

11-30-2021

Utility of Blood Cellular Indices in the Risk Stratification of Patients Presenting with Acute Pulmonary Embolism.

Brett Slajus
Loyola University Medical Center

Yevgeniy Brailovsky
Thomas Jefferson University

Iman Darwish
Loyola University Medical Center

Jawed Fareed
Loyola University Chicago

Amir Darki
Loyola University Medical Center
Follow this and additional works at: <https://jdc.jefferson.edu/cardiologyp>

 Part of the [Cardiology Commons](#)

[Let us know how access to this document benefits you](#)

Recommended Citation

Slajus, Brett; Brailovsky, Yevgeniy; Darwish, Iman; Fareed, Jawed; and Darki, Amir, "Utility of Blood Cellular Indices in the Risk Stratification of Patients Presenting with Acute Pulmonary Embolism." (2021). *Division of Cardiology Faculty Papers*. Paper 93.
<https://jdc.jefferson.edu/cardiologyp/93>

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Division of Cardiology Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

Utility of Blood Cellular Indices in the Risk Stratification of Patients Presenting with Acute Pulmonary Embolism

Clinical and Applied
Thrombosis/Hemostasis
Volume 27: 1-8
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10760296211052292
journals.sagepub.com/home/cat



Brett Slajus, MPH¹ , Yevgeniy Brailovsky, DO² , Iman Darwish, BS¹ ,
Jawed Fareed, PhD, FAHA³ , and Amir Darki, MD, MSc¹

Abstract

Pulmonary embolism (PE) clinical manifestations vary widely, and that scope is not fully captured by current all-cause mortality risk models. PE is associated with inflammatory, coagulation, and hemostatic imbalances so blood cellular indices may be prognostically useful. Complete blood count (CBC) data may improve current risk models like the simplified pulmonary embolism severity index (sPESI) for all-cause mortality, offering greater accuracy and analytic ability. Acute PE patients (n = 228) with confirmatory diagnostic imaging were followed for all-cause mortality. Blood cellular indices were assessed for association to all-cause mortality and were supplemented into sPESI using multivariate logistic regression. Multiple blood cellular indices were found to be significantly associated with all-cause mortality in acute PE. sPESI including red cell distribution width, hematocrit and neutrophil-lymphocyte ratio had better predictive ability as compared to sPESI alone (AUC: 0.852 vs 0.754). Blood cellular indices contribute an inflammatory and hemodynamic perspective not currently included in sPESI. CBC with differential is a widely used, low-cost test that can augment current risk stratification tools for all-cause mortality in acute PE patients.

Keywords

pulmonary embolism, sPESI, complete blood count, inflammation, covid-19

Introduction

Pulmonary embolism (PE) is a life-threatening condition with variable severity that results from dysregulation of complex inflammatory and hematologic processes. In the United States, the incidence of acute PE is estimated to be 600,000 cases annually.¹ Acute PE is the third leading causing of cardiovascular death in the United States, accounting for over 100,000 deaths annually.¹ Additionally, there is higher incidence among those with advancing age as well as among African Americans and Caucasians as compared to other races and ethnicities.¹ Within acute PE manifestations, there is significant variability in severity as well as mortality risk.^{2,3} Short-term all-cause mortality rates differ widely, from 2% among low-risk normotensive patients to 95% among those experiencing cardiac arrest.²

Due to the wide symptom profile at presentation, acute PE are stratified by symptom severity and hemodynamic stability.³ Diagnosis is primarily made using a combination of clinical assessment and confirmatory imaging with supplementary tools like simplified Geneva and Wells scoring systems to assist with pre-test probability.^{4,5} Subsequent testing includes echocardiography, six-minute walk test, and laboratory testing

to further evaluate cardiopulmonary functioning of patients and aid in treatment algorithms.^{3,6,7} In terms of prognostic risk, most commonly the Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) are used to stratify patients by risk of mortality and are adept at identifying low-risk patients suitable for outpatient management.^{2,8,9} However, these models have suboptimal accuracy for higher risk patients due to low specificity, and additional testing can be time and resource dependent as well as costly for patients.^{3,9}

¹ Loyola University Medical Center, Stritch School of Medicine, Maywood, IL, USA

² Advanced Heart Failure, Mechanical Circulatory Support, Heart Transplant, Jefferson Heart Institute, Sidney Kimmel School of Medicine, Thomas Jefferson University, Philadelphia, PA, USA

³ Cardiovascular Research Institute, Hemostasis and Thrombosis Research Division, Loyola University Chicago, Health Sciences Division, Maywood, IL, USA

Corresponding Author:

Brett Slajus, Health Sciences Division, Cardiovascular Research Institute, Loyola University Chicago, 2160 South First Ave, Maywood, IL 60153, USA. Email: bsajus@luc.edu



