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The predictive ability of hematologic parameters for in-hospital mortality in patients presenting with pulmonary embolism

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Abstract

Aim: Acute pulmonary embolism (PE) is one of the leading causes of mortality. Components of complete blood count indicate thrombotic and/or inflammatory status in various clinical conditions. In this study, we aimed to evaluate if hematological parameters could predict in-hospital mortality in patients presenting with PE.

Materials and Methods: Patients hospitalized with a diagnosis of acute PE in our tertiary center between 2016 and 2022 were involved in this retrospective study. Hematologic parameters obtained on admission were analyzed. PESI scores were calculated and comparative statistical and regression analyses were obtained.

Results: There were 254 patients (37.4% male). Thirty-eight patients (14.9%) were died in-hospital and formed 'non-survivors' group. NLr and RDW were found as independent risk factors associated with in-hospital mortality. Our results revealed a strong correlation between hematological parameters and PESI risk score and a cut off value of 5.9 for NLr was associated with 68.4% sensitivity and 68.1% specificity; besides that, cut off value of 14.1 for RDW was associated with 68.4% sensitivity and 62.6% specificity in prediction of in-hospital mortality.

Conclusion: Our current study showed that hematological parameters, assessed by routine blood count analysis, may serve as a promising and useful marker to foresee in-hospital mortality in patients presenting thru acute PE especially when used additive to validated risk scores.

Introduction

Acute pulmonary embolism (PE) is one of the leading reasons for morbidity and mortality especially when associated with to hemodynamic instability [1]. Thrombolytic therapy is recommended in PE patients presenting with hypotension or shock with a high mortality. However, hemodynamic deterioration or sudden death may develop despite adequate anticoagulant therapy in intermediate-risk (also in normotensive) PE patients. Thus, it is essential to define those patients under risk earlier in order to tailor treatment. The pulmonary embolism severity index (PESI) and simplified PESI (sPESI) are validated scores that could detect early mortality risk in pulmonary embolism according to European Society of Cardiology (ESC) Pulmonary Embolism Guidelines [2, 3]. These scores are mainly based on clinical parameters, but their sensitivity has been shown to be increased when used with inflammatory biomarkers [4, 5]. Mean platelet volume (MPV), platelet distribution width (PDW), neutrophil/lymphocyte ratio (NLr) and red cell distribution width (RDW) are components of complete blood count and have been studied to assess prognosis in various cardiovascular diseases [6-10]. Degradation of platelet deposits, hypercoagulability and venous stasis are pathophysiological mechanisms underlying in venous thromboembolism. Inflammatory status in this hypercoagulable environment accelerates the thrombotic process [11, 12]. Since PESI and sPES are regarded as a prominent indexes in determining the risk of mortality with hemodynamic and clinical findings, we evaluated whether hematological parameters can be used for risk assessment in predicting short-term mortality in patients presenting with acute PE. This study was designed to investigate the role of hemogram parameters to foresee in-hospital mortality risk in patients presenting with acute PE.

Materials and Methods

Patients hospitalized with a diagnosis of acute PE in our tertiary center between 2016 and 2022 were involved in this retrospective study. PE diagnosis was based on the European Society of Cardiology Guidelines, and the diag-

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nosis was confirmed by a filling defect in the pulmonary artery system in the computed tomography pulmonary angiography (CTPA), including sub-segmental PE. The local hospital database was used to retrieve demographic, clinical, and laboratory data.

PESI risk score includes 11 variables (age, gender, malignancy, chronic heart failure, chronic pulmonary disease, heart rate ≥110 bpm, systolic blood pressure <100 mmHg, respiratory rate >30/min, temperature <36°C, altered mental status and arterial oxyhemoglobin saturation <90 %). (https://www.mdcalc.com/calc/1304/pulmonary-embolism-severity-index-pesi).

Simplified PESI (sPESI) was created for risk stratification in an easier way and consisted 6 variables (age, malignancy, chronic cardiopulmonary disease, heart rate ≥110 bpm, systolic blood pressure <100 mmHg and arterial oxyhemoglobin saturation <90 %). (https://www.mdcalc.com/calc/1247/simplified-pesi-pulmonary-embolism-severity-index#evidence).

