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The Effect of Plasma Osmolality on Prognosis in Non-Massive Pulmonary Embolism

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What is already known on this topic?

- Plasma osmolality is an indicator of fluid and electrolyte balance and has been linked to mortality risk in various critical illnesses.
- Previous studies suggest that both hypoosmolality and hyperosmolality may be associated with adverse outcomes in conditions such as acute coronary syndrome, renal failure, and heart failure.
- The prognostic value of plasma osmolality in acute pulmonary embolism (PE) remains unclear, with limited research specifically investigating its role in predicting mortality.

What does this study add on this topic?

- This study found no significant correlation between plasma osmolality and short-term mortality in patients with acute PE. While elevated blood urea nitrogen (BUN) and low albumin levels were significantly associated with increased in-hospital mortality, plasma osmolality itself did not show predictive value for mortality in stable PE patients.
- These findings suggest that while plasma osmolality is an important physiological marker, it may not be a reliable standalone predictor of mortality in non-massive PE, highlighting the need for further research with larger and more diverse patient groups.

Abstract

Objective: Plasma osmolality provides insight into fluid and electrolyte balance and can serve as a prognostic marker in critically ill patients. There is limited research on the relationship between plasma osmolality and mortality in pulmonary embolism (PE). The potential role of plasma osmolality in predicting mortality in PE patients is examined in this study.

Methods: A retrospective analysis was conducted on patients admitted to the chest diseases ward with acute PE. Data on demographics, comorbidities, clinical and laboratory results, in-hospital mortality, and 30-day mortality were collected. Plasma osmolality was calculated using sodium, plasma glucose, and blood urea nitrogen (BUN) levels at admission. Patients were categorized into hyposmolality, normosmolality, and hyperosmolality groups.

Results: The study included 226 patients (100 males, 44.2%), aged 23-90 years. In-hospital mortality occurred in 13 patients (5.8%). The mortality rate was significantly higher in patients with a simplified Pulmonary Embolism Severity Index score ≥1 ($P = .031$). In addition, lower albumin levels ($P = .008$) and higher BUN ($P = .007$) and urea levels ($P = .005$) were significantly associated with in-hospital mortality. No significant differences in D-dimer, creatinine, glucose, sodium, and osmolality levels were observed between patients who were discharged and those who experienced in-hospital mortality. Mortality rates within 30 days did not significantly differ across osmolality groups ($P > .05$).

Conclusion: This study did not find a significant correlation between plasma osmolality and short-term mortality in patients with acute PE.

Keywords: Mortality, plasma osmolality, pulmonary embolism

Introduction

Pulmonary embolism (PE) represents a significant global public health concern, as the third most prevalent acute cardiovascular syndrome after myocardial infarction and stroke, with an estimated incidence of 1-2 per 1000 individuals. The mortality associated with submassive PE is considerable, ranging from 5% to 25%, underscoring the importance of accurate risk assessment and timely intervention.[1,2]

To stratify patients based on their risk of mortality, the Pulmonary Embolism Severity Index (PESI) is widely applied in clinical practice. The PESI considers various clinical parameters to categorize patients into different risk groups. The simplified version, Simplified Pulmonary Embolism Severity Index (sPESI), offers a more streamlined approach by incorporating fewer variables while maintaining similar predictive accuracy. An sPESI score of 0 is indicative of a low risk for a poor 30-day prognosis, whereas a score of ≥1 suggests a higher risk of adverse outcomes. This scoring system has been shown to be as effective as the European Society of Cardiology risk assessment model in predicting early mortality in PE patients.[1,3-5]

In addition to clinical scoring systems, biomarkers such as troponin and brain natriuretic peptide are established tools for predicting early mortality in patients with acute PE. Elevated levels of these

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biomarkers are associated with increased right ventricular strain and worse outcomes.[6,7]

Plasma osmolality, a measure of solute concentration in the blood, is another parameter of interest in the context of critically ill patients. It is regulated by key components like plasma sodium, glucose, and blood urea nitrogen (BUN) and plays a vital function in preserving the balance between extracellular and intracellular water distribution. The calculation of serum osmolality is straightforward and can be quickly obtained in a clinical setting.