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use,

reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

Conversely, complete blood count with differential testing is a cost-effective and routinely obtained lab test used throughout the clinical course of patients.¹⁰ Complete blood counts parameters, or blood cellular indices, often are obtained daily during a hospital stay. There is growing literature demonstrating the utility of individual blood cellular indices obtained from complete blood counts in predicting PE patient prognosis.^{11–15} Venous thromboembolisms occur in part due to complex inflammatory and coagulation processes associated with platelet activation and inflammatory cascades.^{16,17} There are increased levels of pro-inflammatory cytokines as well as evolving ratios of immune cells interacting with the thrombus itself.^{18,19} Various diseases like malignancy, infection, and systemic lupus erythematosus associated with acute PE also have hematologic and immunologic abnormalities.¹⁷ Complete blood count with differential includes a broad scope of blood cellular indices and a perspective not captured in existing risk models which relies on clinical history and exam findings.^{2,8}

The primary objective of our study is to determine any associations between blood cellular indices and all-cause mortality. Since PE reflects inflammatory and coagulation imbalances, we hypothesize there will be abnormal findings that suggest

increased risk of all-cause mortality. Our study also sought to assess the predictive ability of complete blood count data for all-cause mortality. As such, a secondary objective was to supplement the current sPESI model with additional blood cellular indices to improve predictive skill of the model. Supplementary parameters to sPESI may boost its prognostic abilities and be useful in accurately identifying high-risk patients.

Material and Methods

Patient Selection and Data Collection

Patients 18 years or older who were diagnosed with and treated for with acute PE between March 2016 and June 2019 at Loyola University Medical Center were prospectively recruited by the PE response team (PERT). Diagnosis was made using CT angiography or ventilation perfusion (VQ) scan confirmed by PERT team. PE severity was classified as low risk, submassive, and massive set forth by guidelines from the American College of Cardiology and American Heart Association.³ Baseline demographics were retrospectively collected using the EMR. Complete blood counts with differentials were collected on patients throughout their hospital course as a part of routine care and were also collected retrospectively from the EMR, using samples obtained within 24 hours of PE diagnosis prior to treatment.

Patients were excluded from the study due to presence of infection, chronic inflammatory condition, or ongoing cancer treatment at time of PE diagnosis. Patients who were missing complete blood count with differential results, were undergoing chemotherapy for cancer treatment, or were on immunosuppressants were excluded from the study as well. If a patient had multiple acute PEs during study period, only the first instance was included in the study analysis. Patients were subsequently followed for all-cause mortality using the EMR until completion of the study in July 2019.

Statistical Analysis

Descriptive statistics were divided by mortality and reported as median and interquartile range for nonparametric variables, mean and standard deviation for parametric variables, and as percentage for categorical variables. Continuous variable distributions were checked using Kolmogorov-Smirnov testing. Statistical significance was analyzed for continuous variables using two-sample t-test, Mann Whitney nonparametric test while categorical variables were analyzed using Pearson's chi-square and Fisher's exact test. P values were two-sided and values <0.05 were considered statistically significant. PLR was calculated as the ratio of platelets to lymphocytes, NLR as the ratio of neutrophils to lymphocytes, PNR as the ratio of platelets to neutrophils, and LMR as the ratio of lymphocytes to monocytes.

Receiver operator curves were created to determine optimal cutoff values using Youden J index to predict all-cause mortality. Univariate and multivariate binary logistic regression were

Table 1. Baseline Demographics, Co-Morbidities, Vital Signs of Living and Deceased Patients with Acute PE.

	Living (n = 180)	Deceased (n = 48)	P-value
Age (median ± IQR)	62 (52.0–70.5)	65.0 (55.0–73.0)	0.13
Female, n (%)	90 (50%)	27 (56.3%)	0.42
CAD, n (%)	19 (10.6%)	8 (16.7%)	0.26
CHF, n (%)	19 (10.6%)	9 (18.8%)	0.14
T2DM, n (%)	40 (22.2%)	12 (25.0%)	0.83
HTN, n (%)	97 (53.9%)	26 (54.2%)	0.89
CPD, n (%)	9 (5.0%)	6 (12.5%)	0.10*
COPD, n (%)	7 (3.90%)	5 (10.4%)	0.14*
Prior DVT, n (%)	22 (12.2%)	14 (29.2%)	<0.01
Prior PE, n (%)	21 (11.7%)	11 (22.9%)	0.05
Prior Stroke, n (%)	14 (7.8%)	5 (10.4%)	0.57
PE severity			
Low-risk, n (%)	60 (33.3%)	13 (27.1%)	0.28
Submassive, n (%)	109 (60.6%)	29 (60.4%)	
Massive, n (%)	11 (6.10%)	6 (12.5%)	
Vitals			
SBP (mmHg) (median ± IQR)	107 (97–118)	100.5 (88–109.8)	0.03
HR (beats/min) (median ± IQR)	102 (90–114)	118.5 (94.5–135.5)	<0.01
RR (breaths/min) (median ± IQR)	23.5 (20–26.3)	23.5 (20.0–35.0)	0.36
O2 Saturation (%) (median ± IQR)	93 (90–95)	90 (85–92)	<0.01

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CPD, chronic pulmonary disease; DVT, deep vein thrombosis; HR, heart rate; HTN, hypertension; PE, pulmonary embolism; RR, respiratory rate; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

performed to identify independent predictors of all-cause mortality. Forward multivariate logistic regression was used to develop a composite sPESI risk prediction model with supplemental parameters. Variables were sequentially added to the multivariate model in order of greatest area under the curve (AUC). For the composite sPESI model including blood cellular indices, one point was added for every additional condition met beyond the original sPESI model. sPESI and the composite sPESI were then compared using ROC curves and optimal cutoffs were determined. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY, IBM Corp).