Diabetes mellitus (DM) [13], hypertension (HT) [14], heart failure [15], coronary artery disease (CAD) [16], chronic obstructive pulmonary disease (COPD) [17], cerebrovascular accident (CVA) [18] were described according to the established definitions. Transthoracic echocardiography data were retrieved from the hospital database (Vivid S70; GE Medical System, Horten, Norway). Right ventricular (RV) failure and dilatation were accepted as stated in the current guidelines [1]. RV was accepted as dilated when RV/LV ratio was ≥1 on computed tomography [19].

In-hospital mortality was accepted as the primary outcome of the study and patients were divided into two groups according to occurrence of in-hospital mortality; patients who survived beyond in-hospital were labeled as 'survivors' while those who deceased within the hospital stay were named as 'non-survivors'. PE related parameters such as treatment with thrombolytic or positive inotrope medication or mechanic ventilation requirement was noted. The indications and contraindications for thrombolytic treatment were accepted as defined in the current guidelines [1]. The standard medication for thrombolytic treatment was alteplase in our center. Intermediate-risk patients as per the guidelines did not receive thrombolytic therapy as well as those who had contraindications for treatment. All patients received parenteral anticoagulant therapy (unfractionated or low molecular weight heparin adjusted to creatinine clearance) initially for the first 2-3 days of hospitalization and then the treatment was switched to oral anticoagulants (vitamin K antagonists, apixaban, rivaroxaban, edoxaban, dabigatran) or remained on parenteral anticoagulants (low molecular weight heparin) based on patient characteristics. Patients with incomplete laboratory, clinical or imaging information were excluded from the study.

The study protocol was approved by the Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital KAEK in agreement with the Declaration of Helsinki (2022/11/11/032).

Statistical analyses

Statistical analysis was conducted with Statistical Package for the Social Sciences (SPSS) 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Normality was analyzed by Kolmogorov-Smirnov test. Parametric quantitative data were stated as percentages and number whereas mean ± standard deviation (SD), non-parametric data were stated as median with interquartile range. The quantitative parameters with normal distribution were assessed between two groups using the independent t-test. Whereas, Mann Whitney U test was applied for non-parametric counterparts, independent variables associated with in-hospital mortality was defined by univariate and multivariate logistic regression analysis. In order to achieve a cut-off value for the hemogram parameters and PESI, receiver operating characteristic (ROC) curves were obtained and the optimal values with the greatest total sensitivity and specificity in the prediction of in-hospital mortality were selected. Significance was assumed at a 2-sided $p<0.05$.

Results

There were 254 patients (37.4% male). Mean age of cohort was 62.7±15.5. There were 77 (30.3%) patients that received thrombolytic treatment. Thirty-eight patients (14.9%) were died in-hospital and formed 'non-survivors', whereas patients who survived beyond in-hospital were categorized as 'survivors' group. There was no difference between groups regarding age, gender, body mass index, HT, DM, CAD, COPD and CVA. History of malignancy (28.9% vs. 5.6%, $p<0.0001$), and heart failure (7.9% vs. 2.7%, $p = 0.048$) were higher in the non-survivor group. Regarding labaratory markers; leukocyte (13.2±3.8 vs. 10.2±3.2; $p<0.0001$), neutrophil (8.9±3.9 vs. 6.8±3.1; $p<0.0001$), MPV (11.2±3.6 vs. 8.2±2.5; $p=0.024$), RDW (15.6±2.9 vs. 14.1±1.8; $p<0.0001$), PDW (17.3±10.1 vs. 14.2±3.5; $p=0.001$) and NLr (7.4±6.1 vs. 4.7±3.8; $p=0.013$) , uric acid (7.8±2.9 vs. 5.7±1.9; $p<0.0001$), BUN (72.1±35.9 vs. 41.9±20.1; $p<0.0001$), C-reactive protein (CRP) [66.1 (6.1-300) vs. 40.5 (0.52-272); $p=0.003$], Tn [1051.2 (10-6000) vs. 212.3 (2-1625); $p=0.014$], NT-proBNP [10800(5890.7-14800) vs. 3863.9(53.7-10400); $p=0.031$], and D-dimer [10.1(0.13-35.9) vs. 4.2(0.12-12.8);

