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## ORIGINAL RESEARCHES



## CASE REPORT



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ORIGINAL RESEARCH

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# Relationship Between D-dimer/Lymphocyte Ratio and CURB-65 Scores in COVID-19 Pneumonia Prognosis and Mortality

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## Abstract

**Objective:** To determine effective factors for predicting mortality and prognosis of COVID-19 pneumonia. We aimed to evaluate the efficacy of D-dimer, lymphocyte count, D-dimer/lymphocyte ratio (DLR), and confusion, uremia, respiratory rate, blood pressure, age ≥65 years (CURB-65) score in predicting 30-day mortality and prognosis.

**Materials and Methods:** We retrospectively analyzed 248 patients with COVID-19 pneumonia presenting. Age, gender, complaint, history of chronic disease, reverse transcription polymerase chain reaction results, D-dimer levels, lymphocyte count, DLR, and CURB-65 scores were recorded, and receiver operating characteristic (ROC) curve analysis was performed to predict 30-day mortality.

**Results:** It was found that the CURB-65 score, D-dimer level, lymphocyte count, and DLR value at the time of admission were significant predictors of mortality within 30 days ($p<0.001$). In the ROC analysis for the diagnostic value of the CURB-65 score and DLR for 30-day mortality, the area under the curve value for the CURB-65 and DLR were 0.862 and 0.82, respectively ($p<0.001$). The median CURB-65, D-dimer, lymphocyte count, and DLR of patients who required intensive care unit were significantly different ($p<0.001$).

**Conclusion:** In patients with COVID-19 pneumonia, CURB-65 score, DLR level, and disease severity are correlated at the time of presentation to the emergency department. Our study is the first to compare the correlation. We found that a positive correlation between biomarkers may be helpful for assessing mortality and prognosis and predicting the need for ICU in patients with COVID-19 pneumonia.

**Keywords:** CURB-65, COVID-19, D-dimer/lymphocyte ratio, emergency medicine

## Introduction

COVID-19 is a disease with multisystem involvement that develops as a result of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection. COVID-19 can be asymptomatic or cause mild, moderate, or severe clinical pictures [1]. Although pulmonary involvement with fever, cough, and dyspnea is at the forefront of COVID-19 clinics, cardiac, gastrointestinal, hepatic, renal, neurologic, olfactory, gustatory, ocular, cutaneous, and hematologic symptoms may also occur due to the involvement of extrapulmonary structures [2]. Most hospitalizations and mortality rates are attributable to lung involvement and associated respiratory failure [3]. COVID-19 is diagnosed by reverse transcription polymerase chain reaction (RT-PCR) of SARS-CoV-2 [4].

The lack of biomarkers for the clinical presentation and prognosis of patients makes it difficult to predict mortality and intensive care unit (ICU) needs.

Laboratory parameters have been studied to predict poor prognosis in patients infected with SARS-CoV-2. Increased D-dimer, cardiac troponins, white blood cell, lactate, lactate dehydrogenase, creatinine phosphokinase, and creatinine

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levels, decreased lymphocyte and platelet counts, and low albumin levels are associated with poor prognosis [5-7].

There are various scoring systems used to predict prognosis in pneumonia. The confusion, uremia, respiratory rate, blood pressure, age ≥65 years (CURB-65) score is a scoring system used to predict 30-day mortality in patients with pneumonia. There are publications reporting that the CURB-65 score is reliable in predicting mortality due to COVID-19 pneumonia [8].

In addition, SARS-CoV-2 infection is associated with coagulopathy, which increases mortality and is characterized by elevated levels of procoagulant factors, such as fibrinogen and predominantly D-dimer [9,10]. In patients with severe SARS-CoV-2 infection, lymphopenia with hypocytokinemia is also noted [11].

Accordingly, the aim of this study was to investigate the efficacy of D-dimer level, lymphocyte count, D-dimer/lymphocyte ratio (DLR), and CURB-65 score in predicting mortality and prognosis in SARS-CoV-2 PCR-positive patients with pneumonia diagnosed by computed thoracic tomography.

## Materials and Methods

This study was conducted Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital (approval number: 2011-KAEK-25 2020/05-02, date: 27.05.2020). Data were obtained from the hospital information management system and patient files. We conducted this study by retrospectively analyzing the data of patients presenting to the adult emergency department of a tertiary hospital with COVID-19 symptoms between April and September 2020.

During the study period, 5988 patients were admitted. Patients with incomplete study data, patients under 18 years of age, patients with negative RT-PCR tests, patients without COVID-19 pneumonia, and pregnant patients were excluded from the study. RT-PCR was positive in 612 non-pregnant patients aged 18 years and older for whom complete study data were available. A total of 248 patients with a positive RT-PCR test and pneumonia were included in the study.

A standardized study data entry form was created, and demographic information (age, gender), date of admission to the emergency department, vital signs (respiratory rate, Glasgow Coma Score (GCS), systolic blood pressure, diastolic blood pressure, oxygen saturation ($SPO_2$), presence/absence of confusion, admission complaints, chronic diseases, thoracic computed tomography imaging and radiology specialist interpretation, laboratory values (BUN, D-dimer, lymphocyte count, DLR), RT-PCR results, and CURB-65 scores were recorded from patients' files. The patient's outcome status in the emergency department (discharge, hospitalization in the ward, ICU hospitalization, and exitus) was added to the data. In addition, the need for ICU admission within 1 week and mortality within 30 days were monitored. After the study was completed, the data in the study forms were saved in an electronic format for statistical analysis.

### Statistical Analysis

IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY: USA. Released 2012) was used for statistical analysis. Mean ± standard deviation or median values and an interquartile range (IQR) of 25-75% were used to express descriptive statistics, whereas categorical variables were explained as numbers and percentages (%). The Kolmogorov-Smirnov test was used to determine the normality of data distribution. Levene's test was used to determine whether the assumption of homogeneity of variances was satisfied. The significance of the difference between the groups in terms of continuous numerical variables for which parametric test statistical assumptions were met was examined using Student's t-test, while the significance of the difference in terms of continuous numerical variables for which parametric test statistical assumptions were not met was evaluated using the Mann-Whitney U test. Receiver operating characteristic (ROC) curves were drawn to investigate the diagnostic values of CURB-65, D-dimer, lymphocyte count, DLR, and 30-day mortality. Logistic regression analysis was performed to identify factors affecting mortality. Results were presented at a 95% confidence interval. $P<0.05$ was considered statistically significant.

## Results

A total of 248 patients were included in the study. The median age of the patients was 63 (IQR 51-74) years. While 125 (50.4%) of the patients were male, and 150 (60.5%) had a history of comorbidity. The most common comorbidities were hypertension (33.9%) and diabetes mellitus (27.8%). The most common symptoms and signs were shortness of breath in 101 (40.7%) and cough in 97 (39.1%) patients, respectively. One-hundred and eighty three (73.8%) of the patients were hospitalized in the ward, while 24 (9.68%) were in the ICU. The clinical and demographic data of the patients are shown in Table 1.

The median CURB-65 score was 1.0 (IQR 0-2.0), the mean D-dimer level was 2.27±7.50 µg/mL, the mean lymphocyte count was 2.05±8.61 $10^3$/mL, and the mean DLR was 2.47±6.03 (Table 2).

Differences in CURB-65 score, D-dimer level, lymphocyte count, and DLR with 30-day mortality. As a result, the median CURB-65 score, D-dimer level, lymphocyte count, and DLR of patients who died within 30 days were statistically significantly different from those in whom mortality did not develop ($p<0.001$) (Table 3).

In the ROC analysis of the diagnostic value of the variables for 30-day mortality, the area under the curve (AUC) of CURB-65 was 0.862 (p<0.001) and the AUC of DLR was 0.820 (p<0.001).

The sensitivity of CURB-65 for 30-day mortality was 76.6% and specificity 82.1%, the sensitivity of D-dimer was 70.2% and specificity 70.1%, the sensitivity of lymphocyte count was 61.7% and specificity 10.4%, and the sensitivity of DLR was 74.5% and specificity 74.6% (Table 4).

There was a difference in the median CURB-65, D-dimer, lymphocyte count, and DLR of hospitalized patients in the ward with the need for ICU admission within 1 week. As a result, the median CURB-65, D-dimer, lymphocyte count, and DLR of patients who required ICU were significantly different (p<0.001) (Table 5).

**Table 1. Clinical and demographic data**

| | | n | % |
|---|---|---|---|
| **Gender** | **Female** | 123 | 49.6 |
| | **Male** | 125 | 50.4 |
| Chronic diseases | | 50 | 60.5 |
| Asthma | | 15 | 6 |
| COPD | | 12 | 4.8 |
| DM | | 69 | 27.8 |
| Hypertension | | 84 | 33.9 |
| Neurological disorders | | 15 | 6 |
| Cardiovascular diseases | | 35 | 14.1 |
| CRF | | 8 | 3.2 |
| Others | | 8 | 3.2 |
| Symptoms | | | |
| Confusion | | 12 | 4.8 |
| Shortness of breath | | 101 | 40.7 |
| Cough | | 97 | 39.1 |
| Fever | | 53 | 21.4 |
| Fatigue | | 46 | 18.5 |
| Nausea-vomiting | | 9 | 3.6 |
| Headache | | 10 | 4.0 |
| Joint pain | | 11 | 4.4 |
| Others | | 39 | 18 |
| Emergency service outcome | Outpatient follow-up | 39 | 15.7 |
| | Service admission | 183 | 73.8 |
| | Intensive care hospitalization | 24 | 9.7 |
| | Exitus | 2 | 0.8 |
| Intensive care hospitalization within a week | | 66 | 26.6 |
| 30 day mortality | | 47 | 19 |

COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CRF: Chronic renal failure

Logistic regression analysis was performed using the variables of age, sex, and comorbidity history, which may affect 30-day mortality. Age [exp. beta=1.051 (95% confidence interval 1,026-1,077), p<0.001] was found to be an effective factor for the diagnosis of 30-day mortality.

In the analysis performed to investigate whether there was a relationship between the patients' CURB-65, D-dimer, lymphocyte count, and DLR ratios, a significant positive correlation was found between DLR and CURB-65 and D-dimer, respectively [(p<0.001, r=0.409), (p<0.001, r=0.878)], and a negative correlation was also detected with the lymphocyte count (p<0.05, r=-0.587) (Table 6).

**Table 2. Analysis of variables**

| | |
|---|---|
| Age, median (IQR 25-75) | 63 (51-74) |
| GCS, median (IQR 25-75) | 15 (15-15) |
| Respiration rate/minute median (IQR 25-75) | 17 (14-21) |
| BUN-mg/dL mean ± standard deviation | 21.56±16.32 |
| DBP-mmHg, median (IQR 25-75) | 80 (70-84) |
| SBP-mmHg, median (IQR 25-75) | 130 (120-140) |
| $SPO_2$-mmHg (mean ± standard deviation) | 93.22±5.65 |
| CURB-65, median (IQR 25-75) | 1 (0-2) |
| D-Dimer-mcg/mL, mean ± standard deviation | 2.27±7.50 |
| Lymphocyte count-mcL, (mean ± standard deviation) | 2.05±8.61 |
| DLR, (mean ± standard deviation) | 2.47±6.03 |

GCS: Glasgow Coma Scale, BUN: Blood urea nitrogen, $SPO_2$: Oxygen saturation, DLR: D-dimer/lymphocyte ratio, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age≥65 years

**Table 3. Thirty-day mortality analysis of variables**

| | 30-Day mortality | n | Median (IQR: 25-75) | p* |
|---|---|---|---|---|
| CURB-65 | No | 201 | 1.0 (0-1.0) | **<0.001** |
| | Yes | 47 | 2.0 (2.0-2.0) | |
| | Total | 248 | 1.0 (0-2.0) | |
| D-dimer - mcg/mL | No | 201 | 0.67 (0.38-1.08) | **<0.001** |
| | Yes | 47 | 1.97 (0.87-4.46) | |
| | Total | 248 | 0.77 (0.42-1.35) | |
| Lymphocyte mcL | No | 201 | 1.40 (0.95-1.95) | **<0.001** |
| | Yes | 47 | 0.80 (0.52-1.25) | |
| | Total | 248 | 1.31 (0.80-1.87) | |
| DLR | No | 201 | 0.44 (0.24-0.87) | **<0.001** |
| | Yes | 47 | 2.41 (0.82-6.21) | |
| | Total | 248 | 0.54 (0.29-1.57) | |

*Mann-Whitney U test, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age ≥65 years,

n: Frequency DLR: D-dimer/lymphocyte ratio, IQR: Interquartile range

**Table 4. ROC analysis for the 30-day mortality prediction of variables**

| AUC (95% CI) | p | Risk factor | Cut-off | Sensitivity % | Specificity % |
|---|---|---|---|---|---|
| 0.862 (0.812-0.912) | <0.001 | CURB-65 | 1.5 | 76.6 | 82.1 |
| | | | 2.5 | 23.4 | 98.0 |
| | | | 3.5 | 12.8 | 100.0 |
| 0.780 (0.708-0.852) | <0.001 | D-dimer | 0.865 | 76.6 | 62.2 |
| | | | 0.945 | 70.2 | 70.1 |
| | | | 1.150 | 66.0 | 77.1 |
| 0.270 (0.186-0.354) | <0.001 | Lymphocyte | 0.675 | 61.7 | 10.4 |
| | | | 1.095 | 31.9 | 29.9 |
| | | | 1.195 | 27.7 | 34.3 |
| 0.820 (0.758-0.882) | <0.001 | DLR | 0.701 | 85.1 | 69.2 |
| | | | 0.830 | 74.5 | 74.6 |
| | | | 0.901 | 72.3 | 75.6 |

AUC: Area under the curve, CI: Confidence interval, DLR: D-Dimer/Lymphocyte ratio, ROC: Receiver operating characteristic, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age ≥65 years

**Table 5. Analysis of variables from service to ICU admission in a week**

| | ICU need | n | Median (IQR: 25-75) | p |
|---|---|---|---|---|
| **CURB-65** | No | 141 | 1.0 (0-1.0) | **<0.001** |
| | Yes | 42 | 2.0 (1.0-2.0) | |
| | Total | 183 | 1.0 (0-1.0) | |
| **D-dimer - mcg/mL** | No | 141 | 0.63 (0.37-0.96) | **<0.001** |
| | Yes | 42 | 1.62 (0.91-3.84) | |
| | Total | 183 | 0.75 (0.42-1.19) | |
| **Lymphocyte - mcL** | No | 141 | 1.48 (1.03-2.07) | **<0.001** |
| | Yes | 42 | 0.84 (0.60-1.61) | |
| | Total | 183 | 1.33 (0.85-1.95) | |
| **DLR** | No | 141 | 0.37 (0.22-0.75) | **<0.001** |
| | Yes | 42 | 1.70 (0.85-6.31) | |
| | Total | 183 | 0.50 (0.28-1.16) | |

n: Frequency; DLR: D-dimer/lymphocyte ratio; ICU: Intensive care unit, IQR: Interquartile range, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age ≥65 years

**Table 6. CURB-65, d-dimer, lymphocyte count and DLR correlation analysis**

| | | | CURB-65 | D-dimer | Lymphocyte count | DLR |
|---|---|---|---|---|---|---|
| Spearman's rho | CURB-65 | r | 1,000 | 0.420* | -0.217* | 0.409* |
| | | p | | **<0,001** | 0.001 | **<0.001** |
| | D-dimer | r | 0.420* | 1,000 | -0.189* | 0.878* |
| | | p | **<0,001** | - | 0.003 | **<0.001** |
| | Lymphocyte count | r | -0.217* | -0.189* | 1,000 | -0.587* |
| | | p | 0.001 | 0.003 | - | **<0.001** |
| | DLR | r | 0.409* | 0.878* | -0.587* | 1,000 |
| | | p | **<0.001** | **<0.001** | **<0.001** | - |

*Spearman's correlation analysis,

DLR: D-dimer/lymphocyte ratio, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age ≥65 years

## Discussion

Rapid and reliable biomarkers and scoring systems are critical for prognosis and mortality in patients with COVID-19 pneumonia in emergency departments. Unfortunately, we do not have practical usable and easy-to-perform tests in this regard. In this retrospective study, we aimed to investigate whether CURB-65 levels, D-dimer levels, lymphocyte counts, and DLR, which can be easily performed at every hospital, can be used to predict the prognosis and mortality of patients with COVID-19 pneumonia.

The CURB-65 is a scoring system used to predict 30-day mortality in patients with pneumonia, classify patients as low, intermediate, and high risk, and decide on outpatient follow-up, hospital ward, or ICU hospitalization. The higher the CURB-65 score, the higher the mortality rate. In a study by Satici et al. [12] a CURB-65 score of 2 or higher was found to be discriminative in predicting 30-day mortality. Işler and Kaya [13] found that the CURB-65 score was an independent predictor of mortality in patients with COVID-19 pneumonia.

Nguyen et al. [14] reported that the CURB-65 score was strongly associated with poor prognosis. However, in the same study, it was stated that it would not be reliable in determining the outpatient follow-up of patients with COVID-19 pneumonia because 36 of 171 patients with CURB-65 score 0-1, which is considered a low-risk group, had a poor prognosis. In a multicenter retrospective cohort evaluating severity indices in COVID-19 pneumonia, the AUC of the CURB-65 score in predicting mortality was found to be 0.825 and it was stated that the CURB-65 score was suboptimal in predicting the need for intensive care [15].

In our study, the median CURB-65 score of the patients was 1.0. On the other hand, the median CURB-65 score of patients who developed mortality within 30 days was 2.0. In the ROC analysis of the diagnostic value of the CURB-65 score for 30-day mortality, the AUC was 0.862. In the study by Zhou et al. [16] it is seen that patients with a CURB-65 score of 2 had the highest number of deaths. In our study, the CURB-65 score of patients who required ICU within a week and had a fatal course was 2. Patients with COVID-19 pneumonia who had a CURB-65 score of 2 were likely to need ICU but were ignored and hospitalized in the wards. This should be taken into consideration in pneumonia that may develop in possible COVID-19 outbreaks because, in community-acquired pneumonia, a CURB-65 value of 3-5 for the need for ICU increases the mortality risk (15-40%) [17,18]. In our study, unlike CAP, we believe that a CURB-65 value of 2 is more appropriate for the need for ICU in COVID-19 pneumonia.

According to many studies, a high D-dimer level is a reliable coagulation parameter for predicting poor prognosis and mortality. D-dimer levels were found to be higher in patients requiring ICU admission [19,20]. In our study, a correlation was found between high D-dimer levels and 30-day mortality. In the ROC analysis of the diagnostic value of D-dimer level for 30-day mortality, the AUC was 0.780. Among the patients who were hospitalized in the ward, D-dimer levels were higher in those who needed ICU within one week. In our study, the need for ICU significantly increased in patients with D-dimer levels above 1.62 mg/L. In addition, the D-dimer level was found to be 1.97 mg/L for 30-day mortality.

The relationship between the need for ICU within 1 week and the development of one-month mortality with D-dimer levels was found to be consistent with the literature. In a case-control study by Yao et al. [21] it was reported that D-dimer was the only parameter that was significantly correlated with mortality in multivariate analysis, and a D-dimer level of >2.14 mg/L was significant. Therefore, elevated D-dimer levels at presentation may indicate poor prognosis. Hachim et al. [22] stated that COVID-19 patients with D-dimer levels of >1.5 mg/dL, urea levels of >6.5 mmol/L, and troponin levels of >13.5 ng/mL need to be admitted to the ICU due to the risk of a more mortal course.

In many studies, lymphopenia has been associated with the severity of COVID-19, accepted as a prognostic factor in the course of the disease, and shown to be a mortality marker [23,24]. In a study by Tan et al. [25] the lymphocyte count was found to be associated with mortality; the lymphocyte count and the ratio of patients who died were significantly lower than surviving patients. The cutoff lymphocyte count was found to be ≤0.65 $10^9$/L [25]. In a meta-analysis, the presence of lymphopenia at presentation was associated with severe disease progression and death [26]. A meta-analysis by Huang and Pranata [27] found a relationship between low lymphocyte counts and COVID-19 severity, ARDS development, and mortality.

The peripheral blood lymphocyte counts and subsets have been shown to be significantly lower than normal in the majority of COVID-19 patients, especially in severe cases with previously reported and confirmed SARS [28]. In our study, a statistically significant relationship was found between low lymphocyte counts and 30-day mortality. The cutoff lymphocyte count was found to be ≤0.80 $10^9$/L. Similar to other studies, there was a relationship between lymphopenia presence and mortality.

DLR can be used to evaluate both the effects of SARS-CoV-2 infection on immune cells and the coagulopathy caused by it [10,29]. In addition, DLR can be a risk factor indicator in the mortality of COVID-19 patients. Peng et al. [30] found that the combination of DLR was more effective against COVID-19-induced mortality than considering D-dimer or lymphocyte values individually.

Similarly, our study found that DLR was more effective in predicting the need for ICU admission within 1 week and 1 month in patients with COVID-19 pneumonia than D-dimer elevation and low lymphocyte levels.

These findings suggest that DLR can also be used as a marker to determine the need for ICU within 1 week.

### Study Limitations

This study has several limitations. First, the findings were obtained from a limited number of patients admitted to our emergency department. Second, this was a single-center, retrospective study.

## Conclusion

We believe that lymphocyte count, CURB-65 score, D-dimer level, and DLR, which are among the parameters studied to predict the prognosis of COVID-19 pneumonia, can be used to predict the need for ICU hospitalization within 1 week and 30-day mortality. We believe that the use of these values, which can be easily obtained at every hospital, can reduce mortality and determine the need for ICU admission. In this regard, studies with higher participation rates should be conducted.

### Ethics

**Ethics Committee Approval:** This study was conducted Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital (approval number: 2011-KAEK-25 2020/05-02, date: 27.05.2020).

**Informed Consent:** A retrospective study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: B.S., Y.İ., H.K., Concept: M.Y., M.O.A., Design: B.S., M.O.A., Data Collection or Processing: B.S., Y.İ., H.K., Analysis or Interpretation: B.S., H.K., M.Y., M.O.A., Literature Search: B.S., Y.İ., M.O.A., Writing: B.S., Y.İ., H.K., M.Y., M.O.A.

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# HAPS (Harmless AP Score) in Determining Poor Prognosis in AP

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## Abstract

**Objective:** Acute pancreatitis (AP) is a common disease of the gastrointestinal tract. Gallstones are the most common cause of AP etiology. Most prognosis scoring systems are non-practical in emergency departments (EDs). Harmless acute pancreatitis score (HAPS) is a scoring system that is easily used for detecting non-severe AP (SAP).

