores and the decrease in violent behaviors of the children in the intervention group were higher than the control group children (p<.05). Parents in the intervention group stated that they started to empathize with their children and use the "I" language after the program.	Gardner's Multiple Intelligence Theory

Table 1 continued Main characteristics of the studies included in the systematic review (n = 15)

Author/ Year/ Country	Study Design	Sample Characteristics	Intervention	Control Group Intervention	Intervention Duration	Instruments	Primary Outcome	Theory/ Model
Akcan and Ergun, 2019/ Turkey	Quasi-Experimental Design T0: Fifth week of the education T1: 19th week of the education T2: End of the education year (38th week of the education period)	N: 90 (Children and Parent) (IG:45; CG:45) Children Age: 5-6	Aggressive Behavior Prevention Program (for children) (ABPP) A training program consisting of 8 face-to-face sessions to prevent aggressive behavior (for parents)	Standard School Curriculum	12 Sessions	Aggressiveness of the Eyberg Child Behavior Inventory (T0 T1 T2) Preschool Social Behavior Scale-Teacher Form (T0 T1 T2) Victimisation Scale (T0 T1 T2)	It was determined that the program reduced the aggressive behavior of children in the intervention group. There was no significant difference between the two groups in terms of peer bullying (p > .05).	Bandura's Social Cognitive Theory
Sezici et al, 2017/ Turkey	Randomized Controlled Trial T0: Before the start of the intervention T1: After intervention T2: 3 months after completion of intervention	N: 79 (IG: 39; CG: 40) Children Age: 4-5	Play Therapy	Standard School Curriculum	16 sessions	Social Competence and Behavior Evaluation Scale (T1 T2 T3)	It has been determined that play therapy helps preschool children develop their social, emotional and behavioral skills. It has also been determined that it provides benefits such as reducing children's fear and anxiety levels, improving their communication and coping skills, and increasing their self-confidence.	Bandura's Social Cognitive Theory
Sigaud et al, 2016/ Brazil	Quasi-Experimental Design T0: Before the start of the intervention T1: After intervention	N: 44 Children Age: 3-6	Tooth Brushing Program	-	Three sessions	Behavior Assessment Questionnaire (T1 T2)	A significant increase in the adoption of appropriate behaviors regarding tooth brushing was detected (p<0.01).	Theory or Model not used.

Interventional Methods

When the school-based studies included in this systematic review and conducted by nurse researchers for children aged 3-6 years were examined; Personal Hygiene Program to help children introduce personal hygiene habits (18), Hand Hygiene Program to improve hand hygiene (28,30), Nasal Hygiene Behavior Development Program to improve nasal hygiene behavior (26), Tooth Brushing Program to gain appropriate tooth brushing habits (16,29), Home Accident Prevention Risk Reduction Training to reduce the risk of home accidents (22), Sexual Abuse Prevention Training Program to increase body awareness and safety (19), Body Safety Training Program (27), Sexual Harassment Prevention Training Program (23), Social and Emotional Development Program (CRECES) (17) and Play Therapy (20) were applied to improve social and emotional competence. In the studies, it was determined that the duration of the intervention was between 2 sessions and 16 sessions.

When the studies included in the Systematic Review and conducted by nurse researchers and involving parents were examined, the Hand Hygiene Program (21) to increase hand hygiene, Aggressive Behavior Prevention Program, and Social Skills Program (24,25) were applied to prevent violent behaviours. In the studies, it was determined that the duration of the intervention was between 8 and 30 sessions.

Didactic Resources Used in Educational Interventions

It is effective to implement educational interventions with preschoolers to help them acquire proper conduct. The techniques and playthings used in these interventions ought to be suitable for the age group of the child. (29). When the studies in the systematic review were examined, it was found that modelling, using posters, stickers, game activities (21,28), animation video, models, toy with fluorescent features (18,30), puppets, stories, crepe paper with gelatin, picture card games (26), presentation with pictures, toy, educational music video (16), model, toy, toothbrushes, music video, picture cards (29), hide and seek game, model house (22), creative drama (19,27), videos, pictures (23), game activities (17,20), stories, cartoons, pictures, puppets, flower seeds, flower pots, emotion cards, and poetry (24,25).