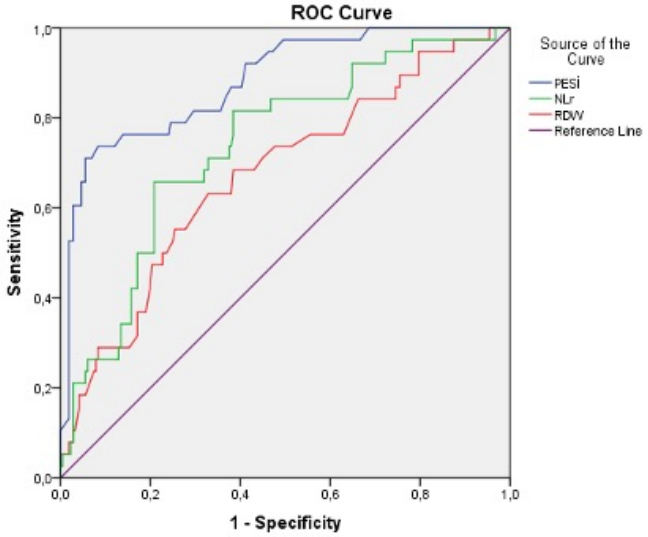

Figure 1. ROC curves of PESI, NLr and RDW for predicting in-hospital mortality.

Table 1. Clinical, demographic and laboratory variables of all chort and groups according to in-hospital mortality.