Emerging evidence suggests that plasma osmolality may have prognostic significance in various conditions. For instance, research indicates that reduced serum osmolality correlates with an increased mortality risk in patients undergoing dialysis and individuals with heart failure. Conversely, high serum osmolality has been linked to increased mortality in patients with acute coronary syndrome, acute renal failure, the elderly, and those with intermediate-high risk PE.[8-13] These findings highlight the potential importance of serum osmolality in patient prognosis. However, its role in hemodynamically stable PE patients remains unexplored.

This study seeks to explore the significance of plasma osmolality in forecasting outcomes among patients diagnosed with hemodynamically stable acute PE. By analyzing the link between osmolality values and mortality in this patient cohort, our goal is to enhance understanding of the potential role of plasma osmolality as a supplementary tool in assessing the risk profile of PE patients.

Methods

Patient Enrolment Methods and Study Parameters

This retrospective study was carried out at a third-level care hospital in Türkiye. A total of 442 patients hospitalized with a pre-diagnosis of acute PE in our clinic between 2016 and 2023 were retrospectively analyzed. Of these, 61 patients were excluded because the diagnosis of PE could not be confirmed, 13 were excluded due to chronic hemodialysis, and 42 were excluded because they had been transferred to the ward after being diagnosed at an external center or in an intensive care unit. Additionally, 84 patients were excluded due to incomplete data records, and 16 due to duplicate entries. Consequently, a total of 216 patients were excluded, and 226 were included in the study.

Serum osmolality for each patient was determined using the Dorwart–Chalmers formula as follows:[14]

Plasma osmolality formula = 1.86 × sodium mmol/L + (glucose mg/dL/18) + (BUN mg/dL/2.8) + 9.

Patients were categorized into 3 groups depending on their osmolality levels.

Normal serum osmolality ranged between 275 and 295 mOsm/kg. Values below 275 mOsm/kg are classified as hypoosmolality, and values exceeding 295 mOsm/kg are defined as hyperosmolality.

Simplified Pulmonary Embolism Severity Index is a clinical scoring tool used to estimate the short-term mortality risk in patients with PE. The sPESI assesses 5 clinical parameters: age, chronic cardiopulmonary disease, history of cancer, blood pressure, heart rate, and peripheral oxygen saturation. Each parameter is assigned 1 point. An sPESI score of 0 signifies minimal risk, whereas scores exceeding 1 denote elevated risk for mortality.[1] The sPESI score for each patient with PE was calculated and recorded.

The participants were separated into 2 groups based on clinical outcomes: those who died in the hospital and those who were discharged. Patients' age, gender, comorbid diseases (chronic kidney disease [CKD], diabetes mellitus, hypertension, chronic cardiovascular disease, chronic cerebrovascular disease [CVD], malignancy), atrial fibrillation, deep vein thrombosis (DVT), history of surgery or fracture within the last month, immobility, and laboratory values (D-dimer, creatinine, albumin, troponin, glucose, sodium, BUN, urea) were recorded. Immobility was defined as the inability to ambulate independently for more than 3 days before hospital admission due to medical or physical conditions (e.g., recent surgery, severe illness, or neurological impairment).

All patient data utilized in this research were obtained from electronic health records. The study was conducted in accordance with the Declaration of Helsinki and received permission from the ethics committee of Dr. Lütfi Kırdar City Hospital (Approval no: 2023/514/260/33, Date: October 30, 2023). Informed consent was waived due to the retrospective nature of the study.

Statistical Analysis

Statistical analysis of the study data was conducted using the Statistical Package for Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA). Normality was assessed through the Kolmogorov–Smirnov test, revealing that the parameters did not follow a normal distribution. Descriptive statistical methods, including minimum, maximum, mean, SD, median, and frequency, were employed. The Kruskal–Wallis test was utilized for the inter-group comparison of parameters in the assessment of quantitative data, with Dunn's test applied to determine the group responsible for observed differences. Comparison of parameters between 2 groups was conducted using the Mann–Whitney *U* test. Qualitative data were compared through the Chi-square test, Fisher's exact test, Fisher-Freeman-Halton test, and Yates's correction for continuity. The level of statistical significance was set at $P < .05$.

Results

Patient Demographics Characteristics

In this study, a total of 226 cases were included, comprising 100 males (44.2%) and 126 females (55.8%). The mean age was 61.62 ± 17.23 years, with a median age of 63 years. The most frequent comorbid conditions were hypertension (43.8%), malignancy (33.6%), and diabetes mellitus (22.6%), respectively. Table 1 presents the baseline laboratory values of the study. In-hospital mortality was observed in 13 cases (5.8%).