**Materials and Methods:** In this study, patients aged >18 years and with International Classification of Diseases code K85 were retrospectively reviewed. After excluding trauma, recurrent pancreatitis, and cancer, 150 patients were included in the study. First, all patients were divided into two groups; HAPS0 and HAPS+. Radiological examination, necrosis, need for intensive care unit, mortality rates, and hospitalization durations of HAPS0 and HAPS+ were compared. Then, we calculated the HAPS and Ranson score (RS) for all patients and compared their odds ratio (OR).

**Results:** Of all patients, 58.5% were male. Biliary pancreatitis was observed in 72% of HAPS0 patients and 66.2% of HAPS+ patients. There was no in-hospital mortality in the HAPS0 group. ORs were 4.229 and 0.885 for HAPS and the RS, respectively.

**Conclusion:** HAPS can be useful for discriminating between non-severe and SAP at the ED.

**Keywords:** AP, prognosis, HAPS, Ranson

## Introduction

Acute pancreatitis (AP) is a gastroenterological disease that is frequently associated with hospitalization, with more than 275,000 cases per year [1,2]. The incidence of AP is 34 per 100.000 people per year [3]. The most common causes of AP are gallstones and alcohol abuse, which account for 30-50% of the etiology [4].

The diagnosis of AP is based on the presence of two of the following three features: (a) Abdominal pain compatible with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back); (b) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (c) characteristic findings of AP on radiological imaging [contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging or transabdominal ultrasonography] [5-7].

The following diagnosis, clinicians must determine the severity of AP to inform subsequent management. The Atlanta classification, revised in 2012, categorizes AP according to severity as follows: mild, moderate, and severe [1]. Patients were divided into two groups: those with severe AP (SAP) and those without (non-SAP), based on the Harmless AP Score (HAPS) and the Ranson score (RS).

The mortality rate in all acute cases was between 3% and 10%. In patients with SAP, this rate increases to 36-50% [8,9].

Although benign AP can have a poor prognosis, it is important to accurately assess disease severity to select an appropriate initial treatment to improve prognosis. The severity of the disease is correlated with the presence and extent of pancreatic necrosis and the extent of inflammatory changes [10].

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Despite the limitations of scanning in the first 48 hours, which may not fully develop necrosis and its extent, CECT is considered the gold standard for the diagnosis of necrotizing pancreatitis [11]. At the emergency department (ED), CECT was utilized to identify local complications (necrosis, abscess, etc.) subsequent to examination, laboratory tests, or consultation.

In Türkiye, the number of admissions to EDs exceeded 130 million in 2022. The proportion of all hospital admissions resulting in admission to the ED was 28% [12]. Consequently, there is an increasing need for simple, effective, and cost-efficient scoring systems to predict prognosis. Several scoring systems have been developed to determine the severity of AP, including the RS, Bedside Index of Severity in AP (BISAP), Acute Physiology and Chronic Health Examination (APACHE II), and modified Glasgow Prognostic Score (mGPS). The limitations of these scoring systems include the time required to complete them, which can range from 24 to 48 hours, and the difficulty of applying many of the parameters in EDs.

Ranson et al. (13) established the Ranson criteria for the prognosis of AP, which included 11 parameters. Each criterion was assigned a value of 1. A score of less than 3 was considered to indicate a non-severe form of AP, whereas a score of 3 was considered to indicate severe pancreatitis (Table 1) [13]. Admission RS was used.

In 2009, Lankisch et al. (14) reported the results of a prospective study in which they found a scoring system called HAPS, which is capable of detecting non-severe pancreatitis with ease. HAPS0 was defined as patients who did not exhibit signs of peritonitis, had a serum creatinine level of less than 2 mg/dL, and had a hematocrit level of less than 43% in men and less than 39.6% in women at the time of admission. Consequently, patients classified as HAPS0 did not require further examination or interventional treatment [14].

Although other prognostic systems place greater reliance on laboratory values, HAPS incorporates physical examination (palpation).

It is recommended that HAPS be employed to distinguish between mild and severe cases, as evidenced by the literature. The objective of this study was to demonstrate that HAPS is effective in detecting severe cases and contribute to the existing literature on this topic.

## Materials and Methods

We conducted this retrospective study in the ED of a tertiary university hospital, to which approximately 300.000 patients applied annually. Approval for this study was session of the Non-interventional Research Ethics Committee of Fırat University (decission number: 2020/02-52, date: 10.02.2022). The files of patients who applied to the ED between 2019-2022 and entered the K85 ICD-10 code were retrospectively reviewed in the patient registration system. Based on the results of laboratory and radiological examinations, 150 patients were included in the study, and trauma, cancer, and recurrence cases were excluded from the study. The study was planned as a retrospective file review, informed consent was not obtained from the patients.

The demographic, clinical, laboratory, and radiological data of 150 patients were recorded as AP. We initially divided all patients into two groups according to HAPS scores: HAPS0 and HAPS+. The rate of computed tomography, rate of necrosis, need for intensive care unit (ICU), death rates and hospitalization durations of HAPS0 and HAPS+ were statistically compared.

In-hospital mortality, ICU admission, and necrotizing pancreatitis were considered poor prognoses, and then we compared the prediction value of HAPS and Ranson for poor prognosis.

**Table 1. Ranson criteria [13]**

| Biliary | Non-biliary |
|---|---|
| At admission or diagnosis | At admission or diagnosis |
| Age> 70/year | Age> 55/year |
| WBC> 18000/$mm^3$ | WBC> 16000/$mm^3$ |
| Glucose> 220 mg/dL | Glucose> 200 mg/dL |
| LDH> 400 IU/L | LDH> 350 IU/L |
| AST> 250 IU/L | AST> 250 IU/L |
| During the initial 48 h, | During the initial 48 h, |
| Hematocrit fall> 10% | Hematocrit fall> %10 |
| BUN rise > 2mg/dL | BUN rise> 5mg/dL |
| Calcium< 8 mg/dL | Calcium< 8 mg/dL |
| Arterial $PO_2$< 60 mm Hg | Arterial $PO_2$<60 mm Hg |
| Base deficit> 5 mEq/L | Base deficit>4 mEq/L |
| Estimated fluid sequestration> 4 lt | Estimated fluid sequestration>6 lt |

WBC: White blood cell, LDH: Lactic dehydrogenase, AST: Glutamic oxaloacetic transaminase, BUN: Blood urea nitrogen

Each criterion is 1 point. A score of less than 3 is considered non-severe, and a score of 3 or more is considered severe pancreatitis [13].

### Statistical Analysis

Data were analyzed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous variables are expressed as mean±standard deviation. Categorical data are expressed as numbers and percentages. The chi-square test was used to compare categorical variables, and the Mann-Whitney U test was used to compare continuous variables that were non-normally disturbed variables. Logistic regression analysis, receiver operating characteristics (ROC), analysis curve, and area under the curve (AUC) were used to compare HAPS and RS for predicting poor prognosis. Statistical significance was set at $p<0.05$.

## Results

After excluding cases of trauma, cancer, and recurrence cases, the remaining 150 patients were included in the study. 82 patients had non-SAP according to the HAPS. Of these patients, 48 (58.5%) were male and 34 (41.5%) were female. The sex of the HAPS0 and HAPS+ groups was similar (p=0.612) (Table 2).

Biliary pancreatitis was identified as the underlying cause in 72% of HAPS0 patients and 66.2% of HAPS+ patients. Only one patient had a history of alcohol consumption. There was no significant difference in the etiology between the two groups (p=0.445) (Table 2).

Computed tomography (CT), scanning was performed in 24.4% and 39.7%, respectively, in the HAPS0 and HAPS+ groups The CT scan and necrosis rates were found to be statistically similar between the two groups (p=0.044 and p=0.130) (Table 2).

A total of 16.2% of HAPS+ patients and 3.7% of HAPS0 patients were treated in the ICU. A greater proportion of patients with HAPS+ were followed up in the ICU (p=0.009) (Table 2).

The median length of hospitalization was 7.4±7.5 days for HAPS0 and 8.9±6.8 days for HAPS+ (p=0.08) (Table 2).

The overall mortality rate was 2%. Although no in-hospital deaths occurred in the HAPS0 group, there was no significant difference between the two groups (p=0.091) (Table 2).

The specificity and positive predictive value of HAPS were 75% and 95.1%, respectively, and the odds ratio (OR) was 4.229 [95% confidence interval (CI) for EXP(B) 1,283-13,941, p=0.012] (Table 3).

**Table 2. Demographic and radiological profile of the patients**

| | | Total | HAPS0 | HAPS+ | p |
|---|---|---|---|---|---|
| **Gender, n (%)** | | | | | |
| | Male | 85 (56.7) | 48 (58.5) | 37 (54.4) | 0.612* |
| | Female | 65 (43.3) | 34 (41.5) | 31 (45.6) | |
| **Age, (mean±SD)** | | 54.8±18.5 | 50.4±18.6 | 60.1±17.1 | **0.001**** |
| **Cause, n (%)** | | | | | |
| | Biliary | 104 (69.3) | 59 (72) | 45 (66.2) | 0.445* |
| | Non-biliary | 46 (30.7) | 23 (28) | 23 (33.8) | |
| **Computed tomography, n (%)** | | | | | |
| | CT performed | 47 (31.3) | 20 (24.4) | 27 (39.7) | **0.044*** |
| | CT not performed | 103 (87.7) | 62 (75.6) | 41 (60.3) | |
| **Complications, n (%)** | | | | | 0.130* |
| | Necrosis | 5 (3.33) | 1 (0.67) | 4 (2.67) | |
| **Intensive care unit** | | | | | |
| | ICU (+) | 14 (9) | 3 (3.7) | 11 (16.2) | **0.009*** |
| | ICU (-) | 136 (91) | 79 (96.3) | 57 (83.8) | |
| **Hospital stay time (days), (mean±SD)** | | 8.1±7.2 | 7.4±7.5 | 8.9±6.8 | 0.08** |
| **Exitus, n (%)** | | | | | |
| | Exitus (+) | 3 (2) | 0 | 3 (5) | 0.09* |
| | Exitus (-) | 147 (98) | 82 | 65 (95) | |

*Chi-square test, **Mann-Whitney U test.

HAPS: Harmless acute pancreatitis score, US: Ultrasonography, CT: Computed tomography, ICU: Intensive care unit, SD: Standard deviation

The ROC curves of HAPS and RS demonstrated that the AUC of HAPS was significantly greater than that of RS (p=0.03, p=0.893) (Figure 1, Table 3).

## Discussion

Acute abdominal pain represents a significant proportion of ED admissions. A study of 5.340 cases of acute abdominal pain revealed that AP constituted 1.89% of all cases [15]. The pathogenesis of AP is attributed to the reflux of pancreatic enzymes, bile, duodenal fluid, and increased duct pressure [16].

Gallstones and alcohol consumption are the most common etiological factors of AP [17]. A prospective study of 2144 patients was conducted in 17 tertiary care centers in Türkiye revealed that the most common etiologies were biliary (67.1%), idiopathic (12%), hypertriglyceridemia (6%) and alcohol (4.2%) [18]. In the current study, 72% of patients exhibited gallstones. It is postulated that the rate of alcohol consumption in the current study was lower than that reported in the literature. This is attributed to the low rate of alcohol consumption in Türkiye and the reluctance of patients to provide an accurate history. Given the absence of a division of etiology according to HAPS and the use of RS for comparison, we divided etiology into biliary and non-biliary categories.

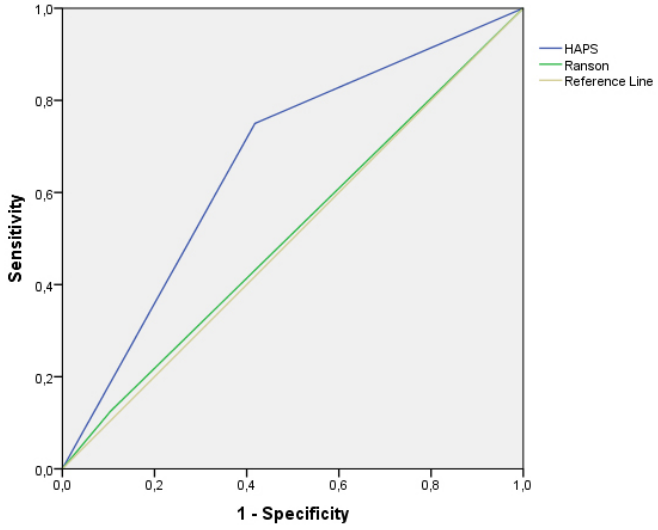


**Figure 1.** Receiver operating characteristic analysis for Ranson and HAPS

HAPS: Harmless acute pancreatitis score

The mean age of the study population was 54.8±18.5 years, with 43.3% of patients being female. In a study comprising 398 patients, the mean age of patients with pancreatitis was 58.87±18.65 years [19]. Although the mean age of HAPS+ patients was older than that of HAPS0 patients (p=0.001), there was no statistically significant age difference between patients with severe and non-severe pancreatitis (p=0.230). Consequently, we hypothesized that age may not be an effective predictor of prognosis.

A comparison of the number of CECT examinations performed in patients with HAPS0 versus those with HAPS revealed a significant difference. The former group required less ICU treatment. A recent study indicated that patients with HAPS0 require less-invasive treatment [20]. As previously stated, SAP is associated with increased medical costs [21,22]. Therefore, it is crucial to identify these patients at an early stage and at a low cost. In this context, HAPS is an efficacious prognostic system capable of reducing examination and treatment costs.

In the medical literature, the mortality rate of patients diagnosed with HAPS0 is between 0% and 2.67%. In contrast, the mortality rate of patients diagnosed with HAPS+ is between

**Table 3. Prediction of HAPS and Ranson for poor diagnosis (ICU, exitus and necrosis)**

| | | HAPS0 | HAPS+ | Ranson< 3 | Ranson≥ 3 |
|---|---|---|---|---|---|
| **Poor Diagnosis** | | | | | |
| | Yes | 4 | 12 | 14 | 2 |
| | No | 78 | 56 | 120 | 14 |
| | Odds ratio | 4.229 | | 0.885 | |
| | 95% CI for EXP(B) | 1.283-13.941 | | 0.175-4.468 | |
| | p* | **0.012** | | **0.802** | |
| | Sensitivity | 58,2 | | 89.5 | |
| | Specificity | 75 | | 12.5 | |
| | PPV | 95.1 | | 89.5 | |
| | NPV | 17.6 | | 12.5 | |
| | Area under the curve | 0.67 | | 0.51 | |
| | p** | **0.030** | | **0.893** | |

*Chi-square test. **ROC Analysis, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

8.7% and 9.1% [23,24]. Although no HAPS0 patients died and the in-hospital mortality rate was 5% in the HAPS+ group, the mortality rates in the two groups were statistically similar and consistent with the literature.

In this study, the ORs for HAPS and Ranson were 4.229 (95% CI: 1.283-13.941, p=0.018) and 0.885 (95% CI: 0.175-4.468, p=0.882), respectively. The predictability of HAPS was found to be higher than that of Ranson. In one study, the OR of HAPS was 5.57 (1.51–20.50, p=0.009), indicating a statistically higher prognosis predictability of HAPS than that of Ranson [23].

In a study comparing five scoring systems, including HAPS, HAPS demonstrated the highest AUC value and OR [25]. In this study, the AUC of HAPS was significantly greater than that of the RS (p=0.03, p=0.893).

A plethora of scoring systems have been devised to predict the severity of AP, the earliest of which was the RS, developed in 1974. Other notable scoring systems include the Japan Severity Index, APACHE II, BISAP, and mGPS. However, these scoring systems require a minimum of 24-48 hours of evaluation and repeated evaluations to predict the severity of AP. For instance, the guidelines recommend APACHE II scoring as the most effective method for distinguishing the severity of AP at the time of initial admission, with the application of this scoring system recommended during the first 3 days [26]. Given the increasing number of patients presenting to ED and the inherent complexity of other prognostication systems, it is impractical to use these systems in the context of emergency care.

### Study Limitations

This study employed a single-center, retrospective design with a relatively small sample size.

## Conclusion

Consequently, the HAPS scoring system is a straightforward and cost-effective method for prognosticating the outcome of AP. It is our opinion that this issue should be subjected to further investigation in the form of multi-center, prospective studies involving a larger number of patients.

### Ethics

**Ethics Committee Approval:** Approval for this study was session of the Non-Interventional Research Ethics Committee of Fırat University (approval number: 2020/02-52, date: 10.02.2022).
**Informed Consent:** Retrospective study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: A.K., Concept: A.K., Design: M.Ş., Data Collection or Processing: M.Ş., Analysis or Interpretation: A.K., M.Ş., Literature Search: M.Ş., Writing: A.K., M.Ş.

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# Evaluation of The Effects of Laboratory Values, Oxidation Parameters, Scoring Systems, and Ventricular Diameter Measurements on Prognosis in Patients Diagnosed with APE in The Emergency Department

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## Abstract

**Objective:** This study aimed to investigate the role of oxidant and antioxidant levels in the diagnosis of acute pulmonary embolism (APE).

**Materials and Methods:** Participants diagnosed with APE were included in group 1, and healthy volunteers were included in Group 2. In addition, Group 1 was divided into two groups according to 30-day mortality.

**Results:** Sixty-five participants diagnosed with APE were included in Group 1. A total of 52 healthy volunteers were included in Group 2. The total antioxidant capacity (TAC) levels of Group 1 were lower than those of Group 2, and the total oxidant capacity (TOC), oxidative stress index (OSI), and ischemia-modified albumin levels were higher. When receiver operating characteristic analysis was performed for TAC, TOC, OSI, and ischemia-modified albumin, the highest area under the curve was found for OSI, TOC, and ischemia-modified albumin, respectively. Fifteen (23%) participants in Group 1 died within 30 days of admission to the emergency department (Group 1A), and 50 (77%) survived after 30 days (Group 1B).

**Conclusion:** The oxidant-antioxidant balance is impaired in APE. Therefore, oxidants and antioxidants can be used to diagnose and exclude patients with suspected APE.

**Keywords:** Antioxidant, ischemia, oxidant, oxidative stress, pulmonary embolism

## Introduction

Acute pulmonary embolism (APE) is a potentially fatal disease, with mortality reaching up to 15% in the risk group. Reducing mortality is possible with correct diagnosis and treatment in the early period [1-3]. In the diagnosis of APE, clinical decision rules, such as the WELLS and Revise Geneva scores, electrocardiography (ECG), laboratory tests, and imaging tools, are used together with clinical evaluation [4,5]. Computed tomography (CT)-pulmonary angiography is an imaging tool with high sensitivity in the diagnosis of pulmonary embolism [1,3,4,6]. However, reasons such as excessive exposure to ionizing radiation, complications related to the use of intravenous contrast material, and fetal risks of use in pregnant women limit the use of CT pulmonary angiography scans [7]. The risk of mortality should be determined together with the diagnosis of APE to ensure appropriate treatment management. The risk of mortality is high in patients with unstable clinical findings, hypotension, and shock. In patients with stable clinical findings, a more advanced classification is performed using prognostic criteria. In the prognostic criteria, the participants' comorbidities, clinical findings, laboratory test results, and imaging tools are used. Pulmonary Embolism Severity Index (PESI), Simplified Pulmonary Embolism Severity Index (sPESI), and Bova score are scores that evaluate prognostic parameters

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together and determine the risk of early death associated with pulmonary embolism. Studies have shown that PESI and sPESI can identify high- and low-risk patients for all-cause 30-day mortality [4,8-11].

The formation and removal rates of free radicals are normally in equilibrium in an organism, and this is called "oxidative balance". The imbalance between oxidants and antioxidants leads to the production of extremely reactive oxygen species and can cause oxidative damage. This condition is referred to as "oxidative stress" [12]. Reactive oxygen species, reactive nitrogen species, and sulfur-centered radicals are classified as oxidants. Reactive oxygen species are capable of reacting with biological molecules such as proteins, lipids, and DNA. An increase in reactive oxygen species levels disturbs cellular functions by damaging lipid membranes, enzymes, and nucleic acids [13]. In recent years, the role of oxidative stress in the etiopathological processes of diseases has aroused great interest. Oxidants and antioxidants have been studied in many diseases [13-15].

The aim of this study was to investigate the role of oxidant and antioxidant levels [Total antioxidant capacity (TAC), total oxidant capacity, and Oxidative Stress Index (OSI)] in the diagnosis of APE in the emergency department and to determine the 30-day mortality associated with pulmonary embolism, and to compare oxidant and antioxidant levels with the clinical findings, laboratory test results, CT pulmonary angiography results, and sPESI score of the patients.

## Materials and Method

### Selection of Participants and Ethics Committee Approval

This prospective study was performed in the emergency department of a tertiary hospital after obtaining the University of Health Sciences Antalya Education and Research Hospital Clinical Research Ethics Committee (approval number: 14/15, date: 30.05.2019). Power analysis was performed using G*Power version 3.1.9.7 (2020) for Windows 10 (University of Dusseldorf, Germany) with reference to similar studies in the literature. The sample size was calculated as 49 with 95% power and 0.05 type 1 error rate. Patients who were admitted to the emergency department between June 15, 2019 and March 10, 2020, diagnosed with APE by CT-pulmonary angiography, over the age of 18, and not receiving thrombolytic therapy were included in the study. Patients under 18 years of age, who were using drugs or nutritional supplements that could affect oxidant-antioxidant levels, whose laboratory test results could not be reached or the laboratory tests were not studied as needed in our study, whose CT-pulmonary angiography scans were not performed, who were pregnant, and who did not give consent to participate in the study were excluded from the study. As the control group, healthy volunteers over the age of 18 years who did not use nutritional supplements that could affect oxidant-antioxidant levels, did not have comorbid diseases, and gave consent to participate in the study were included.

Participants were divided into two groups according to whether they were diagnosed with pulmonary embolism or were healthy volunteers. Participants diagnosed with pulmonary embolism were included in group 1, and healthy volunteers were included in Group 2. In addition, Group 1 was divided into two groups according to its 30-day mortality status. Group 1 participants who died within 30 days of admission to the emergency department were included in Group 1A, and those who survived after 30 days were included in Group 1B (discharged from the hospital).

All patients included in the study were evaluated according to the diagnosis and treatment process of "2019 ESC Guidelines for the diagnosis and management of APE developed in collaboration with the European Respiratory Society" [4] and "American College of Cardiology Management of Pulmonary Embolism: an Update on 2020" [16]. This study was conducted in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from all participants and their relatives. An ECG interpretation was made by an emergency physician. All blood samples were analyzed by a medical biochemistry physician at the hospital laboratory. In terms of consistency, ECG comments were interpreted by a single emergency physician, and blood samples were studied by a single medical biochemistry physician.

