**Original** Article

# The Impact of Low Albumin Levels on the Severity of Acute Pulmonary Embolism and its Prognostic Significance

Mais Zamlout<sup>1</sup>, Mohammad Alkhayer<sup>2</sup>, Ibrahim Sulaiman<sup>3</sup>

<sup>1,2</sup>Department of Respiratory Medicine – Tishreen University Hospital, Latakia, Syria. <sup>3</sup>Department of Renal Diseases – Tishreen University Hospital, Latakia, Syria.

<sup>1</sup>Corresponding Author : mais.zamlout@outlook.com

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Abstract - Objective: To investigate the impact of low albumin levels on the severity of acute pulmonary embolism (PE) and its prognostic significance. Materials and Methods: A prospective cohort study was conducted on 65 patients admitted to the department of respiratory medicine and ICU at Tishreen University Hospital between 2021-2023. Data on age, gender, albumin levels, platelet count, WBC count, D-dimer, hemoglobin, creatinine clearance, right ventricular dilation, blood pressure, heart rate, and oxygen saturation ratio were collected at the presentation. Patients were followed up for 90 days. Independent t-tests and chi-square tests were used for comparison analysis, linear regression was used for exploring relationships, and Kaplan-Meier curves were used for survival analysis. Results: Patients with low albumin levels exhibited lower mean values of SPO2, blood pressure, heart rate, and hemoglobin, as well as higher SPESI scores and platelet counts and higher mortality percentages. Regression analysis showed that low albumin levels were a significant predictor of PE severity. Age, mean blood pressure and WBC count also significantly impacted SPESI scores. Survival analysis indicated that the majority of patients deteriorated between 17-20 days from diagnosis, with the low albumin levels group showing higher mortality rates. Conclusion: Low albumin levels are associated with increased severity and mortality in acute PE. Other factors such as age, blood pressure, and WBC count also play a significant role in predicting PE severity. Early identification and management of low albumin levels may improve outcomes in patients with acute PE.

Keywords - Albumin, Pulmonary embolism, SPESI, Venous thrombosis.

# **1. Introduction**

Pulmonary embolism is a life-threatening medical condition that results from the sudden blockage of the major pulmonary vessels by a clot or embolus that usually travels from a distant location, such as the pelvis or lower extremities, which leads to serious consequences or even death if immediate medical intervention is not undertaken. [1, 2] The incidence of PE increases with age, with a peak in the seventh decade of life [3].

PE can be classified into acute and chronic forms based on the onset and development of symptoms. Acute PE is characterized by chest pain, dyspnea, and cough, while chronic PE may present with gradual symptoms such as exertional dyspnea, fatigue, and exercise intolerance. [3, 4]

Risk factors for developing PE include immobilization, surgery, trauma, cancer, pregnancy, hormone therapy, and genetic predisposition. [5] Identifying these risk factors is crucial for early detection and prevention of PE. Additionally, silent PE has been reported in up to 50% of patients with deep vein thrombosis (DVT), underscoring the importance of screening high-risk patients for PE. [6]

Prognostic factors play an important role in predicting outcomes and guiding treatment decisions in patients with PE. Low albumin levels have been approached in previous studies as a prognostic factor in PE, as hypoalbuminemia is associated with inflammation, malnutrition, and poor overall health status. [7] Although previous studies have addressed the role of hypoalbuminemia in PE severity, but there is still a lack of consensus on its real impact.

This research aims to fill this gap in the literature by conducting a comprehensive follow-up of patients with normal albumin levels versus those with low albumin levels and subsequently measuring the severity of PE using the Simplified Pulmonary Embolism Severity Index (SPESI) score. By doing so, this study seeks to provide a clearer understanding of the prognostic value of hypoalbuminemia in acute PE and potentially identify a possible marker for risk stratification and management of these patients.

## 2. Materials and Methods

# 2.1. Study Design

A prospective cohort study was conducted to investigate the potential association between low albumin levels at admission and the severity of acute pulmonary embolism, as assessed by the Simplified Pulmonary Embolism Severity Index (SPESI) score. We aim to explore any association between these two variables.