Comparison Between the Group with In-Hospital Mortality and the Group Without In-Hospital Mortality

In the comparison between patients who had in-hospital mortality and those who did not, age and gender were not found to be statistically significant. However, CKD and malignancy were significantly more prevalent among the patients who died. Specifically, CKD was present in 30.8% of the patients with in-hospital mortality compared to 9.9% in those who survived ($P = .042$). Additionally, malignancy was observed in 69.2% of patients who died in the hospital, whereas it was present in 31.5% of those who survived ($P = .012$).

In the analysis of laboratory parameters between patients with and without in-hospital mortality, several significant differences were observed. Specifically, BUN and urea levels were significantly higher in patients who died in the hospital ($P = .007$ and $P = .005$, respectively). No significant differences were observed in D-dimer, creatinine, glucose, sodium, or osmolality levels between the 2 groups.

The proportion of patients with an sPESI score ≥1 was significantly higher in the mortality group, with 91.7% of those patients scoring ≥1 on sPESI, compared to 5.7% in the non-mortality group ($P = .031$).

Table 1. Evaluation of Demographic Characteristics and Comorbidities

	Discharged (n = 213)	In-Hospital Mortality (n = 13)	Total (n = 226)	
	n (%)	n (%)	n (%)	*P*
Age/years Mean ± SD (median)	61.30 ± 17.37 (62)	66.85 ± 14.24 (72)	61.62 ± 17.23 (63)	.349[1]
Sex/male	92 (43.2)	8 (61.5)	100 (44.2)	.315[+]
CKD*	21 (9.9)	4 (30.8)	25 (11.1)	**.042**
Diabetes	45 (21.1)	6 (46.2)	51 (22.6)	.079
Hypertension	93 (43.7)	6 (46.2)	99 (43.8)	1.000[+]
Cardiovascular disease	35 (16.4)	2 (15.4)	37 (16.4)	1.000
CVD**	15 (7)	1 (7.7)	16 (7.1)	1.000
Malignancy	67 (31.5)	9 (69.2)	76 (33.6)	**.012**
AF***	17 (8)	2 (15.4)	19 (8.4)	.300
Surgery	26 (12.2)	3 (23.1)	29 (12.8)	.224
Deep vein thrombosis (DVT)	82 (38.7)	5 (38.5)	87 (38.7)	1.000[+]
Fracture	13 (6.1)	0 (0)	13 (5.8)	1.000
Immobility	72 (33.8)	7 (53.8)	79 (35)	.229

Fisher's exact test. In the tables, *P*-values shown in bold represent statistically significant results. In this study, a *P*-value of less than .05 was considered the threshold for statistical significance.
AF***, atrial fibrillation; CKD*, chronic kidney disease; CVD**, cerebrovascular disease.
[+]Continuity (yates) fix.
[1]Mann–Whitney *U* test.

Tables 1 and 2 provide detailed findings and general characteristics of the in-hospital mortality and discharged groups.

Comparison of the Osmolality Groups

Regarding osmolality levels, 39.8% of the patients exhibited low osmolality, 56.6% had normal osmolality, and 3.5% had high osmolality (Figure 1).

There was a statistically meaningful variation in mean age between the osmolality groups (P = .047). Post hoc analysis revealed that patients in the high osmolality group had a significantly higher mean age compared to those in the low osmolality group (P = .024). Additionally, gender distribution showed a statistically notable difference across the osmolality groups (P = .047), with a markedly greater percentage of male patients in the high osmolality group (87.5%) compared to both the low (43.3%) and normal (42.2%) osmolality groups (P < .05).

Rates of CKD, CVD, and immobility were considerably elevated in the high osmolality group compared to the low and normal osmolality groups (P < .05).

Additionally, the prevalence of malignancy in the low osmolality group was markedly greater compared to the normal and high osmolality groups (P < .05).

Significant statistical differences were detected in mean oxygen saturation levels across the osmolality groups (P = .033). Post hoc analysis demonstrated that the mean oxygen saturation was notably lower in the high osmolality group when compared to both the low (P = .028) and normal (P = .010) osmolality groups. Similarly, creatinine levels varied significantly between the groups (P = .001), with post hoc analysis showing elevated creatinine levels in the high osmolality group compared to the low (P = .002) and normal groups (P = .024).