A standardized data record form was created before the study. Age, gender, comorbidities, smoking habit, ECG findings performed at admission, WELLS score calculated at admission, the test results of high sensitive troponin t, D-dimer, lactate, and CT pulmonary angiography interpretations performed at admission, the values measured at the admission of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, $SaO_2$ (measured with a pulse oximeter), and body temperature of participants included in group 1 were recorded in this form. In addition to the laboratory tests taken from the Group 1 participants at the time of admission, the TOC, TAC, and ischemia modified albumin (IMA) levels were studied from the blood taken simultaneously. TAC, TOC, and IMA levels were assessed studied from blood taken from the participants included in Group 2.

### Blood Samples and Laboratory Measurements

Blood samples were placed in biochemistry tubes containing gel and a vacuum cap at the time of participant admission. The blood samples taken from groups 1 and 2 were centrifuged for 10 minutes at 4000 rpm with an uncooled centrifuge device within the first 30 minutes after blood samples were

taken and their serums were separated. In Group 1, highly sensitive troponin t and D-dimer were studied immediately in the emergency department laboratory, and lactate was studied from venous blood gas in the bedside blood gas auto analyzer. In groups 1 and 2, the blood samples separated for the measurement of oxidant and antioxidant levels were transferred to Eppendorf tubes with plastic caps and stored at minus 80 °C until the day of analysis. TAC, TOC, and IMA levels were determined from these stored serum samples.

### Measurement of TAC

It was studied on Abbott Architect ®c16000 auto analyzer using a fully automatic RL0031 RelAssay® (Gaziantep-Türkiye) commercial kit. The results are given as µmol H2O2 Equiv./L [13].

### Measurement of TOC

It was studied on Abbott Architect ®c16000 auto analyzer using a fully automatic RL0031 RelAssay® (Gaziantep-Türkiye) commercial kit. The results are given as µmol H2O2 Equiv./L [13].

### Calculation of OSI

The ratio of TOC level to TAC level was accepted as OSI. The OSI was calculated using the following formula: OSI= [TOC (µmol H2O2 Equiv./L) / TAC (µmoltroloksEquiv./L)]

### Measurement of the IMA

IMA measurements were performed using the albumin–cobalt binding test described by Bar- Tekkanat et. al [13]. The results were recorded in absorbance units.

Oxidant and antioxidant measurements were performed by a single physician. All measurements were performed within 1 day. The centrifugation time of the oxidant and antioxidant blood samples was 10 min. The measurement of serum levels was 15 min in IMA and 7 min in TAC and TOC, and OSI was calculated.

### Measurement of High-sensitivity Troponin T

Analyzed by the chemiluminescence method. Results are presented as ng/mL. The measurement of serum high-sensitivity troponin t level took 45 min.

### Measurement of D-dimer

Measured using a HemosIL D-dimer HS kit. The results were given as µg/L. The measurement of the serum level of D-dimer took 45 minutes.

### Lactate Measurement

Venous blood gas samples were collected from the patients on a bedside radiometer (ABL-800 flex brand) in the emergency department. Results are presented in mmol/L. The measurement of the serum lactate level took 90 s.

### sPESI and Lactate-sPESI (L-sPESI)

The sPESI was developed to classify the risks of pulmonary embolism patients [4]. A sPESI score ≥1 is considered high-risk for 30-day mortality. The L-sPESI score was obtained by adding the lactate value to the sPESI (supplementary material 1). Thus, sPESI used 6 parameters, while L-sPESI used 7 parameters. An L-sPESI score ≥2 is considered a high-risk factor for 30-day mortality.

### Computed Tomography-Pulmonary Angiography and Cardiac Measurements

A 64-slice CT scanner (HITACHI ECLOS) was used for CT pulmonary angiography in the emergency department. For CT-pulmonary angiography, a wide vascular access was made from the antecubital region (16 G or larger), and 80 mL of intravenous contrast material was administered. Imaging was performed in the early arterial phase 10-15 seconds after contrast agent injection. CT and pulmonary angiography scans were interpreted by a radiologist. For the purposes of standardization, a single radiologist interpreted all CT-pulmonary angiography. In CT-pulmonary angiography, pulmonary embolism was grouped as sub-segmental, segmental, and main pulmonary artery emboli according to anatomical localization. In the end-diastolic images, the diameter of the heart chambers was calculated by measuring the distance between the septum and the inner wall of the ventricular cavity. The right and left ventricular diameters (LVD) were measured just below the tricuspid valve, and the left ventricular diameter was measured just below the mitral valve. A longitudinal straight line was drawn at the level of the apex for interventricular septum deviation, and a reference point was established by drawing a vertical line from the inner surface of the right ventricular septum. The measurement was made from this reference point in the presence of septum deviation. Measurements were performed in mm [1,17].

### Outcomes

The primary outcome of this study was to evaluate the accuracy of oxidant and antioxidant levels in the diagnosis and prediction of mortality in the presence of APE. The secondary outcome of our study was to compare the accuracy of oxidant and antioxidant levels in predicting mortality with comorbid diseases, vital signs, D-dimer, high-sensitivity troponin t, lactate, cardiac measurements in CT pulmonary angiography scans, sPESI, L-sPESI, and WELLS scoring.

### Statistical Analysis

All data were analyzed using SPSS Statistics for Windows version 21.0. First, analyses were performed on demographic data (age, sex etc.). For this reason, frequency distributions and chi-square tests were used. The Shapiro-Wilk test was used to determine the distribution of the groups. For comparison of

groups, for paired groups, The Student's t-test was used for parametric distributions and the Mann-Whitney U test for non-parametric distributions. In comparison of more than two groups, the One-way ANOVA test was used for parametric distributions, and the Kruskal-Wallis H test was used for non-parametric distributions. A $p<0.05$ value was considered statistically significant.

## RESULTS

### Primary Results

Sixty-five participants diagnosed with APE were included in Group 1. Of Group 1 participants, 43 (66%) were female and 22 (34%) were male. A total of 52 healthy volunteers were included in Group 2 (Figure 1). Of Group 2 participants, 26 (50%) were female and 26 (50%) were male. There were no statistically significant differences between Groups 1 and 2 in terms of gender ($p=0.091$). The mean age was 65±18 years in Group 1 and 59±12 years in Group 2 ($p=0.112$). The participants included in Group 1 had a medical history of malignancy in 17%, hypertension in 15%, chronic obstructive pulmonary disease in 9%, diabetes mellitus in 6%, and smoking habits in 17%. In Group 1, ECG revealed sinus tachycardia in 29 participants, right bundle branch block in 8 participants, atrial fibrillation in 3 participants, and an S1Q3T3 pattern in 1 participant. The ECGs of the remaining participants were in normal sinus rhythm.

When Groups 1 and 2 were compared, there was a statistically significant difference between TAC, TOC, OSI, and IMA levels. TAC levels in Group 1 were lower than those in Group 2, and TOC, OSI, and IMA levels were higher. When receiver operating characteristic (ROC) analysis was performed for TAC, TOC, OSI, and IMA, the highest area under the curve (AUC) was observed for OSI, TOC, and IMA, respectively. When the cutoff value for OSI was determined to be 3.0, sensitivity was 62%, specificity was 92%, positive predictive value was 94%, and negative predictive value was 92% (Tables 1A, 1B and Figure 2A).

Of the Group 1 participants, 22 (34%) were admitted to the intensive care unit and 43 (66%) to the outpatient unit. Fifteen (23%) participants in Group 1 died within 30 days of admission to the emergency department (Group 1A), and 50 (77%) survived after 30 days (Group 1B).

When Group 1A and Group 1B were compared in terms of comorbid diseases, malignancy was identified as more common in Group 1A (Table 2).

### Secondary Results

When pulmonary embolism was evaluated in terms of anatomical location in the pulmonary arteries, main pulmonary artery embolism was detected in 29 participants, segmental embolism in 18 participants, and sub-segmental embolism in 18 participants in Group 1. When the patients in Group 1A and Group 1B were compared, there was no statistically significant difference in terms of anatomical location of pulmonary embolism ($p=0.330$), age, gender, body temperature, $SaO_2$, TAC, TOC, OSI, IMA, D-dimer, and high-sensitivity troponin t. Compared with Group 1B, SBP and DBP were lower, and heart rate was higher in Group 1A. In laboratory studies, lactate levels were found to be higher in Group 1A (Tables 3A, 3B). When Groups 1A and 1B were compared, there was no difference in the WELLS score. However, the sPESI and L-sPESI scores were higher in Group 1A participants (Table 4A). LVD measured on CT pulmonary angiography were higher in Group 1B than in Group 1A. There were no differences in right ventricular diameters (RVD) and RVD/LVD ratio between Group 1A and Group 1B (Table 4B).

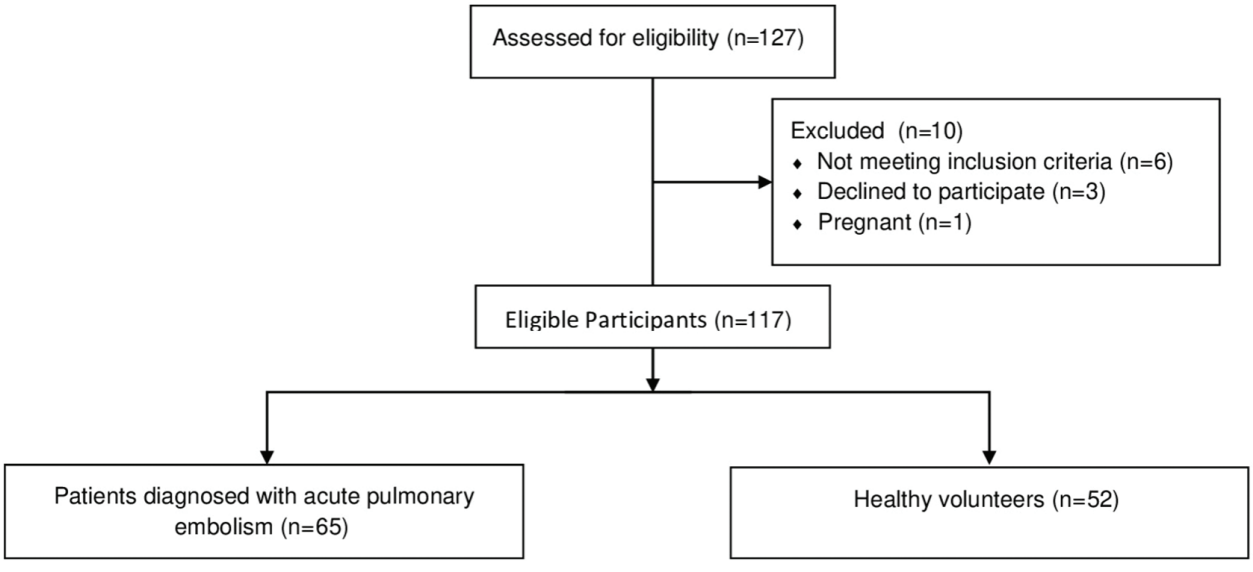


**Figure 1.** Data collection flow chart

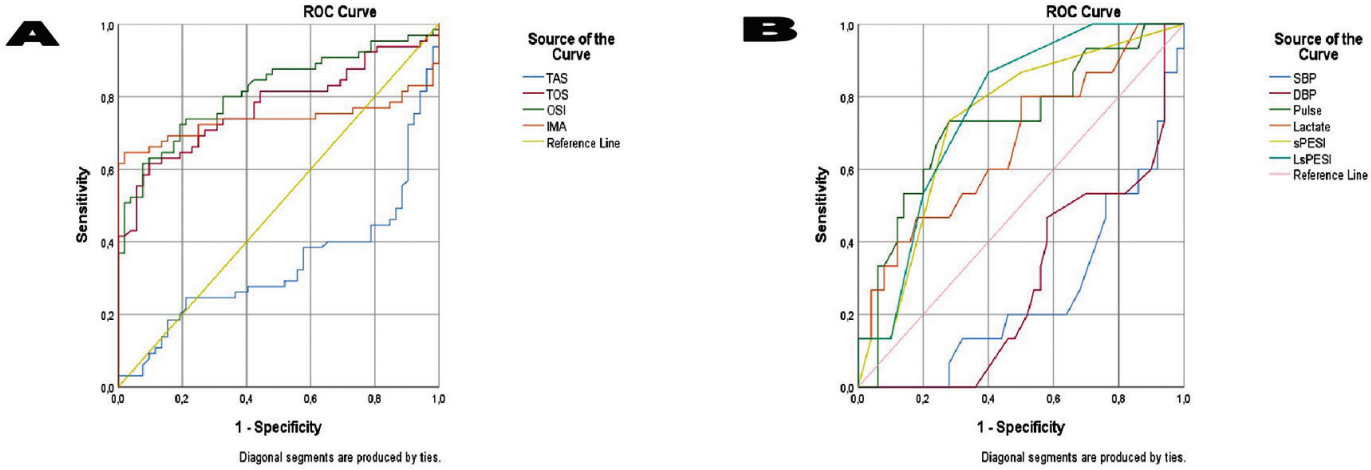


**Figure 2.** A. ROC analysis of TAC, TOC, OSI, and IMA levels in the diagnosis of patients with APE, B. ROC analysis of SBP, DBP, pulse, lactate, sPESI, and L-sPESI values in mortality prediction

ROC: Receiver operating characteristic, TAC: Total antioxidant capacity, TOC: Total oxidant capacity, OSI: Oxidative stress index, IMA: Ischemia modified albumin, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, sPESI: Simplified pulmonary embolism severity index; L-sPESI: Lactate-simplified pulmonary embolism severity index

**Table 1A. Comparison of oxidant and antioxidant levels of participants included in Group 1 and Group 2**

| Oxidant/antioxidant | Patients/ healthy volunteers | Median (min.-max.) | p |
|---|---|---|---|
| TAC* | Group 1 | 1.6 (1.1-2.4) | 0.002 |
| | Group 2 | 1.8 (1.2-2.3) | |
| TOC† | Group 1 | 6.1 (1.7-22.6) | 0.001 |
| | Group 2 | 3.5 (2.1-7.3) | |
| OSI‡ | Group 1 | 3.5 (0.9-13.7) | 0.001 |
| | Group 2 | 1.8 (1.2-4.8) | |
| IMA§ | Group 1 | 0.6 (0.6-0.9) | 0.001 |
| | Group 2 | 0.5 (0.5-0-6) | |

Group 1: Patients diagnosed with acute pulmonary embolism, Group 2: Healthy volunteers, *TAC: Total antioxidant capacity, †TOC: Total oxidant capacity, ‡OSI: Oxidative stress index, §IMA: Ischemia modified albumin, AUC: Area under the curve

**Table 1B. ROC analysis of TAC, TOC, OSI and IMA levels in participants included in Group 1**

| Test result variable(s) | AUC | P | Asymptotic 95% confidence interval | |
|---|---|---|---|---|
| | | | Lower bound | Upper bound |
| TAC* | 0.336 | 0.002 | 0.236 | 0.436 |
| TOC† | 0.773 | 0.001 | 0.688 | 0.859 |
| **OSI‡** | **0.816** | **0.001** | **0.740** | **0.893** |
| IMA§ | 0.738 | 0.001 | 0.638 | 0.838 |

Group 1: Patients diagnosed with acute pulmonary embolism, Group 2: Healthy volunteers, *TAC: Total antioxidant capacity, †TOC: Total oxidant capacity, ‡OSI: Oxidative stress index, §IMA: Ischemia modified albumin, AUC: Area under the curve, ROC: Receiver operating characteristic

**Table 2. Comparison of characteristics of participants included in Group 1A and Group 1B**

| Variables | Group 1A* | Group 1B† | p |
|---|---|---|---|
| Diabetes mellitus | 0 (0%) | 4 (8%) | 0.56 |
| Hypertension | 0 (0%) | 10 (20%) | 0.10 |
| Malignancy | 7 (47%) | 4 (8%) | **0.002** |
| COPD‡ | 0 (0%) | 6 (12%) | 0.32 |
| Smoking habits | 2 (%13) | 9 (18%) | >0.99 |
| Being male | 6 (40%) | 16 (32%) | 0.76 |
| Massive embolism | 7 (47%) | 13 (26%) | 0.20 |

*Group 1A: Participants who died within 30 days of being diagnosed with pulmonary embolism, †Group 1B: Participants who survived after 30 days of being diagnosed with pulmonary embolism,
‡COPD: Chronic obstructive pulmonary disease

When ROC analysis was performed for SBP, DBP, heart rate, lactate, sPESI, and L-sPESI to be used in mortality prediction, the AUC was calculated to be highest for L-sPESI (Figure 2B, Table 5).

## Discussion

APE results in pulmonary circulatory insufficiency, hypoperfusion, hypoxia, and pulmonary ischemia. These conditions cause inflammation and oxidative stress. Therefore, changes occur in inflammatory parameters and oxidant and antioxidant levels [5,17,18]. In this study, we investigated the role of TAC, TOC, OSI, and IMA levels in the diagnosis of APE. The TAC level of patients was lower than that of healthy volunteers,

**Table 3A. Comparison of clinical findings of participants included in Group 1A and Group 1B**

| Group | | Age | SBP‡ | DBP§ | Pulse | Body temperature | SaO2‖ |
|---|---|---|---|---|---|---|---|
| Group 1B† | Median | 72 | 117 | 78 | 95 | 36.2 | 93 |
| | Min. | 18 | 77 | 47 | 56 | 36.0 | 74 |
| | Max. | 93 | 193 | 129 | 181 | 37.6 | 100 |
| Group 1A* | Median | 65 | 104 | 70 | 124 | 36.0 | 90 |
| | Min. | 23 | 76 | 53 | 70 | 36.0 | 40 |
| | Max. | 98 | 131 | 80 | 148 | 37.0 | 99 |
| p | | 0.42 | **0.004** | **0.01** | **0.008** | 0.32 | 0.11 |

*Group 1A: Participants who died within 30 days of being diagnosed with pulmonary embolism, †Group 1B: Participants who survived after 30 days of being diagnosed with pulmonary embolism,

‡SBP: Systolic blood pressure, §DBP: Diastolic blood pressure, ‖SaO2: Oxygen saturation, ¶TAC: Total antioxidant capacity, **TOC: Total oxidant capacity, ††OSI: Oxidative stress index, ‡‡IMA: Ischemia modified albumin, Min.: Minimum, Max.: Maximum

**Table 3B. Comparison of laboratory results of participants included in Group 1A and Group 1B**

| Group | | TAC¶ | TOC** | OSI†† | IMA‡‡ | Lactate | High sensitive troponin t | D-dimer |
|---|---|---|---|---|---|---|---|---|
| Group 1B† | Median | 1.6 | 5.9 | 3.1 | 0.6 | 2.5 | 20 | 737 |
| | Min. | 1.1 | 1,7 | 1.4 | 0.5 | 0.8 | 0 | 112 |
| | Max. | 2.3 | 14.4 | 9.0 | 0.8 | 8.6 | 307 | 19872 |
| Group 1A* | Median | 1.6 | 6.4 | 4.2 | 0.6 | 3.2 | 37 | 970 |
| | Min. | 1.2 | 2.1 | 0.9 | 0.5 | 1.4 | 10 | 354 |
| | Max. | 2.4 | 22.5 | 13.8 | 0.9 | 12.0 | 137 | 11820 |
| p | | 0.57 | 0.20 | 0.28 | 0.74 | **0.044** | 0.067 | 0.061 |

*Group 1A: Participants who died within 30 days of being diagnosed with pulmonary embolism, †Group 1B: Participants who survived after 30 days of being diagnosed with pulmonary embolism,

‡SBP: Systolic blood pressure, §DBP: Diastolic blood pressure, ‖SaO2: Oxygen saturation, ¶TAC: Total antioxidant capacity, **TOC: Total oxidant capacity, ††OSI: Oxidative stress index, ‡‡IMA: Ischemia modified albumin, Min.: Minimum, Max.: Maximum

and the TOC, OSI, and IMA levels were found to be higher. In a study investigating the parameters of inflammation and oxidative stress in pulmonary embolism, significant increases were found between the TOC and OSI ($p<0.0001$ for both parameters) levels of the patient and control groups. However, no difference was observed between the TAC ($p=0.800$) levels [5]. In a similar study, TOC (p:0.080) and OSI (0.024) levels were found to be higher and TAC levels were found to be lower (p:0.011) in patients compared with the control group [18]. The results of our study were found to be compatible with the literature. These results show that the TOC and OSI levels increase and the TAC levels decrease or remain unchanged in patients with APE. TAC and OSI levels increase in the presence of APE; thus, they provide an advantage in the diagnosis of APE.

Elevated plasma troponin concentrations on admission may be associated with worse prognosis in the acute phase of pulmonary embolism [4]. In our study, high-sensitivity troponin t levels of participants who survived and died were compared to predict 30-day mortality. There was no difference between the high-sensitivity troponin t levels of the two groups. Lactate is a marker of an imbalance between tissue oxygen supply and demand, and consequently of severe pulmonary embolism. with overt or imminent hemodynamic compromise. Elevated arterial plasma levels of >2 mmol/L can predict PE-related complications, both in unselected and initially normotensive pulmonary embolism. patients. [4]. In a study, lactate levels of the high-risk pulmonary embolism patients were statistically higher than those of the other patients (3.7 vs. 1.9 and 1.3). In our study, the lactate levels of participants who survived and died were compared to predict 30-day mortality. On the other hand, lactate levels were higher in participants who died. This result is important because it indicates that the lactate level measured in a very short time at the bedside in the emergency department is a strong predictor of mortality.