Table 2 Table 2 Results of JBI critical appraisal tools for randomized controlled trials

JBI Critical Appraisal Checklist for Randomized Controlled Trial		Questions													Score
		1	2	3	4	5	6	7	8	9	10	11	12	13	
1	Bıyıkoglu Alkan et al., 2023	Unclear	No	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
2	Kemer and İşler Dalgıç, 2022	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
3	Zhang et al., 2021	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	9
4	Akkaya and Sezici, 2021	Unclear	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9
5	Bermejo Martins et al., 2019	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	9
6	Sezici et al., 2017	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	10

Question: 1- Was proper randomization used for the assignment of participants to treatment groups? 2- Was allocation to treatment groups concealed? 3- Were treatment groups similar at the baseline? 4- Were participants blind to treatment assignment? 5- Were those delivering treatment blind to treatment assignment? 6- Were outcomes assessors blind to treatment assignment? 7- Were treatment groups treated identically other than the intervention of interest? 8- Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analyzed? 9- Were participants analyzed in the groups to which they were randomized? 10- Were outcomes measured in the same way for treatment groups? 11- Were outcomes measured reliably? 12- Was appropriate statistical analysis used? 13- Was the trial design appropriate, and were any deviations from the standard randomized controlled trials design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Theories-Model Used in the Intervention

It was determined that the Social and Emotional Competence Development Model, Gardner's Multiple Intelligence Theory, and Bandura's Social Cognitive Theory were used in the studies (17,18,20,24,25).

Discussion

This systematic review provides a comprehensive analysis of school-based studies involving nurses as researchers and, to the best of our knowledge, is the first study to analyze experimental studies (Randomized Controlled Trials (RCTs) and quasi-experimental studies) on this topic.

When the compiled studies were examined, many activities of nurses, which can be defined as protecting and improving the health of preschool children and preventing diseases, were emphasized. Despite the various health education programs included in the studies, many of them focus on physical health (16,18,21,26,28,29,30) or it has been determined that programs are implemented for situations that may affect physical, emotional and social health together (19,22-25, 27). It was determined that only two of the studies conducted by nurse researchers in the preschool period, when development accelerated, were conducted to support social and emotional development such as communication and coping skills, emotional perception and resilience (17,20).

Interventions to Support Physical Health

Although effective hand washing is the cheapest, simplest, and easiest practice to control infections in the community, hand washing rates are pretty low. Hand hygiene training is fundamental in preventing epidemics that may affect the school population (31). Three studies in the review investigated the impact of a hand hygiene program (21,28,30). As a result of the studies, it was determined that the level of knowledge about hand hygiene increased after the intervention, significant improvements were observed in hand hygiene performance, and absenteeism due to infection decreased in the children in the intervention

Table 3 Results of JBI critical appraisal tools for quasi-experimental designs

JBI Critical Appraisal Checklist for Quasi -Experimental Studies		Questions									Score
		1	2	3	4	5	6	7	8	9	
1	Mbakaya et al., 2023	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8
2	Ayyıldız and Cimete, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
3	Akcan and Ergun, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
4	Costa et al.,2019	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	7
5	Suen and Cheung, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
6	Sigaud et al., 2016	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8
7	Aboelmagd et al., 2019	Yes	Yes	Unclear	No	Yes	Yes	Yes	No	Yes	6
8	Çıtak Tunç and Yavaş, 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
9	Altundağ and Körükçü, 2023	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9

Question:1- Is it clear in the study the 'cause' and the 'effect' (i.e., there is no confusion about which variable comes first)? 2- Were the participants included in any comparisons similar? 3- Were the participants in any comparisons receiving similar treatment/care other than the exposure or intervention of interest? 4- Was there a control group? 5- Were there multiple measurements of the outcome, pre- and post-intervention/exposure? 6- Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analyzed? 7- Were the outcomes of participants included in any comparisons measured in the same way? 8- Were outcomes measured reliably? 9- Was appropriate statistical analysis used?

group. Therefore, interventions carried out by nurses can increase the hand hygiene compliance of preschool children and parents, prevent the spread of diseases and infections, and play a significant role in reducing absenteeism from school due to infections.

Schools, essential in shaping children's healthy habits, pose a risk factor for respiratory tract infections. The findings of a cohort study of 1827 children from 1797 parents showed a rapid increase in respiratory tract infections two months after starting kindergarten (32). As a result of the Nasal Hygiene Behavior Program implemented for health promotion and prevention of respiratory diseases, it was determined that the children participating in the study were effective in healthy nasal hygiene behaviours (26).

Oral and dental health is an integral part of general health. Regular and effective tooth brushing protects oral and dental health and prevents dental caries. Dental caries in children can affect their nutrition, growth, and general development (33). In the tooth brushing behaviours reported by parents for the preschool population, it was determined that only 7.8% of children performed all procedures related to tooth brushing correctly (34). Since children spend a significant portion of their day at school, acquiring social skills and health habits, including oral health habits, is mainly applicable, which can lead to the acquisition of lifelong positive behaviours (35). In this context, it can be said that nurses are in an appropriate position to protect and improve preschool children's oral and dental health, especially in terms of providing information and support to children and parents (36). In the study conducted by Akkaya and Sezici, 2021; Sigaud et al., 2017, in which the effect of the tooth brushing program was examined, it was determined that significant improvements were observed in the adoption of appropriate behaviours related to tooth brushing as a result of both studies (16, 29).

In a study included in the compilation, a personal hygiene program was implemented to ensure hand and oral hygiene, and as a result of the program, a significant increase was observed in the scale scores of the intervention group for hand washing and oral dental health compared to the control group (18).