Results

There were 383 consecutive patients enrolled in the study with 228 patients included for analysis after exclusion criteria was applied. Of the patients analyzed, 180 (79%) were survivors with 48 (21%) non-survivors at the end of the study period (Table 1). Patients were followed for a median of 56 days (IQR=17-182) from time of PE diagnosis to end of study or mortality. Of the 48 deceased patients, 7 (14.6%) deaths were related to PE, 26 (54.2%) were related to non-PE causes such as hospice care, metastatic cancer, or septic shock at a later time point, and 15 (31.2%) were due to unknown causes.

Based on PE severity, 73 (32%) of patients were defined as low risk, 138 (60.5%) as submassive, and 17 (7.5%) as massive.

Table 2. PESI Scores and Laboratory Parameters by All-cause Mortality in Patients with Acute PE.

	Living (n = 180) (median ± IQR)	Deceased (n = 48) (median ± IQR)	P-value
PESI score	91 (69.3–124)	131.5 (107–185)	<0.01
sPESI score	1.0 (0.0–2.0)	2.0 (1.0–4.0)	<0.01
WBC (K/ μ L)	9.2 (7.0–11.2)	9.4 (6.0–11.7)	0.77
Neutrophil Count (K/ mm^3)	6.3 (4.73–8.5)	6.7 (4.1–9.6)	0.95
Lymphocyte Count (K/ mm^3)	1.5 (1.1–2.2)	0.9 (0.6–1.3)	<0.01
Eosinophil Count (K/ mm^3)	0.1 (0.1–0.2)	0.0 (0.0–0.1)	<0.01
Basophil Count (K/ mm^3)	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.91
Monocyte Count (K/ mm^3)	0.7 (0.5–0.9)	0.6 (0.4–0.9)	0.13
HCT (%) ^a	39.5 ± 6.5	33.7 ± 6.8	<0.01
HGB (g/dL)	13.3 (11.7–14.7)	10.8 (9.5–12.5)	<0.01
MPV (fL)	8.3 (7.7–9.0)	8.3 (7.4–8.8)	0.19
RDW (%)	14.2 (13.4–15.7)	16.5 (15.4–19)	<0.01
Platelet Count (K/ μ L)	226.5 (175–282)	214 (126–297.3)	0.43

Abbreviations: HCT, hematocrit; HGB, hemoglobin; MPV, mean platelet volume; PESI, pulmonary embolism severity index; RDW, red blood cell distribution width; sPESI, simplified pulmonary embolism severity index.

^aAnalysis reported as mean ± standard deviation.

There were higher mortality rates with increasing PE severity from low-risk (17.8%), submassive (21.0%) and massive (35.5%), which did not reach statistical significance. Decreased systolic blood pressure (100.5 vs 107 mmHg; $p=0.03$) and oxygen saturation (90 vs 93; $p<0.01$), as well as elevated heart rate (118.5 vs 102; $p<0.01$) were associated with all-cause mortality. There were no other significant differences between mortality groups for demographic data or past medical history.

As seen in Table 2, deceased patients were more likely to have both a higher PESI (131.5 vs 91.0; $p<0.01$) and sPESI score (2.0 vs 1.0; $p<0.01$). Red cell distribution width (RDW), PLR, and NLR were elevated in deceased patients while hematocrit, hemoglobin, lymphocyte count, eosinophil count, and LMR were lower in deceased patients (all $p<0.01$). White blood cell count was higher in deceased patients, while platelet count was lower, but neither was significantly different from alive patients or outside clinical reference value ranges.

ROC curves depicting the predictive value of blood cellular indices to predict all-cause mortality are demonstrated in Figure 1. The Youden J index derived cutoff value of RDW was ≥ 15.15 , hematocrit was ≤ 34.15 , hemoglobin ≤ 11.15 , NLR ≥ 5.50 , PLR ≥ 256.70 , eosinophil count ≤ 0.06 , LMR ≤ 1.61 . RDW was shown to have the highest predictive value with an AUC of 0.776, followed by hemoglobin (0.741), hematocrit (0.737), NLR (0.688), eosinophil count (0.664), LMR (0.664), and PLR (0.659). Parameter cutoff value sensitivity and specificity are demonstrated in Table 3.