#### 2.2. Participants and Data Collection

A total of 65 patients diagnosed with acute pulmonary embolism and confirmed by computed tomography pulmonary angiography (CTPA) were admitted to the Department of Respiratory Medicine and Intensive Care Unit at Tishreen University Hospital between 2021-2023. Demographic information, comorbidities, medication use, and laboratory values, including albumin, complete blood blood chemistry, creatinine clearance, count. and echocardiography, were collected on admission. Patients were followed up for 90 days, and those whom all of the aforementioned tests had not evaluated on the first day of admission were excluded from the study. Patients who were admitted multiple times due to pulmonary embolism were included only once.

#### 2.3. Statistical Analysis

Descriptive and inferential statistics were performed to assess the data distribution and relationships between variables. Continuous variables were presented in terms of mean and standard deviation scores, while frequencies and percentages were used for discrete variables. Independent tstudent and Chi-square tests were used to compare independent variables.

The severity of acute pulmonary embolism, represented by the SPESI score, is the outcome of interest in our study. Linear regression was used to fit each independent variable against the outcome at the beginning (*Model 1*). Subsequently, the regression model was adjusted for age, gender, albumin, white blood cell count, mean blood pressure, platelets, and creatinine clearance values (*Model 2*). We considered an alpha error of 0.05 as a cutoff for P-value significance in our results. The goodness of fit was evaluated using the R-squared value, while the F-statistic and P-value were used to evaluate the overall significance of the fitted model.

Finally, the Kaplan-Meier test was performed to get an insight into survival rates and trajectories in our sample. The results were visualized and summarized regarding survival curves and Log-Rank test value, respectively.

# 2.4. Ethical Considerations

The study protocol was reviewed by the Scientific Committee of Medical Research at Tishreen University, and written informed consent was obtained from each enrolled patient. For patients who were unable to provide informed consent, approval was obtained from their guardians after a thorough explanation of the research goals and the anonymity of their information.

# **3. Results**

The study population consisted of 29 males (44.6%) and 36 females (55.4%), with ages ranging from 35-80 years (49.6  $\pm$  10.2 years). During the follow-up period, 19 patients died (29.2%). The comparison of variables between the Low Albumin and Normal Albumin groups yielded statistically significant differences in terms of age, SPO2, systolic and diastolic blood pressure, heart rate, and hemoglobin. Patients with Low Albumin levels (<3.5 g/dl) exhibited lower mean values for each of the aforementioned variables. Conversely, patients with Low Albumin levels displayed higher mean values for the SPESI score and platelet count and higher mortality percentages. No statistically significant differences were observed between the two groups regarding WBC count, D-dimer, or Creatinine clearance (Table 1).

We utilized a linear regression model to explore the relationship between serum albumin level and acute pulmonary embolism (PE) severity. Our findings revealed that serum albumin level was a significant predictor of PE severity (p < 0.001), indicating that patients with low albumin levels (<3.5 g/dl) had, on average, a 1.38 point increase in the Simplified Pulmonary Embolism Severity Index (SPESI) score. Additionally, our results demonstrated that WBC count was also a significant predictor of PE severity (p<0.001), with a one unit ( $10^9$  U/L) increase in WBC count resulting in a 0.23 point decrease in SPESI score.

Furthermore, age and mean blood pressure had statistically significant impacts on SPESI scores (p=0.05 and p=0.001, respectively), although the clinical significance of these effects was limited (+0.04 and -0.032 points, respectively). In contrast, gender and creatinine clearance did not exhibit a statistically significant relationship with SPESI score (p=0.59 & p=0.15, respectively), nor did they have a notable clinical impact (+0.1 & -0.03 points, respectively). Lastly, while right ventricular dilation demonstrated a clinical impact on the SPESI score (+0.59 points), its statistical significance was not detected. The linear regression model had a good fit with an R-squared of 87 and an adjusted R-squared of 85.1. The F-statistic was 46.7, indicating that the model was statistically significant (Table 2).

In the comparative analysis between Survived and Non-Survived groups, the former exhibited younger patients and higher levels of oxygen saturation, systolic and diastolic blood pressure, hemoglobin, and serum albumin. Conversely, Non-Survived patients displayed lower levels of D-dimer. There were no statistically significant differences in terms of gender, heart rate, white blood cell count, or creatinine clearance between the two groups (Table 3).

Survival analysis using Kaplan-Meier curves indicated that the majority of patients deteriorated between 17-20 days from diagnosis, particularly in the low-albumin group. The majority of surviving patients after the 17th day survived until the end of the study. The normal albumin level group did not exhibit such a deterioration in mortality rates (Table 4 & Fig 1).