Variables	All n=254	Survivors (n=216)	Non-survivors (n=38)	p
Clinical Characteristics				
Age (years)	62.7±15.5	61.9±15.1	66.5±16.9	0.096
Male, n (%)	95 (37.4)	82 (37.9)	13 (34.2)	0.659
Body mass index (kg/m^2)	29.4±5.7	28.7±4.8	29.6±6.1	0.574
Heart Rate>110, beats/min, n (%)	252 (99.2)	214 (99.1)	38 (100)	0.551
Respiratory Rate>30, times/min, n (%)	51 (20.1)	25 (11.6)	26 (68.4)	<0.0001
Systolic Arterial Pressure<100, mmHg, n (%)	144 (56.7)	120 (55.6)	24 (63.2)	0.047
Saturation O_2<90%, n (%)	201 (79.1)	170 (78.7)	31 (81.6)	0.055
Mental status, n (%)	25 (9.8)	9 (4.2)	16 (42.1)	<0.0001
Body Temperature (°C) <36, n (%)	8 (3.1)	4 (1.9)	4 (10.5)	0.019
Right ventricle/Left ventricle >1 (Computerized Tomography), n (%)	164 (64.6)	131 (60.6)	33 (89.2)	0.001
Comorbidity				
Hypertension, n (%)	127 (50.0)	110 (50.9)	17 (44.7)	0.482
Diabetes Mellitus, n (%)	56 (22.0)	49 (22.7)	7 (18.4)	0.559
Previous coronary artery disease, n (%)	34 (13.4)	29 (13.4)	5 (13.2)	0.964
Previous congestive heart failure, n (%)	9 (3.5)	6 (2.7)	3 (7.9)	0.048
Previous Malignancy, n (%)	23 (9.1)	12 (5.6)	11 (28.9)	<0.0001
Chronic obstructive pulmonary disease, n (%)	33 (13.0)	31 (14.4)	2 (5.3)	0.094
Previous cerebrovascular Accident, n (%)	11 (4.3)	9 (4.2)	2 (5.3)	0.510
Deep venous thrombosis, n (%)	49(19.3)	39(17.8)	10(27.1)	0.202
PESI	132.8±39.7	122.8±29.3	189.4±43.8	<0.0001
Simplified PESI $\geq$1	132(52)	104(48.1)	28(73.7)	<0.0001
Laboratory Findings				
Haemoglobin, (g/dl)	12.2±1.9	12.4±1.9	11.9±2.2	0.185
Platelet, (10^3/µl)	228.5±79.8	227.9±75.4	231.6±100.3	0.799
Leukocytes, (10^3/µl)	10.7±3.5	10.2±3.2	13.2±3.8	<0.0001
Neutrophile, (10^3/µl)	7.2±3.3	6.8±3.1	8.9±3.9	<0.0001
Mean Platelet Volume, (fL)	8.5±1.2	8.2±2.5	11.2±3.6	0.024
Red cell distribution width	14.3±2.1	14.1±1.8	15.6±2.9	<0.0001
Platelet distribution width	16.9±9.4	14.2±3.5	17.3±10.1	0.001
Neutrophile/Lymphocyte ratio	5.2±4.1	4.7±3.8	7.4±6.1	0.013
Serum creatinine, (mg/dl)	1.1±0.8	1.1±0.9	1.2±0.5	0.130
Blood Unit Nitrogen, (mg/dl)	46.4±25.4	41.9±20.1	72.1±35.9	<0.0001
Glomerular filtration rate, (mL/dk/1.73m^2)	77.1±27.2	80.6±26.1	57.3±25.1	<0.0001
Sodium, (mmol/L)	138.5±4.3	138.8±3.9	136.8±6.1	0.009
Potassium, (mmol/L)	4.3±0.5	4.3±0.5	4.5±0.6	0.075
Glucose, (mg/dL)	159.6±75.1	158.3±78.1	167.05±5.3	0.511
Uric acid, (mg/dL)	5.9±2.2	5.7±1.9	7.8±2.9	<0.0001
Albumine, (g/dl)	3.7±0.5	3.8±0.5	3.2±0.7	<0.0001
C-reactive protein, (mg/dL)	24.4 (0.52-300)	40.5 (0.52-272)	66.1 (6.1-300)	0.003
Troponin I, (pg/ml)	120.0 (2-6000)	212.3 (2-1625)	1051.2 (10-6000)	0.014
NT-proBNP, (ng/mL)	4328(53.7-14800)	3863.9(53.7-10400)	10800(5890.7-14800)	0.031
D-dimer, (ng/mL)	4.8(0.12-35.9)	4.2(0.12-12.8)	10.1(0.13-35.9)	0.046
Echocardiography Findings				
Left ventricular ejection fraction, (%)	55.9±4.8	56.5±4.5	53.2±5.7	<0.0001
Left ventricular end diastolic dimension, (mm)	44.7±3.6	44.7±3.4	44.2±4.2	0.357
Right ventricular dimension,(mm)	35.6±5.7	34.9±5.6	39.2±4.8	<0.0001
RVD/LVD ratio >1	21 (8.3)	14 (6.5)	7 (18.4)	0.023
Pulmonary artery systolic pressure, (mmHg)	47.6±10.9	46.3±10.6	54.9±9.7	<0.0001
In-hospital Outcomes				
Length of Hospital Stay, n (days)	6.1±4.9	6.6±4.2	5.4±4.8	0.031
Intensive care unit admission, n (%)	171(67.3)	136 (62.1)	35 (92.1)	<0.0001
Patients receiveing trombolytic n (%)	77(30.3)	55(25.5)	22(57.9)	<0.0001
Advanced Ventilatory Support, n (%)	39(15.4)	11(5.1)	28(73.7)	<0.0001

NT-proBNP: N-terminal prohormone of brain natriuretic peptide ; PESI: The pulmonary embolism severity index; RVD: Right ventricular dimesion; LVD: Left ventricular dimension.

Table 2. Univariate and multivariate forward stepwise logistic regression analysis: predictors of in-hospital mortality.