The final multivariate model included sPESI ($p<0.01$) and independent predictors RDW ($p<0.01$), hematocrit ($p=0.02$) and NLR ($p<0.01$) as seen in Table 4. The addition of hemoglobin, eosinophil count, PLR, LMR were not found to be independent predictors of all-cause mortality and did not improve the composite model further. Illustrated in Figure 2, the composite model of cellular indices and sPESI offered improved predictive ability (AUC 0.852, 95% CI: 0.791-0.912) as compared to sPESI alone (AUC 0.754, 95%CI: 0.678-0.829) both with a cutoff value of ≥ 2 . The specificity of the composite model improves as compared to sPESI alone (81.0% vs 64.2%); however, sensitivity was slightly lower (70.8% vs 72.9%). Positive and negative predictive value of the composite model was 50% and 91.3%, respectively, while 35.4% and 89.9% for sPESI alone.

Discussion

Risk prediction models like PESI² and sPESI⁸ score are presently used to assess both disease severity and prognosis for PE to optimize patient care. Current PE mortality prediction models make use of medical history and signs of hemodynamic stability only.^{2,3,8} These models can be further enriched with routine laboratory data. With a high negative predictive value and low positive predictive value, sPESI is primarily useful in finding low risk patients.^{9,20} Due to lower accuracy, further testing such as echocardiography and six-minute walk test is often needed to supplement established decision-making tools for intermediate and high risk patients.^{6,7,21} The use of routinely

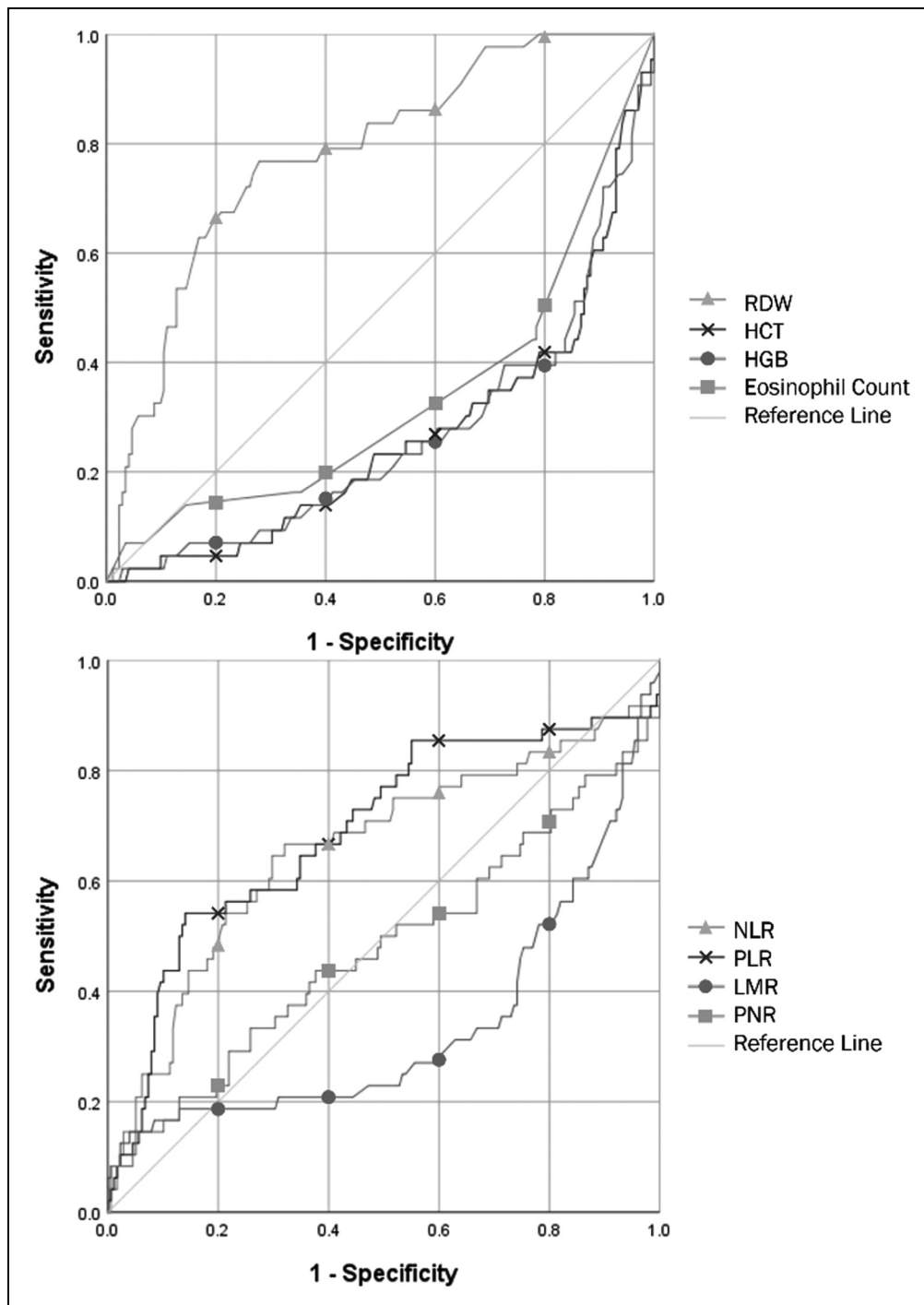


Figure 1. Predictive value of individual blood cellular indices on all-cause mortality in patients with acute PE. Abbreviations: RDW, red blood cell distribution width; HCT, hematocrit; HGB, hemoglobin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PNR, platelet to neutrophil ratio.