Mean glucose levels also differed significantly across osmolality groups (P = .002). The post hoc analysis revealed that the low osmolality group had a significantly lower glucose level than both the normal (P = .014) and high osmolality groups (P = .032).

Table 2. Evaluation of Vital and Laboratory Findings

	Discharged (n = 213)	In-Hospital Mortality (n = 13)	Total (n = 226)	
	Mean ± SD (Median)	Mean ± SD (Median)	Mean ± SD (Median)	*P*
sBP* mm Hg	118.18 ± 21.67 (110)	117.08 ± 20.89 (120)	118.11 ± 21.58 (110)	.893
dBP** mm Hg	72.04 ± 14.01 (70)	67.77 ± 11.61 (70)	71.79 ± 13.89 (70)	.323
Pulse/min	87.53 ± 15.82 (85)	95.08 ± 21.55 (97)	87.98 ± 16.25 (85.5)	.232
Saturation %	93.22 ± 5.97 (95)	90.54 ± 3.93 (90)	93.06 ± 5.9 (95)	**.013**
D-Dimer	7062.28 ± 7812.89 (3880)	7027.14 ± 10227.48 (3550)	7060.38 ± 7911.65 (3875)	.650
Creatinine	0.89 ± 0.36 (0,8)	1.05 ± 0.54 (0.8)	0.9 ± 0.37 (0.8)	.273
Albumin	3.55 ± 0.64 (3,6)	3.09 ± 0.54 (3)	3.52 ± 0.64 (3.6)	**.008**
Glucose	136.35 ± 66.09 (115)	119.08 ± 37.29 (107)	135.35 ± 64.85 (114.5)	.498
Sodium	136.94 ± 4.74 (137)	135.15 ± 6.15 (137)	136.84 ± 4.83 (137)	.579
BUN	17.95 ± 9.1 (15,4)	31.02 ± 23.76 (27)	18.7 ± 10.84 (16)	**.007**
Urea	37.9 ± 19.5 (32)	66.23 ± 50.82 (57)	39.53 ± 23.23 (33.5)	**.005**
Osmolality	277.55 ± 9.17 (277)	278.07 ± 12.91 (283.5)	277.58 ± 9.39 (277)	.536
sPESI ≥ 1 n(%)	118 (5.7%)	11 (91.7%)	129 (57.6%)	[+]**.031**

Mann–Whitney *U* test.
BUN***, blood urea nitrogen; dBP**, diastolic blood pressure; sBP*, systolic blood pressure.
[+]Continuity (yates) düzeltmesi.

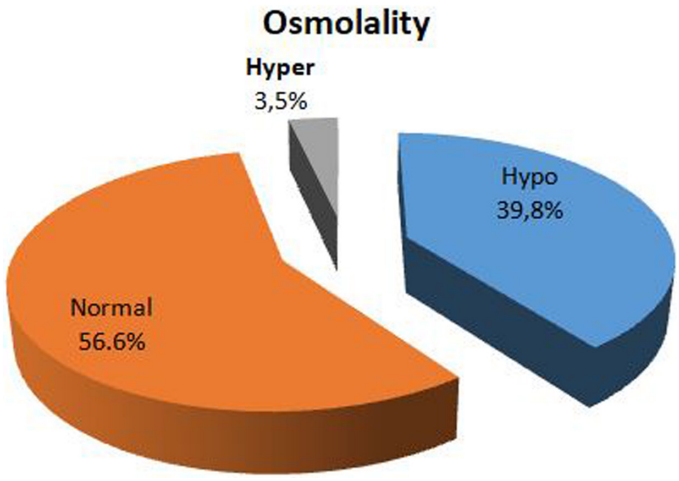

Figure 1. Classification of osmolality in patients with PE.

Statistically significant differences were also observed in sodium levels (P = .001), with the high osmolality group having a higher sodium concentration compared to both the low (P = .001) and normal osmolality groups (P = .020). Additionally, sodium levels in the normal osmolality group were significantly higher than in the low osmolality group (P = .001).

Blood urea nitrogen levels showed significant differences among the groups (P = .001), with the high osmolality group demonstrating elevated levels compared to both the low (P = .001) and normal osmolality groups (P = .001). Similarly, BUN levels in the normal osmolality group were higher than those in the low osmolality group (P = .005). Urea levels also varied significantly between the groups (P = .001), with post hoc analysis confirming higher urea levels in the high osmolality group compared to the low (P = .001) and normal groups (P = .001), as well as in the normal group compared to the low group (P = .004).