In addition to laboratory parameters for predicting 30-day mortality due to pulmonary embolism, PESI and sPESI were investigated [19]. Studies have indicated that PESI and sPESI, which are frequently used in the emergency department, can identify high- and low-risk patients for all-cause 30-day

**Table 4A. Comparison of sPESI, L-sPESI and WELLS scores of participants included in Group 1A and Group 1B**

| Group | | sPESI‡ | L-sPES‖§ | WELLS score |
|---|---|---|---|---|
| Group 1B† | Median | 1 | 1 | 2 |
| | Min. | 0 | 0 | 0 |
| | Max. | 4 | 4 | 6 |
| Group 1A* | Median | 2 | 3 | 2 |
| | Min. | 0 | 1 | 1 |
| | Max. | 4 | 5 | 7 |
| p | | **0.004** | **0.001** | 0.42 |

*Group 1A: Participants who died within 30 days of being diagnosed with pulmonary embolism, †Group 1B: Participants who survived after 30 days of being diagnosed with pulmonary embolism,

‡sPESI: Simplified pulmonary embolism severity index, §L-sPESI: Lactate-simplified pulmonary embolism severity index, ‖RVD: Right ventricle diameter, ¶LVD: Left ventricle diameter, Min.: Minimum, Max.: Maximum

**Table 4B. Comparison of cardiac chamber diameters measured on computed tomography of participants included in Group 1A and Group 1B**

| Group | | RVD‖ | LVD¶ | RVD/LVD |
|---|---|---|---|---|
| Group 1B† | Median | 39 | 38 | 1.2 |
| | Min. | 20 | 18 | 0.5 |
| | Max. | 60 | 54 | 2.8 |
| Group 1A* | Median | 33 | 35 | 1.05 |
| | Min. | 21 | 18 | 0.4 |
| | Max. | 50 | 51 | 2.4 |
| **p** | | 0.58 | **0.02** | 0.41 |

*Group 1A: Participants who died within 30 days of being diagnosed with pulmonary embolism, †Group 1B: Participants who survived after 30 days of being diagnosed with pulmonary embolism,

‡sPESI: Simplified pulmonary embolism severity index, §L-sPESI: Lactate-simplified pulmonary embolism severity index, ‖RVD: Right ventricle diameter, ¶LVD: Left ventricle diameter, Min.: Minimum, Max.: Maximum

mortality [4,8-11]. In a study conducted in patients diagnosed with sub-segmental pulmonary embolism, a high WELLS score was associated with mortality or new venous thromboembolism [20]. In this study, the WELLS score and sPESI were evaluated as predictive of mortality. Among the laboratory studies, L-sPESI was created by adding lactate level (Lactate >2.5 mmol/L) to sPESI because lactate levels are studied at the bedside in emergency department patients. The L-sPESI was evaluated for mortality prediction. Although no difference was observed between the WELLS scores of participants who survived and died, there was a statistically significant difference in sPESI and L-sPESI. The AUC was higher for L-sPESI when ROC analysis was performed. It was concluded that L-sPESI would be a better predictor of mortality.

**Table 5. ROC analysis of SBP, DBP, pulse, lactate, sPESI and L-sPESI values in mortality prediction**

| Test Result Variable (s) | AUC†† | p | Asymptotic 95% confidence interval | |
|---|---|---|---|---|
| | | | Lower bound | Upper bound |
| SBP* | 0.255 | 0.004 | 0.118 | 0.393 |
| DBP† | 0.289 | 0.01 | 0.154 | 0.425 |
| Pulse | 0.725 | 0.009 | 0.573 | 0.878 |
| Lactate | 0.672 | 0.045 | 0.512 | 0.832 |
| sPESI‡ | 0.731 | 0.007 | 0.592 | 0.871 |
| **L-sPESI§** | **0.765** | **0.002** | **0.646** | **0.885** |

‡sPESI: Simplified pulmonary embolism severity index, §L-sPESI: Lactate-simplified pulmonary embolism severity index, *SBP: Systolic blood pressure, †DBP: Diastolic blood pressure, ††AUC: Area under the curve, ROC: Receiver operating characteristic

In addition to CT pulmonary angiography, which is used in the diagnosis of APE, RVD, LVD measured in CT pulmonary angiography images, and the RVD/LVD ratio were investigated in the risk classification. In one study, the RVD/LVD ratios of low-, intermediate-, and high-risk patients diagnosed with pulmonary embolism were found to differ [1]. A previous study indicated that increased RVD was associated with an increase in 30-day mortality due to APE [21]. In another study, an increase in 3-month mortality was observed with an RVD/LVD ratio of ≥0.9-1 [22]. In our study, unlike other studies, there was no difference in the RVD/LVD ratio between participants who survived and died. In most of the studies, right ventricular dilation was assessed as the right-to-left ventricular ratio. In a meta-analysis (21), 34 studies reported on the right-to-left ventricle short-axis diameter ratio, four studies on the right-to-left ventricle volume ratio, and one study on the right-to-left ventricle area ratio. The right-to-left ventricle short-axis diameter ratio was assessed in transverse bi-dimensional images in 28 studies and in reconstructed 4-chamber images in 16 studies. The cutoff values for right-to-left ventricular ratios differed among the studies. In another study (22), the scans were evaluated by measuring the minor axes of the right and left ventricles of the heart in the transverse plane at their widest points between the inner surface of the free wall and the surface of the interventricular septum. In our study, we assessed RVD and LVD by measuring the distance between the septum and the inner wall of the ventricular cavity. Right ventricular diameter was measured just below the tricuspid valve, and left ventricular diameter was measured just below the mitral valve. The assessment of right ventricular dilation was different from that of other studies in our study. The difference in our study results can be attributed to this factor. Additionally, 15 (23%) of the Group 1 participants died within 30 days of admission to the emergency department in our study. The limited number of participants who died in our study

could have also contributed to the results. However, the RVD/LVD ratio was >1 in both groups, and the patients were at high risk of mortality. In this case, LVD was evaluated as the second parameter, and LVD was found to be lower in participants who died than in those who survived. It was thought that low LVD contributed to decrease in cardiac output, hypotension, and hemodynamic instability in patients with an RVD/LVD ratio >1, leading to increased mortality. This result is important because it indicates that LVD is an important parameter as a mortality predictor in patients with an RVD/LVD ratio >1.

### Study Limitations

In this observational study, only patients who were not given thrombolytic drugs were included. Thus, the number of patients was limited. This is a limitation of our study.

### Conclusion

As a result, the oxidant-antioxidant balance is impaired in APE. Therefore, oxidants and antioxidants can be used to diagnose and exclude patients with suspected APE. However, oxidants and antioxidants are insufficient to predict 30-day mortality. Lactate, sPESI, and L-sPESI can be used to predict 30-day mortality. LVD can be used to predict 30-day mortality in patients with an RVD/LVD ratio>1. However, larger studies are needed to support these findings.

### Ethics

**Ethics Committee Approval:** This prospective study was performed in the emergency department of a tertiary hospital after obtaining the University of Health Sciences Antalya Education and Research Hospital Clinical Research Ethics Committee (Approval number: 14/15, date: 30.05.2019).

**Informed Consent:** Informed consent was obtained from all participants and their relatives.

### Footnote

### Authorship Contributions

Surgical and Medical Practices: M.A., N.J., Concept: M.A., N.J., Design: M.A., N.J., Data Collection or Processing: M.A., Analysis or Interpretation: M.A., N.J., Literature Search: M.A., N.J., Writing: M.A., N.J.

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**Supplementary Material 1. Simplified pulmonary embolism severity index and Lactate- Simplified pulmonary embolism severity index**

| Predictors | sPESI* | L-sPESI† |
|---|---|---|
| Age >80 years | +1 | +1 |
| History of malignancy | +1 | +1 |
| Chronic cardiopulmonary disease | +1 | +1 |
| Heart rate ≥110 beats/min | +1 | +1 |
| Systolic blood rate ≥110 mmHg | +1 | +1 |
| Arterial oxyhemoglobin saturation <90% | +1 | +1 |
| Lactate >2.5 mmol/L | - | +1 |

*sPESI: Simplified pulmonary embolism severity index, †L-sPESI: Lactate- Simplified pulmonary embolism severity index

ORIGINAL RESEARCH

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# The Role of Optic Nerve Sheath Diameter in Differential Diagnosis in Patients with Headache, A Prospective, Randomized Controlled Study

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## Abstract

**Objective:** This study aimed to evaluate the usability of the optic nerve sheath diameter (ONSD) in the differential diagnosis of headache.

**Materials and Methods:** This study included non-traumatic patients with headache. Patients were divided into three groups. Primary headache was assigned to group 1, secondary headache to group 2, and healthy volunteers to group 3. ONSD was measured by ultrasonography before computed cranial tomography imaging.

**Results:** A total of 50 patients in groups 1 and 2 and 50 healthy volunteers in group 3 were included. The mean ONSD of healthy volunteers was 4.2 mm, and the mean ONSD difference between eyes was 0.2 mm. The mean ONSD for the primary headache was 4.5 mm, and the mean ONSD difference for both eyes was 0.2 mm. The ONSD of the secondary headache was measured as 6.2 mm, and the ONSD difference between the eyes was 0.3 mm. The ONSD difference in both eyes and the ONSD of patients with secondary headache were higher than those in groups 1 and 3 ($p<0.001$). The ONSD cutoff value, which was positive on CT imaging, was 5.2 mm.

**Conclusion:** The ONSD and difference in ONSD can be used in the differential diagnosis of primary and secondary headache.

**Keywords:** Computed cranial tomography, emergency medicine, headache, optic nerve sheath diameter, ultrasonography

## Introduction

Headache is a common complaint in the emergency department (ED) and accounts for approximately 2.5% of all ED visits. Headache can be classified as primary or secondary, depending on its underlying cause [1]. The international classification of headache disorders defines primary headaches as migraine, tension-type, cluster, or one of the other trigeminal autonomic cephalalgias. Primary headaches comprise about 95-98% of all headaches. Secondary headaches are caused by underlying diseases, such as trauma, cerebrovascular disorders, infection, intoxication, or malignancy [1-3]. The primary goal of the emergency physician is to distinguish life-threatening secondary headache from primary headache. Failure or delay in recognizing a life-threatening headache can result in morbidity and mortality. The second goal of the emergency physician is to alleviate the symptoms [4].

Emergency physicians may need to use neuroimaging to exclude life-threatening conditions in patients with headache

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[1]. Cranial computed tomography (CCT) is the first imaging modality of choice for excluding secondary headache causes (intracranial events) in EDs. However, CCT imaging involves high-dose radiation. Therefore, it is important to correctly identify patients who will undergo CCT imaging [5,6].

The optic nerve is an anatomical structure of the central nervous system, and the optic nerve sheath is associated with the meninges and subarachnoid space. Therefore, events that increase the pressure in the central nervous system cause an increase in the optic nerve sheath diameter (ONSD). ONSD measurement with bedside ultrasonography (US) is a non-invasive, easy-to-apply, fast, and reproducible method [7-13]. Compared with CCT and Magnetic resonance imaging (MRI), US is easy to use and inexpensive, especially in emergency conditions. However, it should be noted that ONSD shows huge variation with age [11,14]. The aim of this study was to evaluate the usability of ONSD for the differential diagnosis of headache in patients admitted to the ED with headache. Thus, to detect intracranial events in the early period, perform ONSD measurement before CCT imaging, and contribute to the literature.

## Materials and Methods

This prospective, single-blind, randomized controlled study was initiated after University of Health Sciences Türkiye, Antalya Training and Research Hospital Clinical Research Ethics Committee (approval number: 3/17 date: 31.01.2019). The study was conducted in the adult ED of University of Health Sciences Türkiye, Antalya Training and Research Hospital between February 4, 2019 - July 18, 2019. Patients were consecutively included in the study. Power analysis was performed using the G*Power program version 3.1.9.7 (2020) for windows 10 (Düsseldorf University, Germany) with reference to similar studies in the literature. Sample size was calculated as 44 with 95% power and 0.05 type 1 error rate. Patients admitted with a complaint of non-traumatic headache, who underwent CCT, who were older than 18 years, and who provided consent to participate in the study were included in the study. Patients with a history of trauma, who were younger than 18 years of age, who have pregnant, who had eye surgery, who have eye prosthesis, who did not have CCT scan, whose data is missing and who did not volunteer to participate in the study were excluded. All patients and volunteers provided informed consent before participation. Patients included in the study were divided into two groups: primary and secondary headache groups according to their final diagnosis. Final diagnoses were decided according to the CCT findings. Patients who did not present with pathology on CCT scans were enrolled in group 1 (primary headache), and those who had pathologies were enrolled in group 2 (secondary headache). Healthy volunteers were included in Group 3. Healthy volunteers were not visualized using CCT.

A standard data record form was created. Vital signs (blood pressure, pulse, fever and oxygen saturation values), visual analog scale (VAS), Glasgow coma score (GCS), ONSD measurements, CCT imaging interpretations, final diagnosis, and outcome patterns of the patients were recorded on the form. The ONSD of all patients and healthy volunteers was measured by a single emergency physician. The physician who measured ONSD was blind to the patient's clinical condition. ONSD was measured immediately before CCT imaging. All CCTs were interpreted by the on-call radiologist within 30 minutes after CCTs were performed.

### ONSD Measurement Technique

ONSD measurements were performed by an emergency physician using a 7-13 MHz linear ultrasound probe (Mindray Portable Ultrasound Systems, M5, Germany) in the ED. The emergency physician who measured the ONSD of the patients was blind to patient history, physical examination, clinical findings, and laboratory results of the patient. Patients were examined in the supine position with a closed eyelid. Ultrasound gel was applied on the eyelid surface. First, both eyes were scanned in the vertical and horizontal planes through the eyelid, and then the optic disk of the eye was viewed and ONSD measurements were performed in the transverse and sagittal planes using hypoechoic lines 3 mm proximal to the optic disk, as references (Figure 1).

### Statistical Analysis

For statistical analysis, Statistical Package for the Social Sciences (SPSS1) version 21 was used. First, a Kolmogorov-Smirnov analysis was performed to evaluate whether the distribution of values is normal or not. Parametric data were analyzed using Student's t-test and one-way analysis of variance tests. Non-parametric data were analyzed using Mann-Whitney and Kruskal-Wallis tests. Pearson's correlation analysis was performed for variables with normal distribution, and Spearman's correlation analysis was performed for variables not showing normal distribution. Categorical variables were expressed as numbers and percentages, and continuous variables were as mean and standard deviation (median and minimum - maximum, where necessary). $X^2$ test statistic was used to compare categorical variables. Receiver operating characteristic curves were used to assess the usefulness of measurements and to determine the sensitivity and specificity of the test. $P<0.05$ was considered statistically significant.

### Study Outcomes

The primary outcome of the study was to evaluate the usability of ONSD for the differential diagnosis of headache in patients admitted to the ED with headache. The secondary outcome of the study was to evaluate the correlation of vital signs (blood pressure, pulse, fever and oxygen saturation values),

VAS, GCS, ONSD measurements, ONSD difference of both eyes, and CCT imaging interpretations in patients with primary and secondary headache.

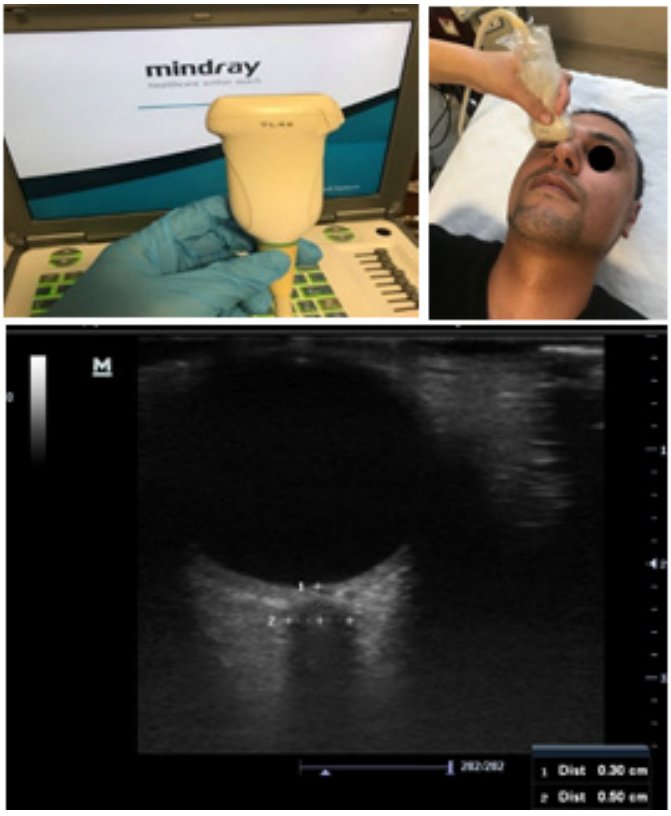


**Figure 1.** ONSD measurement technique. Measurement number 1: for the measurement, the optic nerve is traced 3 mm from the eyeball. Measurement number 2: the diameter is then measured in the transverse plane

ONSD: Optic nerve sheath diameter

## Results

In this study, 50 patients from groups 1 and 2 each and 50 healthy volunteers from group 3 were included. There were no significant differences in age and sex between the groups. There were significant differences in systolic blood pressure (SBP), diastolic blood pressure (DBP), ONSD, and ONSD in both eyes between the groups. The difference in SBP, DBP, ONSD, and ONSD of both eyes in patients with secondary headache was very high ($p<0.001$) compared with the other patients. Patients with primary headache had higher SBP ($p=0.003$), DBP ($p<0.001$) and ONSD ($p<0.001$) than healthy volunteers (Table 1). There was no pathology in the CCT images of patients with primary headache. The CCT images of patients with secondary headaches showed subarachnoid hemorrhage (28%, n=14), intra-parenchymal hemorrhage (28%, n=14), subdural hemorrhage (16%, n=8), intracranial mass (16%, n=8), and acute ischemic stroke (12%, n=6). The ONSD cutoff value, which shows the pathology in the CCT images, was determined as 5.2 mm. At this value, the sensitivity was 98% and the specificity was 100% [area under the curve (AUC): 0.998; 95% confidence interval (CI): 0.992-1.000] (Figure 2). A difference was observed between the GCS scores of patients with primary and secondary headaches ($p<0.01$). On the other hand, there was no statistically significant difference between the VAS scores of the patients ($p=0.148$) (Table 2).

A negative correlation was found between GCS and ONSD in patients with headache. GCS was not correlated with VAS, SBP, or DBP. ONSD was not correlated with VAS, SBP, or DBP (Table 3). Midline shift (MLS) was detected in 9 (9%) patients on CCT images. The ONSD of patients with MLS was 6.3±0.6 mm, and the ONSD of patients without MLS was 5.2±1.0 mm ($p<0.001$).

**Table 1. Comparison of the groups' vital signs and ONSD measurements**

| Findings | | Mean ± SD lower bound | 95% CI | | p |
|---|---|---|---|---|---|
| | | | Upper bound | | |
| SBP | Healthy | 130±18 | 125 | 135 | 0.001 |
| | Primary | 143±24 | 136 | 149 | |
| | Secondary | 156±35 | 146 | 166 | |
| DBP | Healthy | 73±8 | 70 | 75 | 0.001 |
| | Primary | 86±13 | 82 | 89 | |
| | Secondary | 88±19 | 82 | 93 | |
| ONSD | Healthy | 4.2±0.2 | 4.2 | 4.3 | 0.001 |
| | Primary | 4.5±0.4 | 4.4 | 4.6 | |
| | Secondary | 6.2±0.5 | 6.0 | 6.3 | |
| ONSD difference of both eyes | Healthy | 0.2±0.1 | 0.1 | 0.2 | 0.001 |
| | Primary | 0.2±0.1 | 0.2 | 0.3 | |
| | Secondary | 0.3±0.2 | 0.3 | 0.4 | |

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ONSD: Optic nerve sheath diameter, CI: Confidence interval, SD: Standard daviation

Patients with secondary headache were hospitalized, 10 of them were admitted to the neurology and neurosurgery clinic, and 40 of them were admitted to the intensive care unit. Patients with primary headache were discharged after treatment in the ED. Eleven (22%) patients with secondary headache did not survive. The ONSD of the non-surviving patients was 6.9±0.2 mm, and the ONSD of the survivors was 5.1±0.9 mm ($p<0.001$). The cutoff value of ONSD for the detection of mortality was determined to be 6.5 mm. The sensitivity and specificity at this cutoff value were determined as 100% and 92% (AUC: 0.984; 95% CI: 0.963-1,000), respectively (Figure 3).