	Univariate OR	95% CI	p	Multivariate OR	95% CI	p
PESI	1.043	1.031-1.056	<0.0001	1.035	1.018-1.053	<0.0001
Leukocytes	1.061	1.005-1.121	0.034	0.956	0.737-1.240	0.956
Neutrophil	1.189	1.077-1.314	0.001	0.835	0.600-1.161	0.284
RDW	1.329	1.139-1.551	<0.0001	1.548	1.186-2.020	0.001
PDW	0.936	0.872-1.004	0.064			
MPV	1.339	1.007-1.781	0.045	1.152	0.517-2.570	0.729
NLr	1.259	1.140-1.390	<0.0001	1.529	1.125-2.078	0.007
C-reactive protein	1.009	1.003-1.025	0.004	1.001	0.986-1.015	0.919
Troponin I	1.007	1.001-1.016	0.001	0.987	0.952-1.002	0.085
NT-proBNP	1.008	0.821-1584	0.997			
D-dimer	0.932	0.843-1.030	0.168			

MPV: Mean platelet volume; NLr: Neutrophil lymphocyte ratio; PDW: platelet distribution width; PESI: The pulmonary embolism severity index; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

p = 0.046], were significantly higher in the non-survivor group. Moreover, serum sodium (136.8±6.1 vs. 138.8±3.9; p=0.009), albumine (3.2±0.7 vs. 3.8±0.5; p<0.0001) and GFR (57.3±25.1 vs. 80.6±26.1; p<0.0001) were significantly lower in non-survivor group. In terms of echocardiography findings, the non-survivor group had significantly lower ejection fraction (53.2±5.7 vs. 56.5±4.5; p<0.0001), however, pulmonary artery pressure (54.9±9.7 vs. 46.3±10.6; p<0.0001) and right ventricular dimension (39.2±4.8 vs. 34.9±5.6; p<0.0001) were higher. Furthermore, PESI score (189.4±43.8 vs. 122.8±29.3; p.<0.0001) and simplified PESI (73.7% vs. 48.1%, p<0.0001) were significantly higher in non-survivor group. Length of hospital stay (5.4±4.8 vs. 6.6±4.2, p=0.031) was shorter, while admission to intensive care unit (92.1% vs. 62.1%, p<0.0001), need for thrombolytic (57.9% vs. 25.5%, p<0.0001), advanced ventilatory support (73.7% vs. 5.1%, p<0.0001) were more frequent in non-survivor group (Table 1).

To further evaluate individual risk factors associated with in-hospital mortality, we performed univariate logistic regression analysis for PESI, leukocytes, neutrophil, RDW, PDW, MPV and NLr, CRP, Tn, NT-proBNP and D-dimer levels, respectively. By univariate logistic regression analysis, PESI, leukocytes, neutrophil, RDW, MPV, NLr, CRP and Tn levels were correlated with in-hospital mortality. These variables were assessed in the multivariate logistic regression model and PESI [p<0.0001, β: 1.035, OR (95% CI): 1.018-1.053], RDW [p=0.001, β: 1.548, OR (95% CI): 1.186-2.020], and NLr [p=0.007,β: 1.529, OR (95% CI): 1.125-2.078] were documented as independent risk factors associated with in-hospital mortality. PESI, NLr and RDW were consequently analyzed and the optimal cut-off value and area under the curve (AUC) were identified. ROC curve for accuracy of PESI, NLr and RDW for predicting in-hospital mortality in PE patients is shown in Figure 1. The AUC for PESI was 0.882 [%95 CI: 0.823-0.942]. A cut off value 141.5 for PESI score was associated with 76.3% sensitivity and 75.9% specificity; the AUC for NLr was 0.738 [%95 CI: 0.653-0.822]. and a cut off value of 5.9 for NLr was associated with 68.4% sensitivity and 68.1% specificity and moreover, AUC for RDW was 0.673 [%95 CI: 0.577-0.768]. A cut off value of 14.1 for RDW was associated with 68.4% sensitivity and 62.6% specificity in predicting in-hospital mortality (Table 2).