Table 3. Evaluation of Demographic Characteristics and Comorbidities According to Osmolality Classification

	Osmolality			
	Hypo (n = 90)	**Normal (n = 128)**	**Hyper (n = 8)**	
	n (%)	**n (%)**	**n (%)**	***P***
Age/years	59.03 ± 17.57 (60)	62.67 ± 17.01 (66)	73.88 ± 9.33 (73)	**.047**[1]
Sex/male	39 (43.3)	54 (42.2)	7 (87.5)	**.047**[+]
CKD*	7 (7.8)	15 (11.7)	3 (37.5)	**.035**
Diabetes	16 (17.8)	33 (25.8)	2 (25)	.374
Hypertension	34 (37.8)	59 (46.1)	6 (75)	.095[+]
Cardiovascular disease	14 (15.6)	22 (17.2)	1 (12.5)	.908
CVD**	3 (3.3)	10 (7.8)	3 (37.5)	**.001**
Malignancy	39 (43.3)	36 (28.1)	1 (12.5)	**.028**
AF***	4 (4.4)	13 (10.2)	2 (25)	.074
Surgery	12 (13.3)	17 (13.3)	0 (0)	.543
Deep vein thrombosis (DVT)	40 (44.4)	44 (34.6)	3 (37.5)	.367[+]
Fracture	7 (7.8)	6 (4.7)	0 (0)	.487
Immobility	25 (27.8)	48 (37.5)	6 (75)	**.018**

Chi-square test.
AF***, atrial fibrillation; CKD*, chronic kidney disease; CVD**, cerebrovascular disease.
[+]Fisher–Freeman–Halton exact test.
[1]Kruskal–Wallis test.

Table 4. Evaluation of Vital and Laboratory Findings According to Osmolality Classification

	Osmolality			
	Hypo (n = 90)	**Normal (n = 128)**	**Hyper (n = 8)**	
	Mean ± SD (Median)	**Mean ± SD (Median)**	**Mean ± SD (Median)**	***P***
sBP* mm Hg	118.56 ± 20.57 (115)	118.34 ± 22.71 (110)	109.63 ± 11.86 (112)	.666
dBP** mm Hg	71.41 ± 12.78 (70)	72.37 ± 14.84 (70)	66.88 ± 9.61 (65)	.593
Pulse/min	92.01 ± 16.92 (89.5)	86.01 ± 15.37 (83)	75.63 ± 11.03 (74)	**.002**
Saturation %	92.61 ± 5.6 (94)	93.63 ± 6.08 (95)	89.13 ± 4.85 (89.5)	**.033**
D-Dimer	7534.07 ± 8139.51 (3875)	6276.81 ± 7193.84 (3505)	14770 ± 14081.79 (9840)	.072
Creatinine	0.83 ± 0.36 (0.8)	0.92 ± 0.33 (0.9)	1.46 ± 0.64 (1.2)	**.001**
Albumin	3.44 ± 0.66 (3.5)	3.61 ± 0.62 (3.6)	3.14 ± 0.56 (3.3)	.056
Glucose	119.41 ± 41.25 (109)	145.36 ± 76.25 (118)	154.63 ± 50.27 (142)	**.012**
Sodium	133.42 ± 3.5 (134)	138.72 ± 3.99 (139)	145.13 ± 3.6 (146.5)	**.001**
BUN***	15.4 ± 6.97 (14)	19.63 ± 11.25 (17.1)	41 ± 11.7 (42)	**.001**
Urea	32.43 ± 15.1 (29)	41.5 ± 23.99 (37)	87.75 ± 25.18 (90)	**.001**
sPESI≥1 n(%)	56 (62.2%)	67 (53.2%)	6 (75%)	.277[+]

Kruskal–Wallis test.
BUN***, blood urea nitrogen; dBP**, diastolic blood pressure; sBP*, systolic blood pressure.
[+]Fisher–Freeman–Halton exact test.

Table 5. Assessment of Mortality According to the Osmolality Classification

	Osmolality			
	Hypo (n = 90)	Normal (n = 128)	Hyper (n = 8)	
	n (%)	n (%)	n (%)	*P*
In-hospital mortality	6 (6.7)	7 (5.5)	0 (0)	.724
30-day mortality	11 (12.2)	12 (9.4)	0 (0)	.495

Chi-square test.