## Discussion

In the initial evaluation in the ED, secondary headaches that can be potentially life-threatening should be differentiated from primary headaches. However, it is difficult to distinguish between primary and secondary headaches in emergencies. In such cases, extensive laboratory and imaging studies may be required [1,8]. CCT and MRI are frequently used for imaging intracranial events in the ED. Recently, ONSD has been found to increase in intracranial events such as ischemic stroke, hemorrhagic stroke, meningitis, encephalitis, brain edema, intracranial hypertension, and traumatic brain injury (subarachnoid, subdural and epidural hemorrhage) that

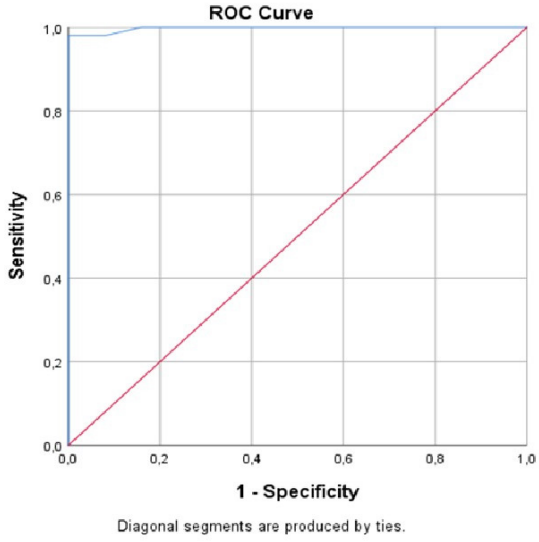


**Figure 2.** ROC analysis of ONSD as a predictor for patients with secondary headache

ROC: Receiver operating characteristic, ONSD: Optic nerve sheath diameter

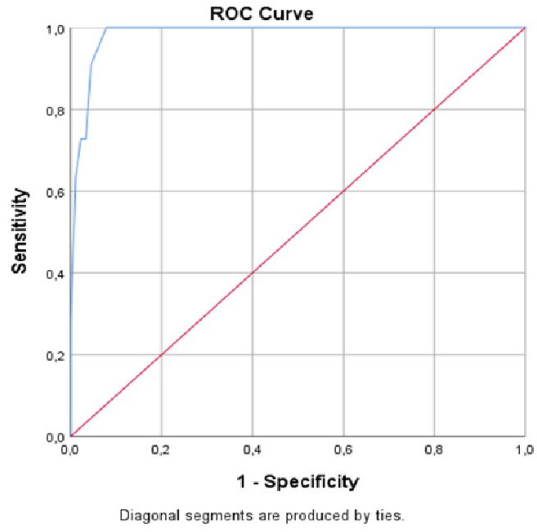


**Figure 3.** ROC analysis of ONSD as a mortality predictor in patients with headache

ROC: Receiver operating characteristic, ONSD: Optic nerve sheath diameter

**Table 2. Comparison of GCS and VAS score of patients with primary and secondary headaches**

| Findings | Groups | Median | Minimum | Maximum | p |
|---|---|---|---|---|---|
| GCS | Primary | 15 | 15 | 15 | 0.001 |
| | Secondary | 12 | 5 | 15 | |
| VAS | Primary | 10 | 6 | 10 | 0.148 |
| | Secondary | 10 | 4 | 10 | |

GCS: Glasgow coma scale, VAS: Visual analog scale

**Table 3. Correlation between patients' GCS, ONSD, VAS, SBP, and DBP**

| | Findings | | ONSD | VAS | SBP | DBP |
|---|---|---|---|---|---|---|
| Spearman's rho (n=100) | GCS | R | **-0.669** | 0.056 | -0.030 | -0.047 |
| | | P | **0.001** | 0.580 | 0.767 | 0.640 |
| | ONSD | R | 1.000 | -0.094 | 0.251 | 0.131 |
| | | P | . | 0.352 | 0.012 | 0.193 |

VAS: Visual analog scale, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GCS: Glasgow coma scale, ONSD: Optic nerve sheath diameter, R: Correlation coefficient

cause increased intracranial pressure. In these studies, ONSD and intracranial pressure (ICP) were found to be correlated [7,10-12,15,16]. There are studies indicates that extra-cranial events such as COVID-19 and alcohol intoxication, increase ONSD [3,17]. Furthermore, ONSD has been found to decrease postdural puncture headache [18] and during migraine attacks [19]. In this study, we investigated the role of ONSD in the differential diagnosis of patients with headache. In CCT scans, subarachnoid hemorrhage, intra-parenchymal hemorrhage, subdural hemorrhage, intracranial mass, and acute ischemic stroke were detected in patients with secondary headache. There were no pathological signs in patients with primary headache. The ONSD values measured by bedside US were 4.2 mm in healthy volunteers, 4.5 mm in patients with primary headache, and 6.2 mm in patients with secondary headache. This result suggests that ONSD can be used to differentiate patients with secondary headache. In a previous study, ONSD values were significantly higher in patients diagnosed with secondary headache compared with those diagnosed with primary headache [20]. In another study, when the intracranial pressure was >20 mmHg, the cutoff value of ONSD was measured as >5.2 mm. At this value, the sensitivity and specificity were 83.3% and the specificity to be 100% [12]. Based on this finding, ROC analysis of ONSD was performed to identify patients with secondary headache. When the cutoff value of ONSD was predicted as 5.2 mm, the sensitivity and specificity were calculated as 98% and 100% (AUC: 0.998; 95% CI: 0.992-1.000), respectively. In some studies, in addition to ONSD, the differences in ONSD of both eyes were also evaluated. In a previous study, the ONSD difference was 0.97 mm in patients with pathology on CCT, whereas the ONSD difference was 0.45 mm in patients without pathology on CCT [7]. In another study, the difference in ONSD was 0.29 mm in patients with acute ischemic stroke, compared to 0.07 mm in healthy adults [9]. In another study contains 20 with idiopathic intracranial hypertension and 20 with intracerebral hemorrhage, the median asymmetry was higher in patients than in healthy subjects (0.45 mm vs. 0.23 mm) [16]. In a study conducted in patients with headache, the ONSD value on the same side as the lesion was found to be higher on the opposite side [10]. In our study, the difference in ONSD among patients with secondary headache was higher than that among the others. The ONSD difference was 0.30 mm in patients with secondary headache, 0.21 mm in patients with primary headache, and 0.20 mm in healthy volunteers. This result shows that differences in ONSD can also be used in differential diagnosis.

The GCS was used to evaluate the patients' consciousness status and intracranial lesions. Studies have shown that GCS decreases as ICP increases. Kshirsagar et al. [21] conducted a study. According to this study, compared with CT, bedside USG ONSD had 86.42% sensitivity and 64.29% specificity for detecting elevated ICP. A highly significant association was found among the GCS, CT results, and ONSD measurements. Patients with low GCS had higher mean ONSD values (6.4±1.0 mm) [21]. Güzeldağ et al. [22] measured the ONSD by US in acute middle cerebral artery stroke patients. They found that ONSD was negatively correlated with GCS at 24 hours. In a recent study, it was determined that ONSD increased as GCS decreased. In a study conducted in the ED, the ONSD of patients with a GCS of 14-15 was measured at 4.9 mm. The ONSD of patients with a GCS of 3-13 was measured as 5.8 mm [7]. Benhur et al. [23] investigated ONSD and GCS. In total, 57 patients underwent elective craniotomy for intracranial tumors. They measured ONSD and GCS at 12$^{th}$, 24$^{th}$ and 48$^{th}$ hours after surgery. A negative correlation was observed between baseline ONSD and 12-h GCS. There was a significant change in GCS scores based on the ONSD status (raised or normal) at 12 hours postoperatively [23]. In our study, the median GCS score of patients with primary headache: 15 (15-15), whereas the median GCS score of patients with secondary headache was 13 (5-15). A statistically significant negative correlation ($r=-0.669$, $p<0.001$) was found between GCS and ONSD. These results suggest that ONSD can be used in addition to GCS to evaluate intracranial lesions. Red flags should be considered when differentiating high-risk patients for headache. Red flags include altered state of consciousness, seizure, fever, neurological symptoms, no previous headache, change in headache severity or worsening within weeks/months, progression, and most severe headaches in life. Neuroimaging should be performed when red flags are detected [24]. Therefore, assessment of pain intensity is important for diagnosis and treatment. The VAS is frequently used to evaluate pain severity in the ED. There is no study in the literature investigating the relationship between VAS scores and ONSD. In this study, we observed no difference between the VAS scores of patients with primary and secondary headaches. The VAS score was 10 in both groups. In addition, VAS score was not correlated with ONSD and GCS. These results show that GCS and bedside ONSD measurement may be more useful than the severity of pain before neuroimaging. As the ICP increases, brain herniation occurs, followed by brain death. In many studies, ONSD was found to be enlarged in patients with brain herniation and death [7,25,26]. In one study, the ONSD was 5.3 mm in patients who developed MLS and 4.42 mm in patients who did not develop MLS. In this study, the ONSD cutoff value for MLS was determined as 5.3 mm [7]. In a study of patients with head trauma, a positive correlation was found between midline shift and ONSD ($r=0.761$ ($p<0.0005$) [27]. In another study, ONSD was found to be 8.34 mm in patients with brain death. In addition, the ONSD cutoff value for brain death was determined to be 7.1 mm in this study [25]. In another study, ONSD changes in patients with middle cerebral artery infarction or malign middle cerebral artery infarction were investigated. The mean ONSD on admission was already larger

in patients who had developed a malignant middle cerebral artery infarction (5.99±0.32 mm) compared to patients with middle cerebral artery infarction (4.98±0.53 mm) [28]. In our study, the ONSD of patients who developed MLS was 6.3 mm, whereas that of patients who did not develop MLS was 5.2 mm. In addition, the ONSD of the non-survivor patients were 6.9 mm, and the ONSD of the survivor patients were 5.1 mm. In addition, the ONSD cutoff value for mortality was determined to be 6.5 mm in our study. At this value, the sensitivity was 100% and the specificity was 92%. These results indicate that ONSD can be used as a predictor of prognosis and mortality in patients with headache.

In our study, only CCT imaging was performed, and MRI could not be performed. We did not take into account the laboratory values of our patients for whom we recorded vital signs (blood pressure, pulse, fever and oxygen saturation values), visual pain scale, GCS, ONSD measurements, CCT imaging interpretations, final diagnosis, and outcome patterns of the patients. Additionally, CCT imaging was not performed in healthy volunteers. These are the limitations of our study.

## CONCLUSION

In conclusion, there is a difference in SBP, DBP, GCS, ONSD, and ONSD between eyes in patients with primary and secondary headache. These parameters can be used in the differential diagnosis of patients with headache after CCT imaging. In addition, ONSD can be used to predict the prognosis and mortality of patients with headache.

### Ethics

**Ethics Committee Approval:** University of Health Sciences Türkiye, Antalya Training and Research Hospital Clinical Research Ethics Committee (approval number: 3/17 date: 31.01.2019).

**Informed Consent:** It was obtained.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: A.İ.Y., F.S., S.Y., M.A., G.Ç.G., N.K., Concept: A.İ.Y., F.S., S.Y., M.A., G.Ç.G., N.K., Design: A.İ.Y., F.S., S.Y., M.A., G.Ç.G., N.K., Data Collection or Processing: A.İ.Y., F.S., S.Y., G.Ç.G., N.K., Analysis or Interpretation: F.S., M.A., G.Ç.G., N.K., Literature Search: F.S., M.A., N.K., Writing: A.İ.Y., S.Y., M.A., N.K.

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# Prevalence and Clinical Significance of Incidental Findings in Cranial Computed Tomography in Patients with Head Trauma

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## Abstract

**Objective:** This study evaluated the prevalence and clinical significance of incidental findings detected on cranial computed tomography in patients admitted to the emergency department (ED) with head trauma.

**Materials and Methods:** This single-center, retrospective study included 12.605 consecutive patients who presented to the ED due to head trauma from January 2017 to December 2019. Patients were divided into those with and without incidental findings. Patients with incidental findings were further categorized according to clinical significance. Demographic and clinical characteristics were compared among the patient groups.

**Results:** The study included 12.605 patients, including 8.771 males (66.2%) and 3.834 females (33.8%), with a mean age of 34.3±22.6 years. Incidental findings were not detected in 86.2% (n=10.864) of the patient population. The frequency of incidental and clinically significant findings increased with advanced age ($p<0.001$ for both). In addition, incidental findings were more common in males ($p<0.001$). Moreover, a statistically significant increase in the frequency of brain atrophy, infarction, ischemia, and intracerebral space-occupying lesions (such as mass, lipoma, and meningioma) was observed, especially in patients of advanced age. Conversely, the frequency of arachnoid cysts, hydrocephalus, megacisterna magna, and sinusitis was more common in the younger age group ($p<0.05$ for all).

**Conclusion:** Overall, 86.2% of patients with head trauma had no incidental findings. Additionally, most incidental findings were benign and non-critical. The frequency of incidental and clinically significant findings increased with advanced age. Furthermore, incidental findings were more common in males.

**Keywords:** Clinical significance, cranial computed tomography, head trauma, incidental findings

## Introduction

Incidental findings are unexpected abnormalities discovered unintentionally during medical evaluation for an unrelated issue [1]. These findings are typically asymptomatic and are not related to current symptoms or the primary reason for the medical assessment [1,2]. Despite being incidental, these findings can indicate serious conditions that require further investigation, testing, imaging, or procedures [3]. In recent years, the use of cranial computed tomography (CT) in emergency departments (EDs) has significantly increased [3,4]. This trend has led to the detection of unexpected and asymptomatic brain anomalies, including brain tumors, calcifications, anatomical variations (such as mega cisterna magna and Dandy-Walker malformation), cysts (such as arachnoid cysts), aneurysms, and other subclinical vascular pathological changes [2,5]. However, the

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actual prevalence of incidental findings in certain populations is unknown. Additionally, these findings frequently require further examination and treatment to determine their clinical significance and appropriate management [5,6]. Importantly, the prevalence of specific incidental findings varies by country, based on genetic and environmental factors [2,5]. For instance, a retrospective investigation conducted in Iran between 1998 and 2001 on 3.000 patients with head trauma revealed that the most common incidental finding was megacisterna magna, followed by brain tumors and arachnoid cysts [5]. Conversely, a retrospective study in Nigeria over 5 years examining 591 patients with head trauma reported that intracranial calcifications were the most frequently detected incidental findings, with a prevalence rate of 61.8% [2]. These regional variations highlight the need for population-based research to inform clinical practice. Currently, there is insufficient information about the prevalence and characterization of incidental findings on cranial CT scan in Türkiye. Moreover, no previous study has attempted to classify these incidental findings into subtypes, which is crucial for understanding their clinical significance and guiding management. This study aimed to determine the prevalence and clinical significance of incidental findings detected on cranial CT scan in patients admitted to the ED due to head trauma.

## Materials and Methods

### Ethics Committee Approval and Patient Consent

This study was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the institutional review board (IRB) of University of Health Sciences Türkiye, Haseki Training and Research Hospital Clinical Research Ethics Committee (decision number: 2020-09, date: 29.02.2020). The IRB did not request patient consent to access the medical records because there were no potentially identifiable markers or patient identifiers

### Study Design and Setting

This single-center, retrospective, and observational study enrolled 21.186 consecutive patients who presented to the ED due to head trauma from January 2017 to December 2019. Data were collected by searching for S00-S10 International classification of disease (ICD) codes in the hospital's automation systems and archives. The patients' demographics (age and sex), initial complaints and diagnoses, comorbidities, vital signs, cranial CT findings, and clinical outcomes were assessed. Patients were divided into two groups: those with incidental findings detected on cranial CT scan and those without. Patients with incidental findings were also divided into two groups: Those with clinical significance and those without. Patients with clinically significant incidental findings include those requiring routine or urgent follow-up for conditions such as intracranial mass, cerebral ischemia or infarction, arachnoid cyst, and hydrocephalus. In contrast, patients whose incidental findings were not clinically significant included benign patients who did not require clinical follow-up if asymptomatic (e.g., sinusitis, intracranial calcification, cerebral atrophy, mega cisterna magna, etc.). Demographic and clinical characteristics were compared among patient groups to identify prevalence and evaluate the clinical significance of incidental findings.

### Study Population and Sampling

To reduce selection bias, all patients who satisfied the eligibility criteria during the study period were included. A total of 21.186 consecutive patients who visited the ED because of head trauma were enrolled in this study. Of these, 3.186 patients who did not undergo cranial CT were excluded. Additionally, 1,805 foreign and refugee individuals were excluded because they did not represent the patient population. A further 2.376 patients were excluded due to incorrect usage of the ICD code. A total of 625 patients underwent CT scan with substandard or poor image quality, and 589 patients were excluded due to the unavailability of their data. Ultimately, 12.605 patients were included in the analysis.

### Cranial CT İmaging Protocol

Cranial CT imaging was conducted using a 128-slice CT scanner (PHILIPS Ingenuity, Netherlands). The scanning protocol comprised non-contrast cranial CT scan in all cases, following standard CT procedures. Patients were positioned in the supine posture with meticulous alignment: The head was centered and positioned perpendicular to the CT table along the canthomeatal line. Additionally, the head was angled approximately 20° downward relative to the orbitomeatal line to optimize visualization. Subsequently, the images underwent post-processing, including axial, sagittal, and coronal reconstructions, in addition to maximum-and minimum-intensity projections. The reconstructed images maintained a slice thickness of 1 mm.

### Statistical Analysis

Data analysis was conducted using SPSS software (version 16.0 for Windows; SPSS Inc., Chicago, IL). Categorical variables (sex and age) are expressed as numbers (n) and percentages (%). Numerical data are expressed as means with standard deviations, minimums, maximums, and medians. Intergroup comparisons were conducted using Student's independent t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Dependent group comparisons among patients with incidental findings were performed using the Wilcoxon test for normally distributed variables and chi-squared test for non-normally distributed variables. The significance level of alpha was set at $p<0.05$.

## Results

Table 1 presents the demographic and clinical characteristics of patients who underwent cranial CT scan due to head

| Table 1. Patient demographic and clinical characteristics | | |
|---|---|---|
| **Age in years, mean ± SD (min.-max.)** | 34.3±22.6 | (0-104) |
| **Sex, n (%)** | | |
| Female | 3.834 | (33.8) |
| Male | 8.771 | (66.2) |
| **Incidental findings, n (%)** | | |
| No | 10.864 | (86.2) |
| 1 finding | 965 | (7.6) |
| 2 findings | 678 | (5.4) |
| 3 findings | 98 | (0.8) |
| Cerebral atrophy | 1.028 | (59.1) |
| Cerebral ischemia | 745 | (42.8) |
| Intracranial calcification | 334 | (19.2) |
| Arachnoid cyst | 246 | (14.1) |
| Sinusitis | 102 | (5.9) |
| Cerebral infarct | 87 | (5.0) |
| Megacisterna magna | 82 | (4.7) |
| Intracranial mass | 26 | (1.5) |
| Meningioma | 26 | (1.5) |
| Hydrocephalus | 24 | (1.4) |
| Lipoma | 14 | (0.8) |

Data are expressed as numbers (n), percentages (%), SD: Standard deviation, min.-max.: Minimum-maximum

trauma. This study included 12.605 patients with head trauma, including 8.771 males (66.2%) and 3.834 females (33.8%), with a mean age of 34.3±22.6 years. Incidental findings were not detected in 86.2% (n=10,864) of the patient population. The remaining 1,741 (13.8%) patients had at least one incidental finding. The most common incidental findings were cerebral atrophy (n=1,028; 59.1%), cerebral ischemia (n=745; 42.8%), and intracranial calcification (n=334; 19.2%), respectively. Patients with incidental findings had a significantly higher mean age than those without (60.3±24.3 vs. 30.2±19.3; p<0.001). In addition, 35.4% of patients with incidental findings were female, compared to 29.6% of those without incidental findings. A statistically significant difference in terms of sex was observed between the patient groups (p<0.001). Moreover, patients with clinically significant incidental findings were older than those with non-clinically significant findings (64.5±23.4 vs 54.5±24.3; p<0.001). Furthermore, 37.8% of patients with clinically significant findings were female, compared with 32.2% of those with non-clinically significant findings. There was a significant difference in sex between the patient groups (p=0.017). Non-clinically significant incidental findings were detected in 41.6% (n=724) of the patient population. The remaining 1.017 (58.4%) patients had clinically significant findings. The most common clinically significant incidental findings were cerebral ischemia and arachnoid cysts. Patients with cerebral ischemia were older than those without (p<0.001). Additionally, there were significantly more females in the cerebral ischemia group than in the non-ischemia group (p<0.001). Conversely, the mean age of patients with arachnoid cysts was significantly lower than those without (p<0.001). Moreover, the number of males was significantly higher in patients with arachnoid cysts than in those without (p<0.001). The most common non-clinically significant findings were cerebral atrophy and intracranial calcification. Patients with cerebral atrophy were significantly older than those without (p<0.001). Additionally, there were significantly more women in the cerebral atrophy group (p<0.001). Conversely, patients with intracranial calcification were significantly younger than those without (p=0.046). However, sex did not differ between patients with and without intracranial calcification (p=0.309) (Table 2).

## Discussion

In this study, we investigated the prevalence of incidental findings, with or without clinical significance, in patients admitted to the ED due to head trauma who underwent CT scan. Given that our tertiary hospital is a major trauma center in Istanbul, we posit that our study cohort is representative of the general healthy population for the detection of incidental skull and brain pathologies.

The prevalence of incidental findings varies among different populations [2-5]. Literature on CT-based studies from various countries has documented that the prevalence of these findings ranges from 1% to 85% [2,5,7,8]. In a study conducted in Türkiye by Köksal et al. [7] the frequency of incidental findings in patients who underwent cranial CT for head trauma was reported to be 3.2%. Another study conducted in Türkiye by Yigit et al. [8] found that the frequency of incidental findings in brain-thorax-abdominal CTs performed on patients admitted to the ED following a traffic accident was 27.3%, with approximately 87.9% of these findings identified as skull and brain pathologies. In the present study, the prevalence of incidental findings was 13.8%. The variability among population-based results can be attributed to several factors, including the demographic characteristics of the population, differences in screening protocols and methods, imaging quality, patients' medical histories and reasons for undergoing scans, and environmental and genetic factors [2-5]. The significant variation in the prevalence of incidental findings in CT-based studies worldwide underscores the importance of considering these factors when interpreting results.

In a study conducted in Nigeria, Ogbole et al. [2] examined the cranial CT findings of 591 patients and reported that 80.7% of the incidental findings were benign and did not require clinical follow-up. Another study, which analyzed the cranial CT images of 3000 trauma patients, also noted that the majority of incidental findings were benign [5]. Similarly, studies

**Table 2. Comparison of demographics (age and sex) between patients with and without incidental findings**

| Incidental findings | | Presence | Absence | p* |
|---|---|---|---|---|
| **Non-clinically significant findings** | | | | |
| **Cerebral atrophy** | Age in years, mean ± SD | 73.4±13.5 | 42.0±24.2 | <0.001 |
| | Female, n (%) | 427 (42.0) | 190 (26.2) | <0.001 |
| | Male, n (%) | 589 (58.0) | 535 (73.8) | |
| **Intracranial calcification** | Age in years, mean ± SD | 59.5±20.9 | 60.5 ± 25.0 | 0.046 |
| | Female, n (%) | 122 (37.9) | 495 (34.9) | 0.309 |
| | Male, n (%) | 200 (62.1) | 924 (65.1) | |
| **Sinusitis** | Age in years, mean ± SD | 31.0±21.0 | 62.1±23.3 | <0.001 |
| | Female, n (%) | 21 (20.8) | 586 (36.3) | 0.002 |
| | Male, n (%) | 80 (79.2) | 1044 (63.7) | |
| **Megacisterna magna** | Age in years, mean ± SD | 29.6±23.7 | 61.8±23.3 | <0.001 |
| | Female, n (%) | 13 (15.9) | 604 (36.4) | <0.001 |
| | Male, n (%) | 69 (84.1) | 1055 (63.6) | |
| **Lipoma** | Age in years, mean ± SD | 64.2±20.5 | 60.2±24.4 | 0.314 |
| | Female, n (%) | 6 (42.9) | 591 (25.2) | 0.193 |
| | Male, n (%) | 8 (57.1) | 1090 (64.8) | |
| **Clinically significant findings** | | | | |
| **Cerebral ischemia/infarct** | Age in years, mean ± SD | 73.9±13.1 | 49.3±25.7 | <0.001 |
| | Female, n (%) | 322 (42.7) | 285 (29.6) | <0.001 |
| | Male, n (%) | 445 (57.3) | 679 (70.4) | |
| **Arachnoid cyst** | Age in years, mean ± SD | 32.1±22.7 | 64.3±21.8 | <0.001 |
| | Female, n (%) | 33 (15.4) | 584 (38.2) | <0.001 |
| | Male, n (%) | 181 (84.6) | 943 (61.8) | |
| **Intracranial mass/meningioma** | Age in years, mean ± SD | 64.3±20.2 | 60.1±23.4 | 0.314 |
| | Female, n (%) | 20 (43.5) | 591 (25.2) | 0.193 |
| | Male, n (%) | 26 (56.5) | 1090 (64.8) | |
| **Hydrocephalus** | Age in years, mean ± SD | 44.8±26.2 | 60.6±24.2 | 0.003 |
| | Female, n (%) | 6 (35.4) | 611 (35.6) | 0.282 |
| | Male, n (%) | 18 (64.6) | 1106 (64.4) | |

Data are expressed as numbers (n), percentages (%),
*Intergroup comparisons were conducted using Student's independent t-test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables
SD: Standard deviations

conducted in Türkiye have reported that most incidental findings were benign [7, 8]. Consistent with the literature, most incidental findings detected in our study were benign and did not require clinical follow-up.