# 4. Discussion

Acute pulmonary embolism (PE) is a critical condition characterized by the obstruction of the pulmonary arteries, which are responsible for transporting blood from the heart to the lungs, leading to serious complications such as right ventricular dysfunction, hemodynamic instability, and even death if not promptly diagnosed and treated. It is estimated to impact approximately 1 in 1,000 individuals in the general population, with the incidence doubling after the age of 40 years. [1, 2] Given the severity and potential danger of acute PE, it is crucial to identify and assess predictors that can help determine the severity and prognosis of the condition. Several predictors, such as age, heart rate, blood pressure, oxygen saturation, comorbidities, biomarkers, and right ventricular dysfunction, have been widely recognized for their impact on the severity of acute PE.

Low serum albumin levels have been shown to be associated with poor outcomes in various medical conditions due to its role in maintaining oncotic pressure and modulating inflammation and oxidative stress. In the context of acute PE, low serum albumin levels may also play a significant role in predicting the severity of the condition. [7]

Multiple risk stratification tools have been developed in order to predict the severity of PE: European Society of Cardiology guideline (ESC), Pulmonary Embolism Severity Index (PESI), Simplified Pulmonary Embolism Severity Index (SPESI), and many other tools. [8] In this paper, we focused on the impact of low serum albumin adjusted for other predictors, using the SPESI score to indicate PE severity. [9]

# 4.1. Demographics

The descriptive statistics in (Table 1 & 3) shows that age was a significant factor in both the Low-Albumin and Nonsurvived groups, with patients being older compared to the Normal Albumin and Survived groups (p<0.05 in both), respectively. However, gender did not exhibit any significant differences across these groups. The findings of the adjusted regression model (**Table 2**) provided insight into the impact of age and gender on the acute pulmonary embolism severity measured by the SPESI score. The statistically significant positive coefficient for age (+0.04, P-value = 0.005) suggests that older patients may have a higher risk of adverse outcomes, which is consistent with previous research indicating that advanced age is a significant risk factor for mortality in patients with acute PE. [10]

The non-significant coefficient for being a male (+0.1, P-value = 0.59), compared to being a female, is in line with some studies that have found no significant association between male gender and PE severity or outcomes, [11] although other research has suggested that male gender may be associated with a higher risk of adverse outcomes in acute PE. [12]

#### 4.2. Labworks and Comorbidities

Tables (1 & 3) indicate that systolic and diastolic blood pressure, creatinine clearance, and hemoglobin were indicators of better cardiopulmonary function in patients with acute PE, as they were higher in Normal-Albumin and Survived groups. These findings suggest that maintaining adequate albumin levels may have a beneficial effect on the prognosis. On the other hand, Platelets count was higher in the Low-Albumin and Non-Survived groups, this is consistent with previous evidence on its association with higher mortality rates. [16]

The findings of the regression model indicate that white blood cell (WBC) count, platelet count, and mean blood pressure are all statistically significant predictors of acute pulmonary embolism (PE) severity as measured by the SPESI score. These results are consistent with existing literature on the prognostic factors for acute PE. [13-15]

The negative coefficient of WBC in our model (-0.23, p<0.001) may initially seem counterintuitive, given the established evidence on the association between elevated WBC count and adverse outcomes in cardiovascular and pulmonary conditions, including acute PE. [13, 16] However, it is important to note that the interpretation of coefficients in regression analysis is not always straightforward and can be influenced by other variables in the model, i.e. when controlling for platelet count, mean blood pressure, and other variables, this unexpected inverse relationship could potentially be influenced by complex interactions between these variables and other unmeasured factors in the analysis.

Similarly, platelet count (-0.005, p=0.02) has been recognized as a prognostic marker in acute PE. Thrombocytopenia, or low platelet count, has been associated with increased mortality and adverse outcomes in patients with acute PE, likely due to its association with more severe disease and hemodynamic instability. [15]

The negative coefficient for mean blood pressure in our analysis (-0.03, p=0.001) is also noteworthy. Hypotension is a well-established marker of hemodynamic instability and is a key component of risk stratification in acute PE. Low mean blood pressure at presentation has been consistently linked to increased mortality and adverse outcomes in patients with acute PE, highlighting its importance as a prognostic factor. [17]

The non-significant coefficients for RV dilation (+0.59, P-value = 0.16) and creatinine clearance (-0.03, P-value = 0.15) are interesting, as RV dilation is a known marker of hemodynamic instability in acute PE and has been associated with increased mortality. [18] Similarly, impaired renal function, as indicated by reduced creatinine clearance, has been linked to worse outcomes in acute PE. [19] The lack of statistical significance in our analysis may warrant further investigation or consideration of potential confounding factors.