Tables 3 and 4 provide a comprehensive summary of these findings and the general characteristics of the osmolality groups. Importantly, no notable statistical differences were observed between the osmolality groups regarding short-term mortality (both in-hospital and 30-day mortality) ($P > .05$, Table 5).

Discussion

This investigation revealed no meaningful association between plasma osmolality measured at admission and early mortality in hemodynamically stable PE patients. However, it was noted that in-hospital mortality and hyperosmolality were significantly higher in patients with an sPESI score ≥1, a predictor of short-term mortality ($P < .005$).

There is a study in the literature investigating the relationship between plasma osmolality and acute PE. In contrast to a study conducted by Öz et al[13] suggesting a predictive value of high plasma osmolality for in-hospital mortality in acute PE patients, our results demonstrated no such association. It is important to note that our study excluded hemodynamically unstable patients (shock, persistent hypotension, vasopressor requirement).

Having an important role in maintaining water distribution between extracellular and intracellular compartments in the human body, plasma osmolality primarily comprises plasma sodium, glucose, and BUN. When evaluating these components individually in our study, only elevated BUN levels were found to be linked to in-hospital mortality ($P = .007$). This finding is consistent with previous studies by Tatlisu et al[15] and Gök et al[16], which reported similar results in PE patients. In contrast, those studies included thrombolytic-administered patients, whereas our study excluded such patients and focused on hemodynamically stable cases. Similarly, another study by Gök et al[16] showed that elevated BUN levels in PE patients with right ventricular dysfunction and high cardiac biomarkers were independent predictors of in-hospital mortality. Unlike these 2 studies, only non-massive PE patients were included in our study.

As we age, body water decreases coupled with an increase in plasma osmolality.[17] This study revealed a significantly higher mean age in the high osmolality group than in the low osmolality group ($P = .024$).

Our study showed that patients with hyperosmolarity had significantly higher levels of creatinine, glucose, sodium, BUN, and urea compared to other groups ($P < .05$). In addition, hyperosmolarity was more common among patients with CKD ($P = .035$). Since 1 of the primary functions of the kidneys is to regulate water and electrolyte balance, impaired renal function may directly influence plasma osmolality by altering sodium and water homeostasis.

Despite these findings, it is noteworthy that no mortality was observed in the hyperosmolar group. This may seem contradictory, as our study showed that higher BUN levels and CKD were more prevalent in the group with in-hospital mortality. However, several factors may explain these findings. First, the hyperosmolar group had a very limited sample size (n = 8), limiting the statistical power to detect an association with mortality. Second, although hyperosmolarity can result from renal dysfunction, it can also occur due to transient and reversible conditions such as dehydration or hyperglycemia, which, if managed effectively, may not lead to adverse outcomes. Third, patients in the hyperosmolar group may have received more aggressive fluid and electrolyte management, potentially mitigating the adverse effects of hyperosmolarity and renal impairment.

Considering comorbidities based on osmolality classification in our study, patients with CVD and immobility exhibited significantly higher plasma osmolality ($P < .05$).

Hyperosmolarity is notably common in patients with CVD due to dehydration.[18]

In-hospital mortality was higher in patients with CKD and malignancy ($P < .05$). Malignancy was significantly more common in patients who experienced in-hospital mortality ($P = .012$). This finding highlights the importance of malignancy as a prognostic factor in PE, consistent with previous studies. Malignancy may contribute to worse outcomes due to its association with hypercoagulability, increased thrombus burden, and reduced physiological reserve. Moreover, patients with low saturation percentage and serum albumin levels also had increased in-hospital mortality ($P < .05$). A study by Hoskin et al[19] identified hypoalbuminemia as an independent determinant of mortality in PE patients.

This study has several limitations. First, it employed a retrospective and single-center design. Second, the number of patients in the hyperosmolar group was very small, limiting the statistical power to detect significant differences in mortality. Therefore, larger, multi-center prospective studies are needed to validate our findings.

In conclusion, our study did not find a significant association between plasma osmolality and short-term mortality in non-massive PE patients. Future studies with larger sample sizes are warranted to better understand the potential role of plasma osmolality in predicting mortality in PE patients.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Approval no: 2023/514/260/33, Date: October 30, 2023).

Informed Consent: Informed consent was waived due to the retrospective nature of the study.

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