collected laboratory data in risk stratifying patients could help reduce time and resources when working up PE patients. PE pathophysiology reflects dysregulation of coagulation, inflammatory and hematologic processes.^{17,18,22} There is growing evidence of laboratory parameters predictive of all-cause mortality, including MPV,^{14,23,24} blood cellular ratios,^{12,13,23,25} RDW,¹⁵ and anemia,¹¹ few studies have incorporated multiple

parameters into existing risk prediction models. It is necessary to further explore using blood cellular indices to predict all-cause mortality to improve current PE treatment algorithms.

Our study found that sPESI could be further optimized for predicting all-cause mortality with the addition of routine laboratory blood cellular indices. Within our patient cohort, the individual parameter with greatest predictive ability was red cell

Table 3. Individual Parameter ROC Area Under the Curve (AUC), Optimal Youden J Index Cut-off Values, Sensitivity and Specificity for Predicting All-cause Mortality Among PE Patients.

	AUC (95% CI)	Cutoff Value	Sensitivity	Specificity
RDW	0.776	≥15.15	0.792	0.698
HCT	0.737	≤34.15	0.583	0.833
HgB	0.741	≤11.15	0.583	0.828
NLR	0.688	≥5.50	0.667	0.683
PLR	0.659	≥256.70	0.542	0.856
Eosinophil Count	0.668	≤0.06	0.558	0.785
LMR	0.664	≤1.61	0.667	0.708
sPESI alone	0.754	≥2.00	0.729	0.642
sPESI + RDW + HCT + NLR	0.852	≥2.00	0.708	0.810

Abbreviations: HCT, hematocrit; HGB, hemoglobin; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; RDW, red blood cell distribution width; sPESI, simplified pulmonary embolism severity index.

distribution width, which was found to be an independent predictor beyond sPESI and other cellular markers. It has been found previously that elevated RDW is a strong prognostic symbol of mortality in hospital admissions.²⁶ RDW was strongest at predicting cardiovascular disease mortality but was also elevated in other disease states.²⁶ Anisocytosis has been found in the context of VTE with strong diagnostic value for risk assessment²⁷ as well as in predicting all-cause mortality in PE patients.¹⁵ Though the underlying pathophysiology of why anisocytosis occurs in PE remains unclear, its presence as a general manifestation of chronic disease and inflammation is apparent. Despite elevated RDW being nonspecific and present in numerous disease states, its predictive ability was better than sPESI alone within our study and contributed to the improved accuracy of the composite sPESI model.

Previously, our group reported PLR and NLR were significantly associated with all-cause mortality in PE patients and could supplement sPESI,²⁵ which was in conjunction with other studies.^{12,13,23} At present, we found elevated ratios of PLR, NLR along with decreased LMR and lymphocyte count associated with all-cause mortality. Other studies have found increased neutrophil count^{12,13,23} or decreased monocyte count,²³ but our study did not find any significant association

Table 4. Forward logistic Regression of Blood Cellular Indices to Supplement sPESI Predictive Model.

	Cutoff value	Multivariate analysis OR (95% CI)	P-value
sPESI	–	1.84 (1.31-2.58)	<0.01
RDW	≥15.15	4.92 (2.0-12.12)	<0.01
HCT	≤34.15	2.67 (1.15-6.19)	0.02
NLR	≥5.50	3.90 (1.72-8.83)	<0.01

Abbreviations: HCT, hematocrit; NLR, neutrophil to lymphocyte ratio; RDW, red blood cell distribution width; sPESI, simplified pulmonary embolism severity index.

with all-cause mortality for these blood cellular indices. There are changes in various inflammatory cell amounts during thrombus development and resolution.¹⁹ If studies are capturing different timepoints within the PE course it may reflect variability in cellular markers though this must be studied further. It may be that lymphocyte count is a key component to these cellular ratios, but more likely the ratios reflect the necessity of using multiple cell counts to obtain a comprehensive assessment of inflammatory processes. As our study shows, there is some overlap in predictiveness of some cellular ratios, but the inclusion of NLR was found to be an independent predictor and a beneficial inclusion to sPESI.