The results of our study indicated that the frequency of incidental and clinically significant findings increased with advanced age. Furthermore, incidental findings were more common among males. Similarly, Ogbole et al. [2] observed that the mean age of patients with incidental findings was significantly higher than those without, with a higher prevalence in males. Another study, which analyzed 5,193 cranial CT images, also noted a greater incidence of incidental findings in males and individuals of advanced age [9].

The most common clinically significant incidental findings in our study were cerebral ischemia and arachnoid cysts, whereas the most common non-clinically significant findings were cerebral atrophy and intracranial calcification. In their study, Ogbole et al. [2] identified calcification as the most prevalent incidental finding in their study, with cerebral atrophy being less common than in our findings. However, their study cohort had a younger mean age than ours. In Razavi-Ratki et al. [9] study, the predominant clinically and non-clinically significant incidental findings were cerebral ischemia/infarction and megacisterna magna, respectively. The prevalence and specific types of incidental findings vary among countries based on population characteristics [2,5,8,9]. These differences may also

be associated with imaging methods and imaging quality. For instance, magnetic resonance imaging (MRI)-based studies often report a lower prevalence of calcifications due to MRI's lower sensitivity for detecting them [10].

### Study Limitations

The prevalence and types of incidental findings vary significantly across studies and populations. Therefore, population-based studies are necessary to identify incidental findings specific to specific societies. Our study is the first to investigate incidental findings detected on cranial CT scans in the Turkish population, categorizing these findings by subtype and evaluating them based on age and sex. However, our study also has several limitations. The most significant is the retrospective design, which was conducted at a single center, which may restrict the generalizability of the findings to other settings or populations. Additionally, we do not routinely perform contrast-enhanced cranial CT examinations for trauma cases, potentially limiting the detection and number of contrast-enhancing lesions. Moreover, alternative imaging modalities, such as MRI, could identify various incidental findings with different prevalences, affecting the overall interpretation of our results. A total of 3.186 patients who did not undergo cranial CT, 625 patients with substandard or poor-quality CT scans, and 589 patients with unavailable data were excluded from the study, potentially introducing bias. Finally, the absence of follow-up data limits our ability to assess outcomes over time.

## Conclusion

The results of our study demonstrated that most incidental CT findings were benign and non-critical. However, 13.8% of patients who underwent cranial CT scan were considered to have serious conditions that require further evaluation and intervention. Our findings highlight the necessity for increased attention, particularly in older patients, to clinically significant findings, such as intracranial mass, cerebral ischemia or infarction, and hydrocephalus.

### Ethics

**Ethics Committee Approval:** This study was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the IRB of University of Health Sciences Türkiye, Haseki Training and Research Hospital Clinical Research Ethics Committee (decision number: 2020-09, date: 29.02.2020).

**Informed Consent:** A retrospective study.

### Footnotes

### Authorship Contributions

Concept: O.D., Design: H.A., A.A., Ö.S., Data Collection or Processing: H.A., Analysis or Interpretation: A.A., Ö.S., Literature Search: H.A., A.A., Ö.S., Writing: H.A., A.A., Ö.S.

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

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ORIGINAL RESEARCH

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# Comparative Effectiveness of Ivermectin and Permethrin in the Treatment of Scabies Diagnosed in the Emergency Department

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## Abstract

**Objective:** We aimed to compare the effectiveness of systemic oral ivermectin and topical permethrin in the treatment of scabies in emergency departments (ED).

**Materials and Methods:** In this prospective, observational, cross-sectional single-center study, patients who presented to the ED with pruritus and were diagnosed with scabies received either topical permethrin or oral ivermectin, based on the clinician's preference. After treatment, the patients were scheduled for follow-up examinations one and two weeks later to assess the treatment effectiveness.

**Results:** A total of 177 patients were included in this study, comprising 106 (59.9%) men and 71 (40.1%) women. No statistically significant difference was found in terms of treatment effectiveness between patients using topical permethrin and those using oral ivermectin at the 7- and 14-day follow-ups (p=0.656 and p=0.604, respectively). After two courses of treatment, 42 (23.7%) patients were considered to have an ineffective response and received alternative treatment.

**Conclusion:** Scabies are managed and treated by dermatologists and emergency medicine physicians in Türkiye. The effectiveness of topical permethrin and oral ivermectin, which are commonly used as first-line treatments for scabies, appears to be similar. The treatment efficacies of both drugs were lower than expected. Improvements in patient adherence and medication access, family member contributions to treatment, and patient education regarding home hygiene can improve treatment outcomes.

**Keywords:** Scabies, itching, sarcoptes scabiei, pruritus

## Introduction

Scabies, which affect more than 200 million people worldwide, are an ectoparasitic infestation caused by Sarcoptes scabiei [1]. It is one of the most common dermatological conditions, significantly contributing to the burden of skin diseases in developing countries [2]. In recent years, the incidence of scabies has increased in Türkiye, mirroring trends observed in many other regions [3]. Because of limited access to dermatologists, many patients in Türkiye seek the emergency department (ED). Consequently, scabies are frequently diagnosed in the ED, where patients often receive their full treatment prescriptions from emergency physicians.

The primary symptom of scabies is intense itching, which typically worsens at night (nocturnal pruritus) [3]. Burrows, also termed sialons, are pathognomonic for scabies. The typical sites of scabies infestation are the submammary region, hands, wrists, and genital area [3]. Diagnosis can be made using microscopy, dermoscopy, Wood's lamp examination, or skin scrapings. However, in emergency settings, treatment is generally initiated based on clinical evaluation alone [4].

Various agents are available for scabies treatment, and patient compliance is crucial for effective treatment. Both topical and systemic treatments can be used. Permethrin, a topical insecticide, is applied as a 5% concentration lotion. The cream

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should be thoroughly applied to the entire body from the neck down when the body is clean, dry, and cool, ensuring that no areas are missed. The lotion is kept on the skin for 8-12 h and then washed off. The success rate of the lotion is high when applied twice within a 1-week interval [3]. Ivermectin, an antiparasitic drug available in tablet form, is recommended at a dose of 200 µg/kg and taken twice with a 1-week interval. Due to resistance to topical treatments or ineffectiveness caused by improper use, systemic treatments have become more prominent. The World Health Organization (WHO) considers oral ivermectin an essential medicine for human health [1]. In this study, we aimed to compare the effectiveness of systemic oral ivermectin and topical permethrin in the treatment of scabies.

## Materials And Methods

### Study Design and Participants

After obtaining ethical approval for this prospective, observational, cross-sectional single-center study, we included adult patients who presented with itching complaints to our hospital's ED over a 6-month period, agreed to participate in the study, and provided written informed consent. Based on the emergency physician's examination and decision regarding the patient, all patients were administered topical permethrin or systemic/oral ivermectin. Due to the lack of Turkish Social Security Information (SSI) reimbursement for oral ivermectin when prescribed by the ED, the inclusion of topical permethrin under SSI reimbursement, and differences in application, the treatments were not randomized but were instead prescribed based on the physician's and patient's choice. Patients were informed about the treatments and were asked about similar symptoms in family members. Follow-up was scheduled for 1 week later. The effectiveness of the treatment was associated with a reduction in symptoms. If a reduction in symptoms occurred after the initial treatment, no additional treatment was provided; the effectiveness of the treatment was assessed and recorded. When symptoms persisted without improvement, the same treatment was re-prescribed; patients were followed up by examination 1 week later to reassess treatment efficacy. If symptoms decreased or disappeared after the second course of treatment, the treatment was considered effective. If the treatment remained ineffective, an alternative drug (not previously prescribed) was administered, and patients were advised to undergo follow-up with a dermatology clinic before discharge. Adult patients who did not consent to participate, those with liver or kidney failure, those who did not attend follow-up visits, pregnant patients, and pediatric patients were excluded from the study.

### Ethics

Ethical approval was obtained from the University of Health Science Türkiye, Haseki Training and Research Hospital Clinical Research Ethics Committee (decision number: 238-2023, date: 20.12.2023). Informed consent was obtained from all participants prior to their inclusion in the study.

### Statistical Analysis

Descriptive statistics for the data included means, standard deviations, medians, minima, maxima, frequencies, and percentages. The distributions of variables were evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was used to analyze non-normally distributed quantitative independent data; the chi-square test was used to analyze categorical independent data. Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

## Results

This study included 177 patients: 106 (59.9%) men and 71 (40.1%) women (mean age: 40.5±15.7 years) (Table 1). In total, 84 (47.5%) patients had family members who also required treatment. Patients were informed accordingly. Treatment was initiated with permethrin in 139 patients and ivermectin in 38 patients There were no significant differences in age or sex distribution between the groups receiving permethrin and ivermectin (p=0.069 and p=0.303, respectively; Table 2). Single-dose treatment was effective in 108 (61%) patients (Table 1).

Among the patients treated with permethrin, 61.9% responded to a single course of treatment, whereas 57.9% of those treated with ivermectin also responded to a single course. However, there was no statistically significant difference in the treatment efficacy between the two drugs at the 7-day follow-up (p=0.656; Table 2). Among the patients who did not respond to the initial treatment and required a second course, 27 (39.1%) showed improvement. Specifically, 37.7% of patients treated with permethrin and 43.8% of those treated with ivermectin benefited from a second course of treatment. Regarding the second course, there was no significant difference in the treatment efficacy between the two drugs at the 14-day follow-up (p=0.604; Table 2).

Among the 42 patients who required two courses of treatment and were subsequently switched to alternative therapy because of persistent symptoms, 23.7% of patients initially treated with permethrin and similarly 23.7% of those initially treated with ivermectin did not respond to treatment. Thus, another medication not previously used was prescribed (Table 2).

## Discussion

Scabies are parasitic infections that affect more than 200 million people worldwide at any given time [1]. In Türkiye, many patients with scabies seek treatment in the ED because

**Table 1. Demographic and clinical characteristics of the patients**

| Characteristic | | Min.-Max. | | | Median | Mean ± SD/n-% | | |
|---|---|---|---|---|---|---|---|---|
| Age | | 18.0 | - | 84.0 | 39.0 | 40.5 | ± | 15.7 |
| Gender | Male | | | | | 106 | | 59.9% |
| | Female | | | | | 71 | | 40.1% |
| Need for family treatment | No | | | | | 93 | | 52.5% |
| | Yes | | | | | 84 | | 47.5% |
| 7-Day follow-up treatment | Ineffective | | | | | 69 | | 39.0% |
| | Effective | | | | | 108 | | 61.0% |
| 14-Day follow-up treatment | Ineffective | | | | | 42 | | 60.9% |
| | Effective | | | | | 27 | | 39.1% |

Data are presented as numbers (n) and percentages (%),
SD: Standard deviation, Mean: Minimum, and maximum values

**Table 2. Comparison of demographic and clinical characteristics between the ivermectin and permethrin treatment groups**

| Characteristic | | Ivermectin | | | | Permethrin | | | | p | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SD/n-% | | | Median | Mean ± SD/n-% | | | Median | | |
| Age | | 44.6 | ± | 16.5 | 44.5 | 39.3 | ± | 15,4 | 37.0 | 0.069 | m |
| Gender | Male | 20 | | 52.6% | | 86 | | 61.9% | | 0.303 | $X^2$ |
| | Female | 18 | | 47.4% | | 53 | | 38.1% | | | |
| Need for family treatment | No | 21 | | 55.3% | | 72 | | 51.8% | | 0.705 | $X^2$ |
| | Yes | 17 | | 44.7% | | 67 | | 48.2% | | | |
| 7-Day follow-up treatment | Ineffective | 16 | | 42.1% | | 53 | | 38.1% | | 0.656 | $X^2$ |
| | Effective | 22 | | 57.9% | | 86 | | 61.9% | | | |
| 14-Day follow-up treatment | Ineffective | 9 | | 56.3% | | 33 | | 62.3% | | 0.604 | $X^2$ |
| | Effective | 7 | | 43.8% | | 20 | | 37.7% | | | |
| End of treatment (switched to the alternative therapy) | Ineffective | 9 | | 23.7% | | 33 | | 23.7% | | 0.519 | $X^2$ |
| | Effective | 29 | | 76.3% | | 106 | | 76.3% | | | |

Data are presented as numbers (n) and percentages (%), [m]Mann-whitney u test, [X]Chi-square test
SD: Standard deviation, Mean: Minimum, and maximum values

of the lack of available appointments with dermatologists and the ease of access to emergency services [5]. Similarly, in the United States, many patients with scabies seek treatment in the ED [6]. Tripathi et al. [6] showed that 52.37% of patients diagnosed with scabies in the ED were men; 41.53% of patients were between the ages of 18 and 39 years. Yurekli and Duran [7] also reported that 54% of the patients in their study were men. In this study, 59.9% of patients were men, and the mean age was 40.5±15.7 years.

Some studies have indicated that the effectiveness and safety of topical permethrin and oral ivermectin, both commonly used as first-line treatments for scabies, are similar [8,9]. However, a meta-analysis revealed an association between oral ivermectin and a significantly higher risk of treatment failure compared with topical permethrin [10]. In our study, we found that the efficacy of both drugs were similar (i.e., they did not significantly differ).

The reported success rate of a single dose of topical permethrin ranges from 89% to 98%; the rate increases to 98-100% when applied at a 1-week interval [2]. The efficacy of a single dose of oral ivermectin has also been noted in European scabies management guidelines [11]. Ranjkesh et al. [12] reported that two doses of topical permethrin were more effective than a single dose of oral ivermectin. Oral ivermectin administration twice at a 1-week interval reportedly improves treatment compliance [7,11]. Owing to its ease of use, oral ivermectin has received considerable attention in endemic communities, and it is considered an essential medicine by the WHO [1,9]. In our study, 61% of patients achieved treatment success with a single dose of the treatment. Treatment efficacy was observed in 61.9% of patients who received a single dose of permethrin, 37.7% of patients who received two doses of permethrin, 57.9% of patients who received a single dose of ivermectin, and 43.8% of patients who received two doses of ivermectin.

Contrary to the literature, the treatment efficacy of both drugs were lower than expected. Notably, 23.74% of patients using permethrin and 23.68% of patients using ivermectin did not respond to treatment. Factors such as treatment resistance, non-compliance by family members, and failure to properly clean household items in contact with scabies mites may have contributed to this outcome. Thus, adherence to recommendations for combined treatments may be a more effective approach [13].

### Study Limitations

This prospective observation, cross-sectional study was conducted with a limited number of patients at a single center. Due to the absence of an on-call or available dermatologist at the hospital, patients presenting to the ED with a presumptive diagnosis of scabies could not be referred for consultation; the diagnosis of scabies could not be confirmed using alternative diagnostic methods. The study might have yielded more robust results if it had been conducted with a larger number of participants at a hospital where an on-call dermatologist was available for consultation regarding all dermatological cases.

## Conclusion

Scabies are managed and treated by dermatologists and emergency medicine physicians in Türkiye. The effectiveness of topical permethrin and oral ivermectin, both commonly used as first-line treatment for scabies, appears to be similar. Although oral ivermectin is convenient, its accessibility is limited because patients must pay for it out-of-pocket when it is prescribed in the ED. In contrast, topical permethrin is financially accessible, but it is challenging to apply correctly. The treatment efficacy of both drugs may be lower than expected. Therefore, combined treatment with permethrin and ivermectin may be a viable treatment option. Improvements in patient adherence and medication access, family member contributions to treatment, and patient education regarding home hygiene can also contribute to better treatment outcomes.

### Ethics

**Ethics Committee Approval:** Ethical approval was obtained from the Haseki Training and Research Hospital Clinical Research Ethics Committee (decision number: 238-2023, date: 20.12.2023).

**Informed Consent:** Informed consent was obtained from all participants prior to their inclusion in the study.

### Footnote

### Authorship Contributions

Surgical and Medical Practices: T.B.Ü., Concept: T.B.Ü., H.A., Design: T.B.Ü., H.E., Data Collection or Processing: T.B.Ü., H.E., H.A., Analysis or Interpretation: T.B.Ü., H.E., H.A., Literature Search: T.B.Ü., H.E., H.A., Writing: T.B.Ü., H.A.

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ORIGINAL RESEARCH

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# A Multidisciplinary Analysis of Adults Referred for Psychiatric Consultation in the Emergency Department: Clinical Insights from a Period of Over One Year on Demographic Characteristics and Outcomes

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## Abstract

**Objective:** Emergency departments (EDs) frequently encounter patients experiencing mental health (MH) crises, which significantly affect healthcare systems. This study analyzed the demographic characteristics and outcomes of adults referred for psychiatric consultation in an ED for more than one year.

**Materials and Methods:** Ethical approval was secured, and data were collected from patients aged 18 years and older who presented to Ankara Mamak State Hospital's ED between November 2021 and December 2023. Data collected included demographics, psychiatric history, active suicidal ideation, medical treatment, and patient disposition. Patient outcomes, including ED discharge, hospitalization in Ankara Mamak State Hospital, referral to a psychiatric clinic, and intensive care unit (ICU) admission, were compared with descriptive data to assess the influence of patient characteristics.

**Results:** Of the 57 patients (66.7% female) included in this study, majority of the visits occurred between 08:00 and 16:00. Thirteen patients exhibited active suicidal ideation, with depressive disorders being the most prevalent diagnosis (n=30). Notably, patients without prior psychiatric diagnoses were more likely to be discharged (p=0.038), whereas those who attempted suicide shortly before admission had higher hospitalization rates (p=0.001).

**Conclusion:** This study identified relevant demographic and clinical factors that may influence psychiatric consultations in the ED. The significant presence of suicidal ideation prior to visits underscores the urgent need for timely intervention. Integrating psychiatric services within emergency care is vital for optimizing patient outcomes and ensuring that individuals with MH crises receive appropriate management. Future research should focus on developing standardized protocols for psychiatric consultations to enhance the quality of care in ED settings.

**Keywords:** Emergency department, psychiatric, emergency medicine, consultation, suicide

## Introduction

According to recent research data, a significant proportion of emergency department (ED) visits are related to mental health (MH) problems and suicide [1,2]. Moreover, the most important underlying risk factor for suicide cases is an MH problem [2]. Psychiatric disorders account for 4%-26% of all ED presentations, contributing substantially to the overall burden [1,3]. Patients presenting with psychiatric crises in the ED often require specialized assessment and management to address their unique needs and concerns [4-6]. Evaluating these patients can pose significant challenges, as assessment may be complicated by the necessity to investigate numerous domains, such as underlying medical conditions, prior psychiatric disorders, substance abuse,

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and psychosocial factors [5,7]. In recent years, the demand for psychiatric services in EDs has increased globally. MH-related visits to the EDs pose unique challenges for healthcare providers because of the complexity of psychiatric conditions and the urgency of these presentations. As a result, the need for psychiatric consultation in the ED has become increasingly crucial in ensuring appropriate evaluation, management, and disposition of patients with psychiatric emergencies [8,9]. Furthermore, the prevalence of psychiatric consultations in the ED has been steadily increasing over the years, underscoring the importance of integrating MH services within emergency care settings [3,10]. For ED clinicians, establishing close relationships with psychiatric consultants and reaching the consultant easily and quickly increases the frequency of psychiatric consultations [11]. The initial identification of psychiatric conditions before formal diagnosis contributes to the high number of such consultations. In fact, suicide cases in EDs are the most frequent reason for psychiatric consultations in many data sources [11]. Despite the recognized significance of psychiatric consultations in the ED, there remains variability in the implementation and delivery of these services across healthcare institutions. Factors such as staffing shortages, limited resources, and lack of standardized protocols can pose challenges to the timely and effective provision of psychiatric care in ED settings [12,13]. However, research suggests that the involvement of psychiatric consultation services can lead to improved patient outcomes, including reduced hospital admissions, decreased lengths of stay, and enhanced linkage to outpatient MH services [12,13]. Given the increasing demand for psychiatric services in the ED and the potential impact of psychiatric consultations on patient care and outcomes, there is a growing need for comprehensive studies that examine the characteristics and outcomes of patients referred for psychiatric consultation in this setting. This retrospective study aimed to address this gap by analyzing the demographic characteristics, clinical presentations, and treatment outcomes of patients referred for psychiatric consultation in the ED of a center in Ankara, in Türkiye. By elucidating the role and significance of psychiatric consultations in the context of emergency care, this study sought to contribute valuable insights into optimizing the management of psychiatric emergencies in ED settings.

## Materials and Methods

### Ethics Approval, Study Permits, Data Collection Design, and Recorded Data

Ethical approval for this study was obtained from the local Gazi University rectorship ethics committee (approval number: 08, date: 10.05.2023). Following this approval, patient data were reviewed retrospectively under data protection regulations from the hospital's electronic patient data system. All data were recorded electronically by the researchers without the inclusion of patient-identifying information. This study was conducted in accordance with the Declaration of Helsinki.

Data were collected for all patients aged 18 years and older who presented to the ED of Ankara Mamak State Hospital, which sees approximately 200,000 patients annually, between November 2021 and December 2023, and for whom a psychiatric consultation was requested by the attending clinician. The majority of these patients are patients in the green zone who present for outpatient care and can be discharged with a prescription. The recorded data included age, gender, time of visit, presence of active suicidal ideation or prior suicide attempts, history of psychiatric diagnoses, psychiatric diagnoses made in the ED, medical treatments administered, whether physical restraint or sedation was used, alcohol consumption (with biochemical analysis or physical examination), substance influence, self-harming or violent behavior, and the patient's final disposition. Patients with incomplete or missing data were excluded from the study.

### Outcome Measures and Comparisons

Patient outcome measures were categorized into four parameters: discharge from the ED without further intervention, hospitalization at Ankara Mamak State Hospital, referral to another hospital's psychiatric clinic, and admission to intensive care unit (ICU). These outcome parameters were then compared with the descriptive data to assess the potential influence of the recorded characteristics.

### Statistical Analysis

Data analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics for patient demographics were reported as frequencies (n) and percentages (%). The Shapiro-Wilk test was used to assess data normality. Because the data did not follow a normal distribution, non-parametric tests were employed. Categorical variables were analyzed using the chi-square test and Fisher's exact test. The Mann-Whitney U test was used for comparisons between two independent groups, and the Kruskal-Wallis test was employed for comparisons between multiple independent groups, with post-hoc analysis conducted using the Mann-Whitney U test. Spearman's correlation test was used to evaluate the relationships between numerical variables. A p-value 0.05 was considered statistically significant.