#### 4.3. Serum Albumin Levels

Several studies have investigated the relationship between serum albumin levels and outcomes in various cardiovascular and pulmonary conditions, including acute PE. Low serum albumin levels have been associated with an increased risk of adverse outcomes in conditions such as heart failure, acute coronary syndrome, and acute respiratory distress syndrome. [20, 21] These findings suggest that serum albumin may serve as a prognostic marker for risk stratification in cardiovascular and pulmonary diseases.

In the context of acute PE, there is evidence to suggest that low serum albumin levels may be associated with a more severe presentation. Multiple studies found that low serum albumin levels were independently associated with an increased risk of adverse outcomes in patients with acute PE, including higher mortality rates and more severe clinical complications. [22, 23] Similarly, another study reported that low serum albumin levels were associated with right ventricular dysfunction and a higher risk of adverse outcomes in patients with acute PE. [24]

The findings from these studies are consistent with the results of our regression analysis, which estimated a coefficient of 1.38 (P-value < 0.001) for being in the low albumin group, indicating a statistically significant association between low serum albumin levels and the prognosis of acute PE severity measured by the SPESI score.

#### 4.4. Survival Analysis

In our study, 46 patients survived the 90-day follow-up period. The descriptive statistics in (Table 3) indicate that the surviving patients were younger and had higher blood pressure, hemoglobin, albumin, and saturation levels, as well as lower D-dimer levels at presentation, all of which were statistically significant (P<0.05) compared to the Non-survived group. Although not statistically significant, the

mean value of Creatinine clearance (P=0.058) and WBC (P = 0.051) were higher in the survived patients, while Platelet counts were higher in the Non-survived group (P = 0.83). There were no statistically significant differences in terms of gender or heart rate.

The Kaplan-Meier survival analysis for Low-Albumin versus Normal-Albumin groups showed a clear difference, with the majority of mortality cases occurring between the 17<sup>th</sup> and 20<sup>th</sup> days (Fig 1). This suggests that low serum albumin may be associated with a higher risk of mortality in patients with acute pulmonary embolism and is consistent with previous studies that reported higher mortality rates in patients with low serum albumin. [14, 25]

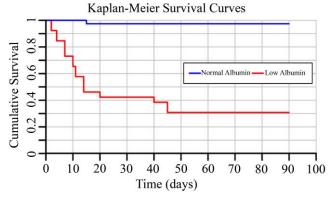


Fig. 1 Kaplan-Meier survival curves for mortality in normal vs low albumin levels groups

Table 4. Kaplan-Meier survival analysis of time-to-death in normal albumin levels vs low albumin levels groups

	Chi-Square	P-value
Log-rank	37.9	< 0.001

#### 4.5. Clinical Implications and Future Directions

The clinical implications of this study are significant and suggest that clinicians should consider albumin levels as a prognostic factor in acute PE. Future studies could include a larger number of patients and take albumin into account when dividing patients into study categories. Additionally, emphasizing good nutrition with adequate protein intake for patients in hospitalization, especially long-term ones, may positively impact their albumin levels and overall outcomes. Furthermore, conducting future experimental studies to evaluate the desired benefit of intravenous albumin replacement in patients with a high risk of pulmonary embolism could provide valuable insights into potential interventions aimed at improving patient outcomes. Overall, these future directions could build upon the findings of this study and further advance our understanding of the role of albumin in acute PE.

It is important to note that while there is evidence to suggest an association between low serum albumin levels and poorer outcomes in acute PE [14, 22, 23], more research is needed to explore the pathophysiology, mechanisms, and modifiers of this relationship. Future studies should aim to investigate the potential mechanisms underlying this association further and determine whether serum albumin levels can be used as a reliable prognostic marker for risk stratification in acute PE patients.

#### 4.6. Limitations and Strengths

This study has some limitations that may affect its applicability and accuracy. The sample size of 65 patients recruited from a single medical center via convenient sampling technique (as only patients with pulmonary embolism confirmed by CT pulmonary angiography who arrived at the medical center were included) may limit the generalizability and precision and introduce selection bias to a little extent.