Laboratory signs of anemia, specifically low hemoglobin and hematocrit were also found to predict all-cause mortality in acute PE. In a study by Jimenez et al, lower hemoglobin ranges were associated with higher rates of mortality in PE patients regardless of gender.¹¹ Our study found similar cutoffs of <34.15 g/dl for hematocrit and <11.15 g/dl for hemoglobin associated with increased risk of mortality. Both hematocrit and hemoglobin were found to be independently predictive in addition to sPESI, but only hematocrit was included in the final model to avoid redundancy. Anemia may serve as a prognostic marker of worsening renal function or presence of chronic disease that can cause disturbances to erythropoiesis.²⁸

Our study demonstrated the utility of complete blood count data to supplement sPESI, but it is important to explore additional parameters. Other studies found elevated MPV useful in diagnosis of acute PE²⁴ as well as predictive of all-cause mortality.^{14,23} Increased MPV has been associated with platelet activation and adhesion which occur in acute PE.²⁹ In contrast, our study did not find a significant difference in MPV, and interestingly the same median value between living and deceased patients. The incongruous findings may be due to our study obtaining complete blood count data within a 24-hour period prior to PE diagnosis, which may be prior to platelet changes that result in increased MPV. Another interesting finding was the association of elevated eosinophil count with all-cause mortality, though it was not included in the final model. Two case studies were published on patients with eosinophilic disorders with PE suggesting a possible correlation.^{29,30} Further research is necessary to demonstrate a more comprehensive association between eosinophilia and PE mortality, with greater granularity of cell counts. Elevations in both pro-inflammatory and anti-inflammatory cytokines, including IL-4, IL-6, IL-8, IL-10, VEGF, IFN- λ , TNF- α , IL-1 α , IL-1 β , MCP-1 and EGF, have also been associated with increased PE severity.³¹ Like cellular markers, many cytokines likely are elevated in PE due to an enhanced systemic inflammatory response. It is important to assess the utility of these inflammatory markers with clinical outcomes as it may provide an additional perspective not currently encompassed in PE risk prediction models or by cellular indices.

Despite the inclusion of malignancy in sPESI and PESI, often there is an altered hematologic profile, especially in the setting of hematologic malignancy. For this reason, patients with co-morbid cancer were excluded from the study due to the presumed confounding effects on complete blood count data. Future studies

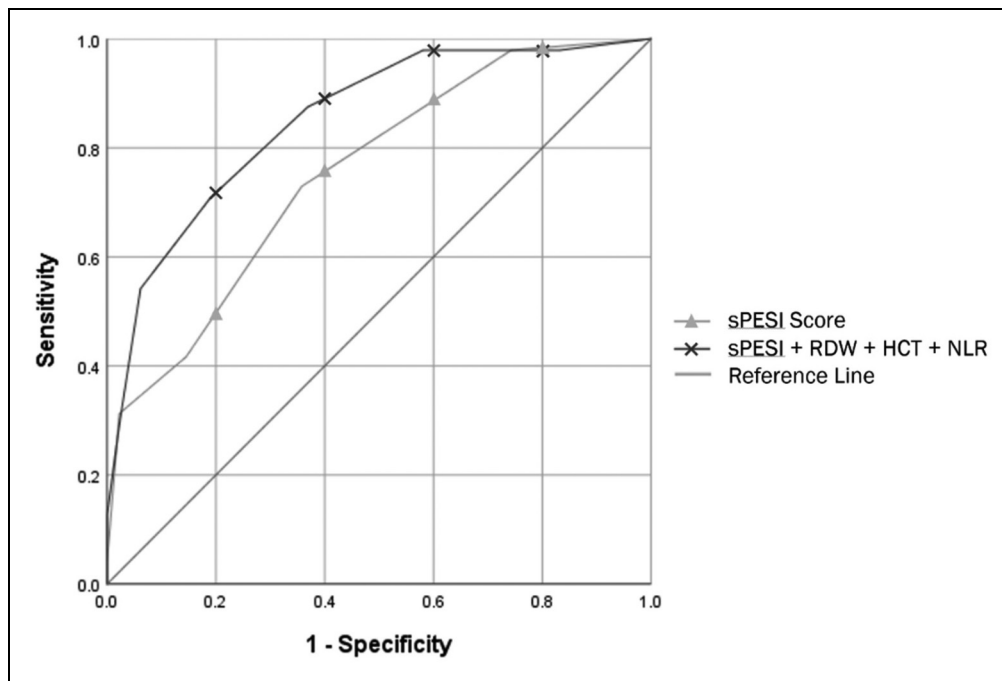


Figure 2. Comparing predictive value of sPESI and composite sPESI for all-cause mortality in acute PE patients. Abbreviations: sPESI, simplified pulmonary embolism severity index; RDW, red blood cell distribution width; HCT, hematocrit; NLR, neutrophil to lymphocyte ratio.

are necessary to elucidate the predictive value of blood cellular indices in a more comprehensive patient cohort, as laboratory data and malignancy may capture similar predictive data. Infected and septic patients were equally excluded for presumed confounding effects to hematologic and inflammatory markers. The inclusion of blood cellular indices may provide greater opportunities to demonstrate mortality risk factors and dysregulation that can predispose patients. Our study was able to illustrate the utility of RDW, NLR, and hematocrit in patients lacking cancer, which suggests multiple disease states including PE itself can contribute to hematologic and inflammatory imbalances. Further research is required to deduce the predictive abilities of blood cellular indices in malignancy, infection and rheumatologic diseases. Within these patient populations it may be that blood cellular indices offer additional information sPESI alone does not provide, which may help in identifying high risk patients who require more substantive therapy.