## Results

### Descriptive Results

A total of 57 patients with complete data were included in the study, of whom 38 were women. Patient visits were more frequent between 08:00 and 16:00 compared to other 8-hour periods. Thirteen patients exhibited active suicidal ideation. Although not statistically significant, anxiety disorders and depressive disorders were the most common past psychiatric

diagnoses (n=7 and n=6, respectively). The most prevalent diagnosis in the ED was depressive disorders (n=30). Only a small number of patients received medical treatment in the ED (n=10), and only 7 patients were restrained with ligatures. Nearly half of the patients had received prior psychiatric treatment (n=26), while the other half had not (n=31). The number of patients under the influence of alcohol was greater than that of patients not affected (n=31 vs. n=26), whereas fewer patients were under the influence of drugs (n=12). More than half of the patients had attempted suicide shortly before admission (n=31). More patients were discharged from the ED than those admitted for further treatment (n=23) (Table 1).

### Findings from the Comparative Analysis

There was no significant relationship between patient outcomes-whether discharged from the ED, hospitalized at Ankara Mamak State Hospital, referred to another hospital's psychiatric clinic, or admitted to an ICU-and variable such as age, gender, presence of active suicidal ideation, psychiatric diagnosis made in the ED, current alcohol use, substance influence, or prior psychiatric treatment ($p>0.05$ for each comparison) (Table 2). However, patients without previous psychiatric diagnosis were more likely to be discharged from the ED ($p=0.038$). The post-hoc analysis revealed that this difference was due to the higher number of patients diagnosed with bipolar disorder being referred to other hospitals' psychiatric clinics ($p=0.009$; $z=-2.602$). Similarly, those who did not receive medical treatment in the ED were discharged more frequently ($p=0.003$). The rate of hospitalization at Ankara Mamak State Hospital was higher among patients who had attempted suicide immediately before their ED visit ($p=0.001$) (Table 2).

## Discussion

This study provides a comprehensive analysis of the demographic and clinical characteristics of patients referred for psychiatric consultation in an ED, along with an in-depth evaluation of these factors in relation to clinical outcomes. By comparing descriptive data with patient outcomes, such as discharge, hospitalization, referral, and ICU admission, this study sheds light on the potential impact of various factors, including prior psychiatric diagnoses, suicidal ideation, and medical treatments administered in the ED.

In this study, the majority of patients were women, which is in contrast to some studies suggesting a higher prevalence of males in similar populations [4,14,15]. This discrepancy can be attributed to our limited sample size. Additionally, sociodemographic factors and cultural beliefs, which were not part of our study, may influence the gender distribution within this patient group. These descriptive data were not included in this retrospective analysis. In a dataset where such factors are accessible, more accurate commentary on gender differences can be made. The findings indicate that the majority of ED visits occurred during the one-third of the day between 08:00 and 16:00. Additionally, our data revealed that the rate of suicide attempts was notably high immediately prior to these visits. This suggests that individuals may plan their visits during specific hours. Stańdo et al. [16] recently researched and published findings on the most frequent searches for the terms "depression" and "suicide" were most frequently searched online. Their results indicated that searches peaks in the late evening and night hours. The findings of this study suggest that suicidal thoughts could intensify during the late evening and throughout the night; however, due to the small sample size and single-center nature of the study, we cannot present this information too assertively. Further research is essential to draw definitive conclusions regarding the impact of hospital visits. Despite the detection of numerous suicide cases, the evaluation in the ED revealed a lower prevalence of active suicidal thoughts. This finding suggests that individuals who present to the ED following a suicide attempt do so out of regret or fear of death. However, due to the study design, patients could not be interviewed to ascertain whether they experienced regret or fear. In this context, valuable insights can be gained through a prospective dataset or by re-establishing patient communication.

The results revealed no significant relationship between clinical outcomes and patient characteristics like age, gender, active suicidal ideation, psychiatric diagnoses made in the ED, alcohol or substance use, or prior psychiatric treatment. However, a notable finding was that patients without a previous psychiatric diagnosis were more likely to be discharged, suggesting that patients with a psychiatric history may require more intensive management or referral to specialized psychiatric services. Additionally, the post-hoc analysis highlighted that patients with bipolar disorder were significantly more likely to be referred to other hospitals for psychiatric care. This finding reflects the circumstances at our institution, where there is no dedicated psychiatric unit, which may have resulted in a higher referral rate for certain diagnoses [4,11]. Furthermore, patients who did not receive medical treatment in the ED were discharged more frequently, which could imply that non-pharmacological interventions or the absence of acute medical needs played a role in their quicker discharge. This finding is consistent with research suggesting that timely psychiatric evaluation and noninvasive management in the ED can facilitate early discharge [12]. On the other hand, patients who had attempted suicide just before admission were more likely to be hospitalized, reflecting the need for close monitoring and intervention in these high-risk cases, which corroborates findings from similar studies that highlight the importance of hospitalization in managing patients with suicidal behavior [3, 10]. These findings emphasize the complexity of psychiatric consultations in emergency settings. They highlighted that

| Table 1. Demographic and descriptive characteristics of adults undergoing psychiatric consultation in the emergency department | | |
|---|---|---|
| | | n (%) |
| Age, years (median, minimum-maximum) | | 27 (16-97) |
| Gender | Male | 19 (33.3%) |
| | Female | 38 (66.7%) |
| Time of visiting ED in day | 00:00-08:00 | 10 (17.5%) |
| | 08:00-16:00 | 29 (50.9%) |
| | 16:00-00:00 | 18 (31.6%) |
| Already active suicidal ideation in ED visit | Yes | 13 (22.8%) |
| | None | 44 (77.2%) |
| Past psychiatric diagnosis | Psychotic disorders | 3 (5.3%) |
| | Depressive disorders | 6 (10.5%) |
| | Bipolar affective disorder | 4 (7%) |
| | Anxiety disorders | 10 (17.6%) |
| | Alcohol use disorders | 2 (3.5%) |
| | Other | 2 (3.5%) |
| | None | 30 (52.6%) |
| Psychiatric diagnosis in ED | Psychotic disorders | 5 (8.8%) |
| | Depressive disorders | 30 (52.6%) |
| | Bipolar affective disorder | 3 (5.3%) |
| | Anxiety disorders | 14 (24.5%) |
| | Alcohol use disorders | 4 (7%) |
| | Other | 1 (1.8%) |
| Medical psychiatric treatment in ED | Haloperidol with biperiden | 5 (8.8%) |
| | Any other antipsychotic | 1 (1.8%) |
| | Benzodiazepines | 4 (7%) |
| | None | 47 (82.5%) |
| Fix the patient by bonding ED | Yes | 7 (12.3) |
| | None | 50 (87.7%) |
| Any prior psychiatric medical treatment | Yes | 26 (45.6%) |
| | None | 31 (54.4%) |
| Alcohol use prior to ED visit | Yes | 31(54.4%) |
| | None | 26 (45.6%) |
| Being under the influence of drugs in ED | Yes | 12 (21.1%) |
| | None | 45 (78.9%) |
| Suicide attempt just before ED visit | Yes | 31 (54.4%) |
| | None | 26 (45.6%) |
| Outcome of ED visit | Discharge from ED | 23 (40.4%) |
| | Hospitalization in Ankara Mamak State Hospital | 19 (33.3%) |
| | Transfer to another hospital's psychiatric clinic | 14 (24.6%) |
| | Hospitalization in any ICU | 1 (1.8%) |

ED: Emergency department, ICU: Intensive care unit

managing patients in such situations requires a detailed and careful approach. The multifaceted nature of patient management further complicates the process. The literature supports the notion that patients presenting with psychiatric emergencies benefit from early and structured psychiatric consultation, which can lead to more appropriate dispositions, whether discharge, hospitalization, or referral [8]. Moreover, the increasing prevalence of psychiatric consultations indicates

**Table 2. Results of comparative analyses of patients' descriptive characteristics and clinical outcomes**

| | | Discharge from ED | Hospitalization in Ankara Mamak State Hospital | Transfer to another hospital's psychiatric clinic | Hospitalization in any ICU | p |
|---|---|---|---|---|---|---|
| | | n | n | n | n | |
| Age, (median, minimum-maximum); years | | | | | | 0.716 |
| Gender | Male | 6 | 6 | 7 | 0 | 0.428 |
| Time of visiting in day | 00:00-08:00 | 4 | 4 | 2 | 0 | 0.767 |
| | 08:00-16:00 | 10 | 8 | 10 | 1 | |
| | 16:00-00:00 | 9 | 7 | 2 | 0 | |
| Active suicidal idea already in ED visit | Yes | 3 | 4 | 5 | 1 | 0.117 |
| Past psychiatric diagnose | Psychotic disorders | 0 | 0 | 3 | 0 | **0.038** |
| | Depressive disorders | 2 | 2 | 2 | 0 | |
| | Bipolar affective disorder | 0 | 1 | 3 | 0 | |
| | Anxiety disorders | 4 | 5 | 1 | 0 | |
| | Alcohol use disorder | 1 | 0 | 1 | 0 | |
| | Other | 2 | 0 | 0 | 0 | |
| | None | 14 | 11 | 4 | 1 | |
| Psychiatric diagnose in ED | Psychotic disorders | 1 | 1 | 3 | 0 | 0.290 |
| | Depressive disorders | 11 | 14 | 4 | 1 | |
| | Bipolar affective disorder | 0 | 0 | 3 | 0 | |
| | Anxiety disorders | 8 | 4 | 2 | 0 | |
| | Alcohol use disorder | 2 | 0 | 2 | 0 | |
| | Other | 1 | 0 | 0 | 0 | |
| | None | 0 | 0 | 0 | 0 | |
| Medical psychiatric treatment in ED | Haloperidol with biperiden | 1 | 0 | 4 | 0 | **0.003** |
| | Any other antipsychotic | 0 | 0 | 1 | 0 | |
| | Benzodiazepines | 0 | 2 | 2 | 0 | |
| | None | 22 | 17 | 7 | 1 | |
| Fix the patient by bonding in ED | Yes | 2 | 0 | 5 | 0 | **0.018** |
| Any prior psychiatric medical treatment | Yes | 8 | 9 | 9 | 0 | 0.278 |
| Alcohol use prior to ED admission | Yes | 11 | 9 | 11 | 0 | 0.159 |
| Being in effect of drug in ED | Yes | 2 | 7 | 3 | 0 | 0.162 |
| Suicidal action just before admission to ED | Yes | 6 | 17 | 7 | 1 | **0.001** |

ED: Emergency department, ICU: Intensive care unit

the necessity of integrating MH services within emergency care environments to address the growing demand and improve patient outcomes [9].

This study has several limitations. Although the study covered a long period of time, the number of patients was limited, and it was a single-center study, which restricts the generalizability of the results. Additionally, important quality data, such as the response times to the psychiatric consultations, were not available. As a result, predictions could not be made in this area. The retrospective nature of data collection limits the ability to gather additional patient information. The data being sourced from a single hospital may overlook differences that could arise in various geographical regions or healthcare settings. Furthermore, psychosocial factors such as socioeconomic status, cultural beliefs, and family structure were not assessed, although they could influence how patients present to the ED and their treatment outcomes. The study also did not evaluate whether patients adhered to their treatment plans or continued

care after discharge, which could have prevented insights into the long-term effectiveness of emergency interventions. In the future, more reliable results could be obtained through multicenter, prospective studies with access to larger datasets. Additionally, a more comprehensive examination of psychiatric patients' emergency visits and long-term treatment outcomes would provide valuable insights into the effectiveness of interventions beyond the ED setting.

## Conclusion

This study underscores the critical demographic and clinical factors influencing outcomes among adults referred for psychiatric consultation in the ED. The high prevalence of depressive disorders and significant presence of active suicidal ideation prior to admission highlight the urgent need for timely and effective psychiatric interventions. Our findings revealed that patients without prior psychiatric diagnoses were more likely to be discharged from the ED, suggesting the necessity for tailored management strategies for those with established psychiatric histories. The study also emphasizes the importance of integrating psychiatric services within emergency care to enhance the management of MH crises. Future research should focus on developing standardized protocols for psychiatric consultations in EDs, as well as exploring long-term outcomes for patients undergoing emergency visits. By addressing these areas, we can improve the quality of care for individuals experiencing MH emergencies and reduce treatment delivery variability.

### Ethics

**Ethics Committee Approval:** Ethical approval for this study was obtained from the local Gazi University rectorship ethics committee (approval number: 08, date: 10.05.2023).

**Informed Consent:** Retrospective study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: M.G., S.Z., Concept: M.G., S.Z., Design: M.G., S.Z., Data Collection or Processing: M.G., S.Z., Analysis or Interpretation: M.G., S.Z., Literature Search: M.G., S.Z., Writing: M.G., S.Z.

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ORIGINAL RESEARCH

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# Changes Occurring in Health Services Provided to Syrian Refugees Between 2017-2023 and the Current Situation after the Kahramanmaraş Earthquake

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## Abstract

**Objective:** The number of Syrian refugees increased day by day. In this study, the changes in health services provided to Syrian refugees in Türkiye between 2017 and 2023, and the current situation of refugees after the Kahramanmaraş earthquakes were investigated.

**Materials and Methods:** In this retrospective, descriptive, observational epidemiological study, the changes occurring in the demographic structure and healthcare field over the above-mentioned years were examined based on the reports and statistics published by various national and international institutions and organisations.

**Results:** Among Syrian refugees in the world, 64.6% live in Türkiye. More than 6,600 Syrian refugees died in the Kahramanmaraş earthquake. It was observed that the number of refugee camps and the health services provided in these camps decreased until the Kahramanmaraş earthquake.

**Conclusion:** The settlement of Syrian refugees in Türkiye for more than 12 years has caused changes in various areas of life in Türkiye. It was observed that the number and quality of health services provided to Syrian refugees increased at a rate greater than the increase in the population of Syrian refugees between the years 2017-2023. Moreover, the natural disasters occurring in Türkiye have also affected the living conditions of refugees.

**Keywords:** Syrian refugees, Kahramanmaraş earthquake, health care systems, access to health services, displaced persons

## Introduction

Following the two earthquakes that occurred in Kahramanmaraş on February 6, 2023, an event regarded as the disaster of the century in Türkiye, 11 provinces were affected. Syrian refugees living in these provinces were also affected along with and local people. Fifty percent of Syrian refugees reside in the provinces affected by the earthquake (Kahramanmaraş, Malatya, Gaziantep, Adana, Adıyaman, Diyarbakır, Elazığ, Hatay, Şanlıurfa, Kilis, and Osmaniye). While some Syrian refugees returned to their country following the earthquake, others continue their lives in container cities and reopened temporary accommodation centres [1].

After the Syrian civil war that broke out in 2011, citizens of that country migrated to other countries, especially the neighbouring countries. This ever-increasing migration of refugees has become a humanitarian crisis over time. As of June 2023, the total number of Syrian refugees in the world is approximately 5,291,289, and 63.5% of these live in Türkiye [2]. Between 2011 and 2016, Türkiye pursued an open border policy for Syrian refugees [3]. The increase in the number of

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Syrian refugees during the past 12 years has affected Türkiye, which hosts more than half of the world's Syrian refugees, demographically, socio-economically, and in terms of the provision of health services. The treatment of wounded people brought to Türkiye from the areas of conflict, the preventive health services provided to healthy refugees who entered the country, and to refugees born and raised in Türkiye over the past 12 years, and the treatment of the diseases occurring during this period, have led to an increase in the number of health services provided and to changes in the healthcare system.

This study investigates the current situation of Syrian refugees, changes in their living conditions after the earthquakes, changes in the demographic structures of Syrian refugees in Türkiye over the last six years, and the development of health services provided to Syrian refugees.

## Materials and Methods

### Study Design

In this retrospective, descriptive, observational epidemiological study, the changes that have occurred over the last six years were examined based on the reports and statistics published by various national and international institutions, and organisations, like United Nations High Commissioner for Refugees (UNHCR), the Presidency of Migration Management of the Ministry of Interior, Disaster and Emergency Management Presidency.

### Study Permission

The study has been designed retrospectively and does not involve the use of any personal data of individuals, biological samples, or experimental procedures on individuals. The study was conducted in accordance with the 1964 Helsinki Declaration and did not require ethical committee approval due to the reasons mentioned above. In addition, data obtained from the statement made by the Presidency of Migration Management of the Ministry of Interior, dated 31.03.2022, were used in our analysis.

### Statistical Analysis

The obtained data were compared with the data of previous years and with the world data. Descriptive statistics were created by analysing the data in the Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (IBM Corporation Chicago, Illinois).

## Results

Situation of Syrian refugees in Türkiye and in the World: According to the data released by the UNHCR on February 2, 2023, there were 5,422,789 Syrian refugees in the world. Among these, 64.6% (3,500,964) lived in Türkiye, 15% (814,715) in Lebanon, 12.2% (661,670) in Jordan, 4.8% (258,541) in Iraq, and 2.7% (145,157) in Egypt [2].

When the 2017 and 2023 data are compared, the Syrian refugee population has decreased in Lebanon, while in other countries, the Syrian refugee population has increased [2,4]. When these countries are compared, it can be seen that the Syrian refugee population has increased the most in Türkiye (Table 1).

When the living areas of Syrian refugees in the world are evaluated, it can be seen that the number of Syrian refugees living in camps has decreased continuously since 2014 [2].

As of February 2, 2023, a total of 3,500,964 Syrian refugees (1,634,881 females and 1,866,083 males) were under temporary protection in Türkiye. There were 440,225 refugees under the age of 5 (212,759 female, 227,466 male), 1,658,100 refugees aged 18 and under (800,178 female, 857,922 male), and 123,190 refugees aged 60 and over (Table 1, Figure 1) [5].

Around 1.3% of Syrian refugees in Türkiye reside in Temporary Accommodation Centres affiliated with the General Directorate of Migration Management. A total of, 47,647 Syrian refugees live in 7 temporary accommodation centres in 5 provinces. According to the latest data available before the earthquake on February 2, 2023, 536,171 of the Syrian refugees living in 81 provinces resided in İstanbul, 460,150 in Gaziantep, 368,223 in Şanlıurfa, and 354,648 in Hatay. In terms of population density, there were 87,409 Syrian refugees in Kilis, representing 37.48% of the city's population [5,6].

**Table 1. Number of Syrian refugees in countries of asylum in 2017 and 2023 and demographic information of Syrian refugees living in Türkiye for 2017 and 2023**

| Parameter | 2017, Number of refugees, (%) | 2023, Number of refugees, (%) |
|---|---|---|
| **Refugee count in the World** | | |
| Türkiye | 2,854,968 (58.2%) | 3,500,964 (64.5%) |
| Lebanon | 1,017,433 (20.7%) | 814,715 (15%) |
| Jordan | 655,496 (13.4%) | 661,670 (12.2%) |
| Iraq | 230,836 (4.7%) | 259,584 (4.8%) |
| Egypt | 116,013 (2.4%) | 145,157 (2.7%) |
| North Africa/other | 29,275 (0.5%) | 41,742 (0.8%) |
| Total | 4,904,021 (100%) | 5,423,832 (100%) |
| **Refugees in Türkiye** | | |
| **Gender** | | |
| Female | 1,571,674 (45.9%) | 1,634,881 (46.7%) |
| Male | 1,852,563 (54.1%) | 1,866,083 (53.3%) |
| Total | 3,424,237 (100%) | 3,500,964 (100%) |
| **Age groups** | | |
| Under 5 | 465,574 (13.5%) | 440,225 (12.5%) |
| 18 and under | 1,622,590 (47.3%) | 1,658,100 (47.3%) |
| 60 and over | 104,811 (3%) | 123,190 (3.5%) |

According to the 2021 data, 10 medical specialists, 40 medical practitioners, 4 dental practitioners, and 70 midwives-nurses worked in Migrant Health Centres located in 7 Temporary Accommodation Centres in 5 provinces. Between 2017 and 2021, 40,878,459 Syrian refugees were provided with examination and treatment services in secondary and tertiary hospitals (8,428,018 in 2017, 10,163,648 in 2018, 9,083,826 in 2019, 6,806,625 in 2020, and 6,396,342 in 2021). Among these patients, 1,560,627 (310,507 in 2017, 388,695 in 2018, 366,805 in 2019, 264,995 in 2020, and 229,625 in 2021) had surgery. Between 2017 and 2021, 25,942 Syrian refugees (5,425 in 2017, 8,484 in 2018, 5,634 in 2019, 3,461 in 2020, and 2,938 in 2021) were transported within Türkiye by ambulance. Within the scope of the vaccination programme, 5,537,388 Syrian refugees (1,435,582 in 2017, 1,135,706 in 2018, 1,199,507 in 2019, 934,373 in 2020, and 832,220 in 2021) were vaccinated between 2017 and 2021 (Table 2, Figure 2) [7].

**Table 2. Camps and number of health personnel working in camps and access to health services between 2011-2016 and 2017-2021 [4,8]**

| Parameter | Years | | |
|---|---|---|---|
| Camps and number of health personnel working in camps | 2016 | 2021 | Change |
| Number of cities where camps are located | 10 | 5 | -50% |
| Number of camps | 26 | 7 | -73% |
| Number of medical specialists | 71 | 10 | -86% |
| Number of medical practitioners | 110 | 40 | -64% |
| Number of dental practitioners | 30 | 4 | -87% |
| Number of allied health personnel | 102 | 70 | -31% |
| Access to health services | 2011-2016 | 2017-2021 | |
| Number of hospital admissions | 815,430 | 40,878,459 | +4900% |
| Number of surgical operations | 686,861 | 1,560,627 | +127% |
| Number of refugees transported by ambulance | 31,590 | 25,942 | -19.1% |
| Number of refugees vaccinated | 1,804,574 | 5,537,388 | +206% |

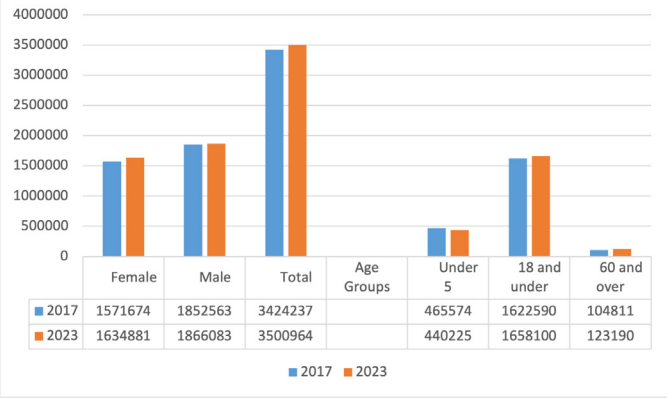


**Figure 1.** Gender and age distribution of Syrian refugees by year

Some refugees from Syria who have sought asylum in other countries since 2011 have also migrated from those countries for various reasons. In 2021, 36,500 Syrian refugees, including 22,300 from Türkiye, returned to their own country [8]. In addition, 25,774 Syrian refugees settled in different countries [9]. Among these, 4,200 Syrian refugees were resettled in Canada, 2,000 were resettled in the United States, and 2,600 were resettled in Sweden [8]. According to the data released on February 2, 2023, a total of 20,520 Syrian refugees were resettled in other countries between 2014 and 2023, and 10,655 of them were in Canada. Within the scope of the "one-for-one formula", 36,789 Syrian refugees left Türkiye [5]. In 2022, 10,584 refugees applied to 13 countries for resettlement. Among these, 5,144 refugees, of whom 79% were Syrian and 8% were Afghan nationals, were resettled in 14 countries [10].