The presence of comorbidities and external modifiers in patients with pulmonary embolism may also affect the relationship between low serum albumin and outcomes.

On the other hand, several strengths of this study can be highlighted. The findings presented in this paper are consistent with previous studies that have demonstrated a correlation of hypoalbuminemia with poorer outcomes in various medical conditions, including cardiopulmonary diseases. However, this study is unique in its focus on the impact of hypoalbuminemia on acute PE. As a prospective cohort study with a 90-day follow-up period, it allowed for a thorough analysis of data from medical records. It provided valuable long-term data on the prognostic value of low serum albumin in patients with acute pulmonary embolism.

The results of this study have important clinical implications for managing patients with acute PE. By identifying hypoalbuminemia as a prognostic factor, clinicians can better assess the severity of the condition and develop appropriate treatment plans. Additionally, the findings open the door for further rationale about interventions aimed at improving albumin levels that may have a beneficial effect on patient outcomes.

This study also addresses an understudied relationship between albumin and severe pulmonary embolism, contributing to the growing body of evidence on predictors of this condition and informing future research on the possible role of albumin in predicting PE severity.

# **5.** Conclusion

In conclusion, the findings from our regression analysis are supported by existing literature suggesting that low serum albumin levels may be associated with a more severe presentation and adverse outcomes in patients with acute PE. However, more research is needed to confirm these findings and explore the potential clinical implications of serum albumin as a prognostic marker for acute PE severity.

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Variable (unit)	Presentation	Normal Albumin (n=39)	Low albumin (n=26)	P-Value *
Gender	Male – N(%)	17 (43.6 %)	12 (46.2 %)	0.920
	Female – N(%)	22 (56.4 %)	14 (53.8 %)	0.839
Age (years)	Mean (SD)	46.5 (8.1)	54.2 (11.3)	0.002
<b>SPO2</b> (%)	Mean (SD)	91.9 (2.3)	84.9 (8.3)	< 0.001
SBP (mmHg)	Mean (SD)	111.8 (24)	100.4 (15.6)	0.037
<b>DBP</b> (mmHg)	Mean (SD)	68.7 (11.1)	62.7 (10.8)	0.033
HR (bpm)	Mean (SD)	112.9 (5.9)	107.8 (11)	0.037
SPESI (points)	Mean (SD)	1.2 (1)	3.3 (1.5)	< 0.001
<b>WBC</b> (x 10 <sup>9</sup> /L)	Mean (SD)	10.2 (3.3)	9.5 (2.7)	0.429
HGB (g/dl)	Mean (SD)	11.2 (1)	9.4 (1.4)	< 0.001
<b>PLT</b> (x 10 <sup>9</sup> /L)	Mean (SD)	200 (64)	250 (53)	0.002
<b>D-dimer</b> (ng/ml)	Mean (SD)	5328 (3873)	6655 (3735)	0.168
CrCl (mL/min)	Mean (SD)	93.3 (6.1)	89 (6)	0.168
Death	N (%)	1 (2.6 %)	18 (69.2 %)	< 0.001
<b>RV</b> dilation	N (%)	22 (56.4 %)	16 (61.5 %)	0.681

Table 1. Comparative analysis of variables between Normal-Albumin and Low-Albumin levels groups.

\* p-value is significant at < 0.05 level. SPO2: Saturation of peripheral oxygen; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; SPESI: Simplified Pulmonary Embolism Severity Index; WBC: White blood cell count; HGB: Hemoglobin; PLT: Platelets count; CrCl: Creatinine clearance; RV dilation: Right ventricle dilation on echocardiography.