Discussion

Our study populations consist of high-risk patients with a high probability of thrombolytic therapy and study conducted in a tertiary level cardiology center. In this study we sought to assess if hematological parameters could predict in-hospital mortality in PE patients. Consequently, we found that NLr and RDW as independent risk factors associated with in-hospital mortality. Our results revealed a strong correlation between hematological parameters and PESI risk score and a cut off value of 5.9 for NLr was associated with 68.4% sensitivity and 68.1% specificity; besides that, cut off value of 14.1 for RDW was associated with 68.4% sensitivity and 62.6% specificity in prediction of in-hospital mortality. Therefore, hematological parameters can be used in conjunction with the PESI/sPESI scores in order to stratify PE patients.

Blood count analysis is one of the essential parameters on hospital admission and each variable provides essential prognostic information in various cardiac conditions. Platelet activation is known to be associated with acute PE as well as thrombotic conditions [20, 21]. Mean platelet volume reflects not only size and also activity of the platelets. High MPV indicates the risk of plaque burden and raised thrombogenic activity [22]. Thrombogenic and metabolic activities of platelets may differ according to sizes and PDW is a marker which indicates the platelets in circulation have various sizes and activities [23]. Both MPV and PDW values were higher in-hospital mortality group in patients hospitalized with acute PE in our study however, they were not detected as independent predictors. The values which were obtained on admission were used for analyses however, changes or maximal values during follow-up were not included. This might explain the difference between our results and previous findings. Widen RDW is an indicator of diminished erythropoiesis and correlated with increased inflammation and oxidative stress. Acute coronary syndrome, CAD, CHF, atrial fibrillation are some of the cardiac conditions in which widen RDW is found to be associated with prognosis. [6, 24]. Similarly, we detected widen RDW as an independent pre-

dictor of in-hospital mortality. NLr provides practical approach to detect inflammatory status by combining two different markers of inflammation [25]. The NLr which was calculated by using blood count parameters on admission in our study revealed as an independent predictor of mortality, indicating the importance of inflammation in acute PE. PESI is mainly based on clinical parameters however it has shown that sensitivity of PESI may be improved by using additive inflammatory markers (hs-C – reactive protein, troponin, etc.). RDW and NLr may give further knowledge when used in conjuction with PESI according to our results.

Thrombolytic therapy may have catastrophic side effects (e.g., bleeding) that may outweigh the benefit. The mortality benefit and reduction in the risk of acute hemodynamic collapse was also shown in intermediate-risk patients when treated with thrombolytics [26, 27, 28]. Consequently, it is crucial to define patients under risk by using additive parameters besides hemodynamic instability. According to the findings in this study, the hematological parameters may give clue to classify PE patients to identify normotensive PE patients at high risk of short-term mortality in conjunction with hemodynamic parameters and PESI. However, its broad applicability should be assessed in prospective randomized controlled studies. The treatment especially decision for thrombolytic therapy mainly directed by the hemodynamic findings of the patient. However, using additional parameters those are available for evaluation, may help while directing therapy. Complete blood count is almost always available and reading subparts may help clinicians about thrombotic and inflammatory status of the patient.

Single-center and retrospective design with a relatively small patient population were the main limitations of the study. The period from the beginning of symptoms up to hospitalization may be a reason for mortality and affect the thrombotic and inflammatory status. This time frame was not assessed in our study and might change the outcomes. Additionally, the patients who were deemed in high-risk or hemodynamically unstable or those with multiple comorbidities were transferred to our clinic for treatment or close follow-up. This might explain the higher mortality rate in our study. Definitely, larger and prospectively designed studies are required to demonstrate the linkage between hematological parameters and PE mortality.

Conclusion

Our current study showed that hematological parameters, assessed by routine blood count analysis, may serve as a promising and useful marker to foresee in-hospital mortality in patients presenting with acute PE especially when used additive to validated risk scores. Thus, concomitant use of hematological parameters and PESI scores to define high-risk normotensive and hypotensive PE patients and to predict poorer short-term prognosis may be clinically applicable with high specificity and positive probability.

Competing interests

The authors declare that they have no competing interests.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital KAEK (2022/11/11/032).

Contributions

SO: Conceptualization, Methodology, Data curation, Software, Writing- Original draft preparation. ED: Conceptualization, Methodology, Data curation, Writing- Original draft preparation.

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