## The Situation of Syrian Refugees and Changes in Their Living Conditions after the Kahramanmaraş Earthquake

It is believed that at least 15 million people, 1.7 million of whom are Syrian refugees under temporary protection, were affected by the two earthquakes that impacted 11 provinces in Türkiye and Syria [11]. The ratio of Syrian refugees residing in the earthquake area to the local population is 11.48%. Forty-five percent of the Syrian refugees residing in the region are between the ages of 0-17, while 3% are over the age of 65 [1]. It is thought that more than 6,600 Syrian refugees died in the earthquakes, in which 50,500 people died [12,13]. According to the statement made on March 27, 2023, 60,000 Syrian refugees voluntarily returned to Syria after the earthquake [14]. According to the UNHCR data, 16,000 Syrians came back to Türkiye [15]. According to the data announced on April 19, 2023, there are 3,411,029 Syrian refugees living in Türkiye [2]. Among the Syrian refugees, 531,098 reside in İstanbul, 450,115 in Gaziantep, 349,919 in Şanlıurfa, and 330,239 in Hatay. According to the data announced on 8 June 2023, there are 3,358,813 Syrian refugees living in Türkiye. Among the Syrian refugees, 531,310 reside in İstanbul, 441,125 in Gaziantep, 335,274 in Şanlıurfa, and 315,380 in Hatay [5]. It can be seen that the number of Syrian refugees residing in the earthquake area has decreased over time (Table 3).

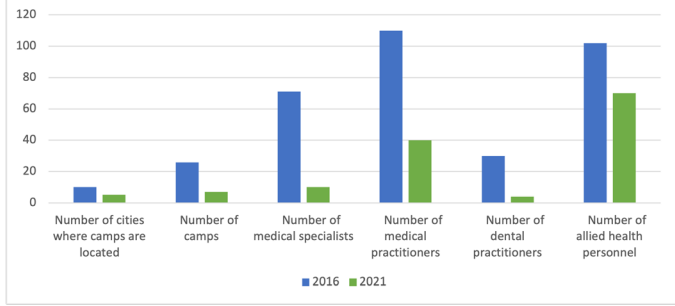


**Figure 2.** The number of camps housing Syrian refugees and the number of healthcare personnel working in these camps

**Table 3. Population of Syrian refugees by province of residence**

| Place of residence | Date/Syrian refugee population | | | | Change in one year |
|---|---|---|---|---|---|
| | 02.02.2023 n (%) | 19.04.2023 n (%) | 08.06.2023 n (%) | 01.02.2024 n (%) | |
| İstanbul | 536,171 (15.3) | 531,098 (15.57) | 531,310 (15.81) | 530,170 (16.66) | -1.11% |
| Gaziantep | 460,150 (13.14) | 450,115 (13.19) | 441,125 (13.3) | 427,563 (13.44) | -7.08% |
| Şanlıurfa | 368,223 (10.5) | 349,919 (10.25) | 335,274 (9.98) | 291,081 (9.14) | -20.94% |
| Hatay | 354,648 (10.13) | 330,239 (9.6) | 315,380 (9.38) | 275,084 (8.64) | -22.43% |
| Toplam | 3,500,964 (100) | 3,411,029 (100) | 3,358,813 (100) | 3,181,222 (100) | -9.13% |

Various arrangements and improvements were made for Syrian refugees in line with their increasing needs following the earthquake. The number of temporary shelters, which had decreased to 7 before the earthquake, was increased to 12. While 47,647 people lived in temporary accommodation centres before the earthquake, this number increased to approximately 88 thousand after the earthquake. In line with the increasing need, 500 extra personnel were appointed in addition to the 7,000 personnel already working in these centres [1].

## Discussion

### Refugee Policy from Past to Present

The Ottoman Empire and later the Republic of Türkiye, frequently opened its doors to people in need of asylum and protection due to its "national understanding that protects those in need". Türkiye, which continues to pursue this understanding today, is the country that hosts the highest number of Syrian refugees in the world. In addition to providing security, the historical and cultural ties between Türkiye and Syria, the suitable living conditions, the economy, and the number and quality of health services provided, are among the reasons why Syrian refugees migrate to Türkiye and continue their lives there [16].

### Demographic Characteristics and Living Conditions of Syrian Refugees in Türkiye

In 2017, the percentage of the world's Syrian refugee population residing in Türkiye was as high as 70%, while it decreased to 64% in 2023 with the return of Syrian refugees to their own countries and their settlement in other countries [2,4]. When the years 2017 and 2023 are compared, it can be seen that the ratio between the female and male populations has not changed, while the population under the age of 18 has increased. In addition to births, the increase in the population under the age of 18 may have been due to the living conditions and healthcare facilities provided to the babies. In a study conducted by Kinik et al. [17], which evaluated the health services received by Syrian refugees, it was found that 15.8% of refugees who received health services between 2011 and 2018 were under the age of 5, while 15.4% were between the ages of 5-9. In addition, it was found that women received more healthcare services than men, and that the group receiving healthcare was mostly women of childbearing age aged [17]. This reflects the importance given to maternal-child health and the high capacity for care in Türkiye.

When the refugee camps and the health services provided in these camps are evaluated, a decrease was seen in the number of camps and the number of health personnel working in, camps, between 2017-2021. However, an increase was observed in the number of health personnel after the Kahramanmaraş earthquake. Support for Syrian refugees under temporary protection, living in temporary accommodation centres, enabled them to transition to life outside the camps and played a role in this decrease. Syrian refugees who could not return to their country created their own living areas, and thus they integrated into social life. During this period, the healthcare needs of Syrian refugees were met in the same way as Turkish citizens, in either hospitals or community health centres and in migrant health centres specifically opened for Syrian refugees. However, the constraints in housing conditions due to the destruction experienced in 11 provinces after the Kahramanmaraş earthquake made it necessary to open the temporary accommodation centres again. This explains why the number of temporary accommodation centres, which had decreased from 26 in 2016 to 7 in 2021, increased again to 12 after the earthquake.

### Health Services in Türkiye

When access to health services between 2011-2016 and 2017-2021 is compared, it can be seen that hospital admissions increased by almost 50-fold in 2017-2021 compared to 2011-2016. Although the Syrian population in 2021 was about 1.3 times the, population of 2016, it can be seen that the number of hospital admissions increased, almost 50 times between those years. It can be said that in addition to the increase in population, the development of health services, the construction of new hospitals, and the free and easy access to health services with the facilities provided to refugees, the humane approach and lack of prejudice of the Turkish people, and the coronavirus disease-2019 (COVID-19) pandemic were effective in this increase. It was observed that the number of surgical operations performed between the above-mentioned years increased by a factor of 2.2. However, a decrease was

observed in the number of refugees transported by ambulance. While the number of refugees transported by ambulance was high before 2017 due to injured people brought to Türkiye from the conflict zones in Syria during the first years of the civil war, this number has now decreased.

Acute infectious diseases are a significant public health concern in densely populated areas such as camps. In temporary housing facilities for Syrian refugees in Türkiye, a total of 1,299,209 respiratory tract infection cases were reported between 2012 and 2016. Additionally, 158,058 cases of diarrhea, including 59 cases of bloody diarrhea, were recorded. Furthermore, 1,354 cases of hepatitis A and 108 cases of active tuberculosis were identified and treated [18]. Another significant issue among infectious diseases is vector-borne cutaneous leishmaniasis, which is widely prevalent in the Aleppo and Damascus regions of Syria. In refugee camps in Türkiye, the number of reported cutaneous leishmaniasis cases was 109 in 2012, 2,835 in 2013, 1,843 in 2014, and 718 in 2015 [19]. Measles is a significant vaccine-preventable infectious disease, with a notable increase in cases observed among Syrian refugees. In 2011, 111 cases were reported among Syrian refugees. In 2012, 31 cases were detected in Syrian refugees, along with 318 local cases, whereas no local cases had been previously recorded. By 2013, the number of measles cases among Syrian refugees rose to 674, with a total of 6,731 cases reported nationwide. In 2014, 114 cases were recorded among Syrian refugees. However, following intensive vaccination campaigns, only 9 cases were identified among foreign nationals in 2016, with no local cases reported. These data highlight the spread of measles outbreaks in refugee populations and the effectiveness of vaccination programs in controlling the disease [20].

One of the most important preventive health services provided in Türkiye is vaccination. According to the data from the General Directorate of Public Health, vaccination rates were 96% for Bacillus Calmette-Guérin (BCG) vaccine, 99% for diphtheria, for diphtheria, tetanus, and pertussis 3 (DTaP3) vaccine, 99% for hepatitis B vaccine, and 97% for measles, mumps, and rubella (MMR) vaccine in 2019. When MMR vaccination rates are compared globally the rate is 97% in Türkiye, it is 96% in the World Health Organization European Region, and 85% in the world [21]. Syrian refugees in Türkiye are vaccinated according to the Turkish National Vaccination Calendar, which includes BCG, DTaP-IPV/Hib, pneumococcal conjugate vaccine, hepatitis B, MMR, chickenpox, hepatitis A, and tetanus-diphtheria vaccines. Women of reproductive age are also vaccinated for tetanus-diphtheria [22]. According to the 2019 UNICEF Annual Report, 60% of Syrian children and 98% of Turkish children received all age-appropriate vaccinations in 2018 [23]. A total of 5.5 million doses of vaccine were supplied within the scope of the SIHHAT project. By the end of June 2020, 4.2 million doses of vaccine were administered to children aged 0-59 months [24]. The number of vaccinated refugees tripled between 2017-2021 compared to 2011-2016. This increase can be explained by both the rise of Syrian refugees entering Türkiye and their inclusion in vaccination programmes under the Temporary Protection Regulation in Türkiye. Moreover, the initiation of vaccinations for COVID-19 in 2021 may also have been effective in this case.

### Syrian Refugee Health Services in Other Countries

Doocy et al. [25] conducted a study in Jordan, one of the regions with a high concentration of Syrian refugees, and found that despite a high need for healthcare services, cost was a significant barrier to accessing these services. In Lebanon, Honein-AbouHaidar et al. [26] conducted a study and found that while refugees had easy access to primary healthcare services, accessing secondary and tertiary healthcare became increasingly difficult due to rising costs. Although UNHCR covers 75% of hospital expenses for registered refugees, this support is limited to emergency and life-threatening conditions. Additionally, the economic crisis has led to rising medication costs and shortages, further restricting access to essential medicines [26].

A review evaluating studies conducted in Syria's neighboring countries, including Iraq, Lebanon, Jordan, and Türkiye, highlighted that chronic diseases and women's health were predominant concerns in Jordan; women's health, mental health, and infectious diseases were major issues in Lebanon; women's health and mental health were prioritized in Iraq; and only mental health problems were emphasized in Türkiye. Additionally, the review underscored the low childhood vaccination rates in Lebanon and Jordan [27].

### Effects of Syrian Refugees on Healthcare Delivery

In a globalized world, the mobility of refugees is remarkably high. Preventive health interventions, particularly vaccination programs, are crucial in preventing outbreaks of infectious diseases not only in the host communities where migrants reside, but also in the societies they may move to in the future. Regarding chronic diseases, early diagnosis and treatment are essential to prevent disease complications, improve patient prognosis, and avoid increased healthcare costs in the refugees' future host countries. Therefore, Türkiye's healthcare policies have a significant global impact. To improve refugee health, it is beneficial to prioritize healthcare services for disadvantaged groups, including the elderly, individuals with chronic diseases, children, mothers with young children, and individuals with disabilities, while also expanding preventive healthcare efforts targeting these populations.

### Current Migration Status of Syrian Refugees

Due to the lack of a safe environment in Syria, Syrian refugees have had to extend their stay in Türkiye. However, Syrian refugees have begun to return voluntarily to the regions made secure by the military operations conducted by Türkiye. According to statements

made on May 5, 2020 and May 23, 2023, 402,011 and 554,000 Syrian refugees returned to their country, respectively [28,29]. Especially after the earthquake that occurred in Kahramanmaraş on February 6, 2023, an increase was observed in the return of Syrian refugees, living in these provinces, to their country [30]. Steps were taken to resettle refugees and normalize conditions in areas made safe by operations such as Operation Euphrates Shield, Operation Olive Branch, and Operation Spring Shield conducted in regions close to the Turkish border. The last attempt made for this purpose, is the project for constructing 240 thousand dwellings, in 9 regions cleared of terrorists by these operations. It is expected that with these dwellings built within the scope of the "Voluntary, Safe, and Dignified Return Project" and the resulting normalisation of life, approximately 1 million Syrian refugees will return to their country within 2.5-3 years [29]. In addition to refugees who have returned to Syria and those who have legally immigrated from countries where they sought asylum to other countries, there are also refugees who wish to settle in other countries illegally. In addition to refugees not being accepted by countries, they are also subjected to sanctions contrary to human rights. One of these is pushbacks. Pushing refugees back to the Turkish-Greek border by European countries has become the dominant strategy [31]. In the reports published by human rights organisations and non-governmental organisations, it was stated that during pushbacks, the excessive use of force, humiliating and inhumane treatment, and arbitrary detentions have been carried out by member states of the European Union [32]. Research published by Lighthouse Reports in 2022 stated that Frontex repelled 957 asylum seekers with at least 22 confirmed incidents between March 2020 and September 2021. Furthermore, it was stated that Frontex was involved in pushbacks known as "prevention of departure" in 222 incidents involving 8,355 asylum seekers between those dates [33]. More than 18,000 refugees crossed the Mediterranean and reached Europe in the first 3 months of 2022. Between 2014 and 2021, 24,400 refugees lost their lives while trying to cross the Mediterranean [34]. In 2021, 1,400 Syrian refugees reached Italy by sea. In interventions made in Libyan territorial waters, 1,482 Syrian refugees were reached [35]. Due to the incidents occurring during pushbacks, refugees are subjected to permanent disabilities and various health problems and may also lose their lives. This situation also continues to be a problem that needs to be resolved.

### Study Limitations

One limitation of our study is that it was conducted retrospectively.

## Conclusion

The exodus of refugees from their own countries for various reasons causes numerous problems for both refugees and host countries. Refugees face difficulties in adaptation as well as in rebuilding their lives in the countries where they have sought refuge. The economy, education, housing, provision of adequate food, security, and protection are affected areas. However, one of the most affected aspects is health.

When we examine the situation of Syrian refugees from 2017-2023, it can be seen that although the rate of migration from Syria to Türkiye has decreased, there has been an increase in the refugee population living in the country. At a rate greater than this growth rate, there has also been an increase in the number and quality of health services provided to refugees. Regarding this increase in quality, besides the routine health services, maternal-child health, vaccination, and pregnancy follow-up come to the fore.

Like local people, Syrian refugees have been adversely affected by natural disasters occurring in the countries where they live. Following the earthquake disaster which took place on February 6, 2023, and affected 11 provinces in and around Kahramanmaraş, Syrian refugees also lost their lives. There has also been a "return migration" to Syria due to the deteriorating living conditions in these provinces after the earthquake. The health services provided to refugees need to be re-evaluated on an international scale in terms of the new demographic picture.

One of the problems that continue to be relevant is the loss of life, disability, and health issues that occur because refugees, who wish to migrate irregularly from Türkiye's western and southern borders to European and Mediterranean countries, are pushed back by neighboring countries of Türkiye. Evaluating this problem, which remains unresolved, on an international basis and finding a solution will be a significant advancement for humanity.

### Ethics

**Ethics Committee Approval:** The study was conducted in accordance with the 1964 Helsinki Declaration and did not require ethical committee approval due to the reasons mentioned above.

**Informed Consent:** Not required.

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

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

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### Footnotes

### Authorship Contributions

Concept: İ.T., Design: B.B., İ.T., Data Collection or Processing: B.K.Z., S.G.Ö., B.B., İ.K., İ.T., Analysis or Interpretation: B.B., İ.T.,

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CASE REPORT

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# Case Report: Anti-Cholinergic Syndrome Induced by Papaver Rhoeas Plant and Its Management

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## Abstract

Anti-cholinergic toxic states are a group of pathological conditions commonly observed in emergency departments (EDs) and are rarely fatal. The plant Papaver rhoeas (commonly known as red corn poppy or common poppy) is used in traditional medicine and as a food source in regions of Türkiye and Iran. The toxic effects of this agent can result from incorrect or excessive use. A 61-year-old female patient with a history of chronic obstructive pulmonary disease presented to the ED after consuming a dish made with Papaver rhoeas. On arrival, the patient presented with hypertension symptoms, altered consciousness, and muscle fasciculations. On monitoring, she was found to be tachycardic with a heart rate of 130 beats per minute and hyperthermic with a temperature of 37.8 °C. Blood pressure measurements showed a systolic pressure of 180 mmHg and a diastolic pressure of 110 mmHg. Supportive therapy was administered and diazepam was used following the development of seizures. The patient was given physostigmine, and after intensive observation, her symptoms improved and she was safely discharged. Anticholinergic toxidrome are common in ED presentations. Allergic reactions, convulsions, and hepatotoxicity may also occur after exposure to Papaver rhoeas. Although these conditions are generally not fatal, appropriate ED management can prevent morbidity and mortality.

**Keywords:** Papaver rhoeas, anti-cholinergic, emergency medicine

## Introduction

Poisoning from environmental factors is a significant issue in emergency medicine. This phenomenon is primarily driven by the consumption of incorrect or toxic plants, leading to poisoning. In emergency medicine practice, mushroom poisoning is frequently noted [1]. However, other types of poisonings are related to the food culture of the region. An example of this in Türkiye is the traditional beverage made from Papaver rhoeas, commonly known as "gelincik otu sherbeti" (Figure 1). Consuming this sherbet or other forms of Papaver rhoea can lead to toxicological effects. This plant is part of the Old world flora and is used in various ways across different cultures [2].

The dried form of the plant, which is used in certain medicinal products and wine, is processed through various methods to create sherbet (gelincik sherbeti) [2]. The plant, known to contain alkaloid-based structures, includes compounds like rhodic acid, papaverin acid, and rhoeagenine. In traditional Iranian medicine, these substances are used to treat inflammation, diarrhea, sleep disorders, and opioid addiction [3]. Low doses of these substances can lead to mucus secretion and sedation [4]. Additionally, anti-dopaminergic and anti-cholinergic effects were observed [5]. This case report discusses the symptoms observed and management after ingesting *papaver rhoeas*.

## Case Report

A 61-year-old female patient presented to the emergency department (ED) approximately 2 hours after consuming a meal made with the Papaver rhoeas plant, commonly known as red corn poppy. She reported symptoms that began an hour

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**Figure 1.** *Papaver rhoeas* plant

earlier, including altered consciousness, flushing, and muscle problems (fasciculations). Her history of chronic obstructive pulmonary disease was managed with daily montelukast and an inhaler. No other chronic conditions, medication changes, smoking, alcohol, or allergies. At ED arrival, her vitals were BP 180/110 mmHg, pulse 130 bpm, respiratory rate, 20 bpm; and temperature, 37.8 °C.

Her physical examination revealed altered consciousness with a Glasgow Coma scale score of E3M4V3. There was no neck stiffness (no signs of meningeal irritation). The patient was agitated. The lung sounds were normal, and the abdominal examination was unremarkable. Cardiac auscultation revealed normal S1-S2 sounds without murmurs. Palpation revealed hyperthermic and dry skin. During her evaluation, the patient underwent electrocardiography, which revealed tachycardia (127 beats per minute), with benign ST-segment depression likely due to hypertension, ruling out acute coronary syndrome. Blood tests, including biochemical analysis, complete blood count, and cardiac biomarkers, revealed no significant abnormalities. Brain computed tomography revealed no major pathology.

After evaluation, the patient was diagnosed with anti-cholinergic syndrome, and supportive therapy was initiated for her safety. During monitoring, the patient developed seizures and was administered 10 mg of intravenous diazepam. A second myoclonic seizure occurred 10 minutes later; therefore, an additional 10 mg of intravenous diazepam was administered, thereby achieving seizure control. Hydration was provided, and physostigmine was administered to address muscle movements, hypertension, and neurological symptoms; 0.5 mg of intravenous physostigmine was administered). The patient was then transferred to the intensive care unit (ICU) for further monitoring. After 3 days of observation in the ICU, her symptoms improved and her consciousness returned to normal. She was discharged with full recovery.

## Discussions

Anti-cholinergic toxidrome are a common cause of ED visits and are rarely fatal [6]. These situations often occur due to an overdose of certain medications, especially those containing atropine, hyoscyamine, and scopolamine, or their synthetic derivatives. This approach is particularly common in geriatric patients who use these medications for chronic disease management [7]. Various toxicological cases involving Papaver rhoeas have been documented in the literature. In a case report by Gunaydin et al. [8], 5 cases with different symptoms resulting from exposure to Papaver rhoeas were reported. Despite their severity, these cases were not fatal and resulted in patient discharge after appropriate management. In a case reported by Gonullu et al. [9], hepatotoxic effects were observed, leading to the need for transplantation. A report by Kocak et al. [10] described three cases in which seizures were the main symptom, with no fatal outcomes occurred. As the literature shows, Papaver rhoeas (red poppy) is a plant used in traditional medicine and nutrition in Türkiye that rarely results in fatal outcomes. The central nervous system is a key site of its effects. Preventive measures and the use of physostigmine are among the recommended methods for protective treatment to avoid fatal outcomes. As demonstrated in our case, patients can be managed without fatal or morbid outcomes if appropriate treatment is administered.

## Conclusion

The key to managing toxidrome in EDs is early recognition, beginning with general resuscitation measures, and combining these with specific antidote treatments targeting the underlying cause.

**Informed Consent:** Written consent was obtained from the patient, and this text was created within the framework of his permission.

### Footnote

### Authorship Contributions

Surgical and Medical Practices: S.D.Ş., F.A.D., Concept: S.D.Ş., S.B., Design: M.P., Ö.Z, Literature Search: Ö.Z, F.A.D., Writing: Ö.Z, M.P.

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