Interventions to Support Social and Emotional Health

Social-emotional competence is considered the cornerstone of academic performance and a protective element for the healthy development of children (37). It is recommended that children and adolescents be educated at an early age to acquire life skills that will increase their well-being. In this respect, schools are of great importance in preparing students for life. Nurses have vital responsibilities in promoting healthy lifestyles in schools, but there are limited studies supporting social and emotional development (38-40).

Considering the importance of early childhood experiences for later development, preschools are environments where children can develop and acquire essential skills to increase their academic, social, emotional, and behavioural competencies before starting primary school (41). When the studies conducted in the preschool period and included in the review are examined, the study conducted by Bermejo-Martins et al., 2019, which examined the effects of the CRECES, which has components such as emotional awareness, emotional regulation, emotional independence, social skills and life skills, were examined, positive effects were found on emotional perception and resilience in children in the intervention group (17). Similarly, Play Therapy was found to help preschool children improve their emotional and behavioural skills (20).

Interventions to Support Physical, Social and Emotional Health

Violence, which can have behavioural, emotional and social consequences, is a leading global public health problem. Interventions in early childhood are important in the primary prevention of violence. Positive behaviours or practices in this age group will prevent problems from occurring in later years (42). When the results of studies conducted to prevent violent behaviour were examined, it was determined that the practices reduced the violent behaviour of preschool children (24,25).

Accidents and injuries are common for people of all ages. However, children have a higher risk of injury because they are curious and desire to explore (43). A retrospective study examining the data of 1333 children admitted to the emergency department due to home accidents determined that 24.8% of children were between the ages of 3-6 (44). Preventing child injuries requires safety education, which includes imparting safety guidelines and best practices (43). A systematic review by Abbassinia et al. found that active interventions, such as education, are more effective in preventing home accidents in children under 5 (45). In the study examining the effects of Home Accident Prevention Risk Reduction Training implemented by nurse researchers on children, after the training in the intervention group, the mean scores of children for recognizing the circumstances that pose a risk of accident in the home environment were determined to increase significantly (22).

Child sexual abuse is a health issue that can have severe short- and long-term effects on children's physical, psychological, and social development. Any negativity experienced in early childhood, when children should create positive feelings about themselves, others, and the world, traumatically affects the child's development as a healthy individual (41,47). Therefore, children receive education on this issue as early as possible. The preschool period, which is the period when gender differences are learned and the child is curious about exploring his/her body and covers the age range of 3-6 years, is the appropriate age period for the child's body recognition and body safety education (27,47). Conducting interventional studies on this issue and planning preventive actions is essential. A systematic review study determined that most of the interventions were implemented by teachers in educational settings, focused on preschool and primary school children, and focused on improving children's understanding of their own bodies and appropriate and inappropriate touch (47). It is emphasized that child and school health nurses are in an ideal position to inform children and parents to prevent sexual abuse (48). The programs included in the systematic review and conducted by nurses using creative drama, videos, and pictures were found to be effective in helping children in the intervention group to know the private parts of the body and body protection skills (19,23,27).

Limitations

This systematic review has some limitations. The inclusion of articles that were only available in English was the systematic review's most significant constraint. If articles published in other languages are included, the number of articles reviewed will increase. The reviewed studies varied in terms of intervention types and follow-up periods. The study is limited to synthesizing the research findings in the systematic review.

Implications for Practice

Schools are suitable environments for the development and maintenance of children's health. School health services; are an important service in protecting and developing health to protect the physical, social and

mental health of children and adolescents, and in providing the foundation of future generations and a healthy society. Studies have shown that nurses have significant effects on protecting and developing the health of school children.

It is thought that this systematic review will guide the interventions planned to be applied to preschool children in the school environment regarding intervention topics, intervention duration, follow-up period, results obtained, and theories used. Studies need to evaluate the effectiveness, applicability, acceptability, and possible difficulties in implementing health education programs for preschool children and parents with children to gain positive health behaviours that will last throughout life.

It was determined that nurse researchers used the Emotional Competence Development Model, Gardner's Multiple Intelligence Theory, and Bandura's Social Cognitive Theory in school-based interventions applied to preschool children (17,18,20,24,25). Planning research based on theories and models provides a systematic approach to evaluating the effectiveness of the intervention (49). Therefore, it is thought that researchers will be guided by the theory- or model-based planning of studies carried out by nurses.

Conclusion

As a result of the systematic review of the studies included in the research, it was determined that school-based programs implemented by nurses and focusing on health promotion for preschool children were effective in improving the physical, social and emotional health of children. Our findings underline that nurses are more focused on improving children's physical health and that more studies are needed to improve children's social and emotional competencies such as emotional awareness, emotion regulation, empathy, coping, and communication skills. These results should be interpreted with caution due to the limited number of studies and small sample size. Comprehensive, high-quality RCTs assessing long-term effects are needed to obtain the best evidence on the effectiveness of interventions.

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