Variable	Model	Estimate	Standard Error	P-value	СІ
Intercept	Model 1 <sup>a</sup>	2.01	0.189	< 0.001	[1.64, 2.39]
	Model 2 <sup>b</sup>	9.08	1.681	< 0.001	[5.71, 12.45]
Gender (female/male)	Reference (female)	Ref	Ref	Ref	Ref
	Model 1 <sup>a</sup> (male)	0.968	0.364	0.01	[0.24, 1.70]
	Model 2 <sup>b</sup> (male)	0.098	0.179	0.587	[-0.26, 0.46]
Age (years)	Model 1 <sup>a</sup>	0.072	0.017	< 0.001	[0.04, 0.11]
	Model 2 <sup>b</sup>	0.044	0.015	0.005	[0.01, 0.07]
A 11	Reference (Normal)	Ref	Ref	Ref	Ref
Albumin	Model 1 <sup>a</sup> (Low level)	2.026	0.294	< 0.001	[1.44, 2.61]
(Normal/Low)	Model 2 <sup>b</sup> (Low level)	1.38	0.201	< 0.001	[0.98, 1.78]
MDD (mmIIa)	Model 1 <sup>a</sup>	- 0.037	0.011	0.001	[-0.06, -0.02]
MBP (mmHg)	Model 2 <sup>b</sup>	- 0.032	0.009	0.001	[-0.05, -0.01]
CrCl (mL/min)	Model 1 <sup>a</sup>	- 0.048	0.03	0.117	[-0.11, 0.01]
	Model 2 <sup>b</sup>	- 0.029	0.02	0.149	[-0.07, 0.01]
<b>RV Dilation</b> (Exist/Not Exist)	Reference (not exist)	Ref	Ref	Ref	Ref
	Model 1 <sup>a</sup> (exists)	1.167	0.358	0.002	[0.45, 1.88]
	Model 2 <sup>b</sup> (exist)	0.587	0.416	0.164	[-0.25, 1.42]
<b>PLT</b> (x10 <sup>9</sup> /L)	Model 1 <sup>a</sup>	0.005	0.003	0.1	[-0.001, 0.011]
	Model 2 <sup>b</sup>	- 0.005	0.002	0.024	[-0.01, -0.001]
<b>WDC</b> $(-109/L)$	Model 1 <sup>a</sup>	- 0.247	0.052	< 0.001	[-0.35, -0.14]
<b>WBC</b> (x10 <sup>9</sup> /L)	Model 2 <sup>b</sup>	- 0.226	0.036	< 0.001	[-0.30, -0.15]

Table 2. Linear Regression Analysis of independent variables with SPESI Score in acute PE patients	5.
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Abbreviations: WBC (white blood cells), PLT (platelets count), CrCl (creatinine clearance), MBP (Mean blood pressure), RV Dilation (Right ventricular dilation). Model 1 examines the univariate association between each independent variable and the SPESI score. <sup>b</sup> Model 2 is adjusted for Gender, Albumin, and Right Ventricular Dilation (as binary variables), and Age, MBP, WBC, PLT, and CrCl values (as continuous variables).

Table 3. Comparative analysis of variables between Survived and Non-Survived Patients.

Variable	Presentation	PresentationSurvived $(n = 46)$ Non-Survived $(n = 19)$		P-Value *	
Gender	Males – N(%)	19 (41.3 %)	10 (52.6 %)	0.402	
	Females – N(%)	27 (58.7%)	9 (47.4%)	0.402	
Age (years)	Mean (SD)	46.9 (7.5)	56.1 (12.7)	0.007	
<b>SPO2</b> (%)	Mean (SD)	92.3 (3)	82.5 (6.4)	< 0.001	
SBP (mmHg)	Mean (SD)	113.3 (22.7)	93.7 (8.1)	< 0.001	
<b>DBP</b> (mmHg)	Mean (SD)	69.8 (10.7)	57.9 (7.9)	< 0.001	
HR (bpm)	Mean (SD)	111.6 (6.4)	109 (12.5)	0.390	
SPESI (points)	Mean (SD)	1.3 (1.1)	3.9 (0.3)	< 0.001	
<b>WBC</b> (x 10 <sup>9</sup> /L)	Mean (SD)	10.4 (3.3)	8.7 (2.7)	0.051	
HGB (g/dl)	Mean (SD)	10.8 (1.4)	9.8 (1.8)	0.037	
<b>PLT</b> (x 10 <sup>9</sup> /L)	Mean (SD)	210.6 (68.3)	240.9 (47)	0.083	
<b>D-dimer</b> (ng/ml)	Mean (SD)	5232 (3848)	7374 (3236)	0.027	
CrCl (mL/min)	Mean (SD)	92.5 (5.8)	89 (7)	0.058	
Albumin (g/dl)	Mean (SD)	3.7 (0.3)	2.9 (0.4)	< 0.001	

\* p-value is significant at < 0.05 level. SPO2: Saturation of peripheral oxygen; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; SPESI: Simplified Pulmonary Embolism Severity Index; WBC: White blood count; HGB: Hemoglobin; PLT: Platelets count; CrCl: Creatinine clearance.