Further research is necessary to determine the best predictive model for PE, making use of additional routinely used clinical tools like laboratory data, echocardiography, and six-minute walk test. As this study purports, complete blood count information can augment current PE risk models. Echocardiography⁶ and six-minute walk test⁷ offer an assessment of cardiopulmonary functioning used in clinical decision making that also may be useful in risk stratifying patients by mortality. Likewise, further development of biochip array technology would offer an efficient way to rapidly assess multiple inflammatory markers associated with greater PE severity like IL-6, EGF, and IL-8 not currently available to most clinical settings.³¹ Though sPESI

includes comorbidities and vital signs as potential risk factors, it does not offer a more comprehensive evaluation of the effects of an acute PE on the patient.⁸ In patients with diminished ventricular or exercise performance, it may suggest poor prognosis but there is limited data assessing their long-term prognostic ability. Furthermore, there may be inter-operator variability in performing these labor and time-intensive tests as compared to the relatively standardized process of obtaining laboratory data. Other laboratory markers such as troponin and BNP have been found to be elevated in acute PE and associated with short term all-cause mortality.^{21,32,33} Santos et al found elevated troponin and BNP cardiac biomarkers to indicate worsened prognosis in patients with intermediate-high risk.³³ There is an abundance of testing options available to risk stratify patients, it is important for future studies to weigh the benefits of each and integrate these results into a comprehensive risk model.

One of the primary strengths of these blood cellular indices is the affordability and accessibility of obtaining complete blood counts. Complete blood counts often are collected daily throughout a patient's hospital stay and can also be obtained in the emergency department. Our study attempted to control the impact of PE treatment protocols on all-cause mortality by using blood cellular metrics obtained within 24 hours prior to PE diagnosis. Due to the evolving cellular and inflammatory nature of a thrombus, it may be worthwhile to assess laboratory data at multiple time points.¹⁹ Not only could blood cellular data at a future time point potentially predict mortality risk, but stronger predictive ability may be elucidated by looking at laboratory responsiveness to treatments.

Study Limitations

Being an observational cohort study, the results should not be used definitively for clinical decision making or risk prediction without further research. As this study was performed at a tertiary care center, there may be overrepresentation of higher acuity PE patients transferred from outside hospitals which could bias the results toward PE patients with increased risk factors and greater degree of laboratory abnormalities. Conversely, since complete blood count data was taken within a 24-hour period prior to PE diagnosis, it is possible some were obtained prior to symptom onset and that could serve as a potential source of variability and confounding. The results included in this study were based on data obtained prior to the covid-19 pandemic and before the introduction of vaccination. Recent reports have suggested increased prevalence of PE in covid-19 patients and there is some indication of thromboembolic complications after vaccination. In terms of statistical analysis, the multivariate logistic regression may reflect overestimates of odds ratio and significance due to the limitations in number of cases and limited power. The sPESI model is validated for predicting 30-days mortality, however, our study followed patients for a longer duration which could impact the accuracy of sPESI and the utility of our findings. Such factors need to be taken into account in future studies to validate the results presented in this manuscript.

Conclusions

The primary goal of the study was to assess if complete blood count data was associated and predictive of all-cause mortality. We found multiple blood cellular indices to be significantly related, including RDW, NLR, and HCT among others. Additionally, our secondary objective was to supplement current risk prediction model sPESI for improved accuracy, which we did through the inclusion of RDW, NLR and HCT. sPESI alone has poor positive predictive value which limits its utility in high-risk patients, our composite model PPV was 50% compared to 35.4% with sPESI alone and offered similar NPV at 91.3% for the composite model and 89.9% for sPESI alone. Complete blood count data is routinely obtained in emergency and inpatient settings. It is a widely used, low-cost, convenient laboratory test that offers an abundance of metrics that can be incorporated within sPESI to improve the model's predictive ability for predicting PE risk mortality. Future studies exploring complete blood count data further, in addition to echocardiogram, six-minute walk test and other lab-based testing may be beneficial in improving current decision-making tools.

Acknowledgements

The authors acknowledge the skillful assistance of the faculty and staff of the Hemostasis Research Laboratories within the Department of Pathology and the Loyola University Medical Center. The authors are sincerely grateful for the support of the Division of Cardiology, Department of Medicine at Loyola University Chicago for their

valuable assistance. We are also thankful to Ms. Erin Healy-Erickson for her skillful input in the completion of this manuscript.


Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


Funding


The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Brett Slajus  <https://orcid.org/0000-0002-4688-4812>

Yevgeniy Brailovsky  <https://orcid.org/0000-0002-4811-5267>

Iman Darwish  <https://orcid.org/0000-0001-6963-1431>

Jawed Fareed  <https://orcid.org/0000-0003-3465-2499>

References

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous Thromboembolism: A Public Health Concern. *Am. J. Prev. Med.* 2010;38:S495-S501.
2. Aujesky D, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am. J. Respir. Crit. Care Med.* 2005;172:1041-1046.
3. Konstantinides SV, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of. *Eur. Heart J.* 2020;41:543-603.
4. Gibson NS, et al. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. *Thromb. Haemost.* 2008;99:229-234.
5. Klok FA, et al. Simplification of the Revised Geneva Score for Assessing Clinical Probability of Pulmonary Embolism. *Arch. Intern. Med.* 2008;168:2131-2136.
6. Dabbouseh NM, Patel JJ, Bergl PA. Role of echocardiography in managing acute pulmonary embolism. *Heart.* 2019;105:1785 LP - 1792.
7. Sista AK, Miller LE, Kahn SR, Kline JA. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Systematic review with meta-analysis. *Vasc. Med.* 2016;22:37-43.
8. Jiménez D, et al. Simplification of the Pulmonary Embolism Severity Index for Prognostication in Patients With Acute Symptomatic Pulmonary Embolism Simplified Pulmonary Embolism Severity Index. *JAMA Intern. Med.* 2010;170:1383-1389.
9. Kohn CG, Mearns ES, Parker MW, Hernandez AV, Coleman CI. Prognostic accuracy of clinical prediction rules for early post-pulmonary embolism all-cause mortality: A bivariate meta-analysis. *Chest.* 2015;147:1043-1062.
10. Goldstein LN, Wells M, Vincent-Lambert C. The cost of time: A randomised, controlled trial to assess the economic impact of

- upfront, point-of-care blood tests in the Emergency Centre. *African J. Emerg. Med.* 2019;9:57-63.
11. Jiménez Castro D, et al. Association of anaemia and mortality in patients with acute pulmonary embolism. *Thromb. Haemost.* 2009;102:153-158.
 12. Karataş MB, et al. Assessment of Prognostic Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in Patients with Pulmonary Embolism. *Acta Cardiol. Sin.* 2016;32:313-320.
 13. Ma Y, et al. The values of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in predicting 30 day mortality in patients with acute pulmonary embolism. *BMC Cardiovasc. Disord.* 2016;16:123.
 14. Díaz JM, et al. Mean platelet volume as a prognostic factor for venous thromboembolic disease. *Rev. Med. Chil.* 2019;147:145-152.
 15. Jurin I, Trkulja V, Ajduk M, Letilović T, Hadžibegović I. Red cell distribution width in acute pulmonary embolism patients: A simple aid for improvement of the 30-day mortality risk stratification based on the pulmonary embolism severity index. *Hear. Lung.* 2019. doi:10.1016/j.hrtlng.2019.02.006
 16. Owens AP3rd, Mackman N. Microparticles in hemostasis and thrombosis. *Circ. Res.* 2011;108:1284-1297.
 17. Branchford BR, Carpenter SL. The Role of Inflammation in Venous Thromboembolism. *Front. Pediatr.* 2018;6:142.
 18. Mosevoll KA, et al. Cytokines, Adhesion Molecules, and Matrix Metalloproteases as Predisposing, Diagnostic, and Prognostic Factors in Venous Thrombosis. *Front. Med.* 2018;5:147.
 19. Nicklas JM, Gordon AE, Henke PK. Resolution of Deep Venous Thrombosis: Proposed Immune Paradigms. *Int. J. Mol. Sci.* 2020;21:2080.
 20. Lankeit M, et al. A Strategy Combining Imaging and Laboratory Biomarkers in Comparison With a Simplified Clinical Score for Risk Stratification of Patients With Acute Pulmonary Embolism. *Chest.* 2012;141:916-922.
 21. Bova C, et al. Identification of intermediate-risk patients with acute symptomatic pulmonary embolism. *Eur. Respir. J.* 2014;44:694 LP - 703.
 22. Watts JA, Gellar MA, Obratzsova M, Kline JA, Zagorski J. Role of inflammation in right ventricular damage and repair following experimental pulmonary embolism in rats. *Int. J. Exp. Pathol.* 2008;89:389-399.
 23. Ertem AG, et al. Relation between lymphocyte to monocyte ratio and short-term mortality in patients with acute pulmonary embolism. *Clin. Respir. J.* 2018;12:580-586.
 24. Lipinska A, Ledakowicz-Polak A, Krauza G, Przybylak K, Zielinska M. Complex calculation or quick glance? Mean platelet volume - new predictive marker for pulmonary embolism. *Ther. Clin. Risk Manag.* 2018;14:2221-2228.
 25. Phan T, et al. Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios Predict All-Cause Mortality in Acute Pulmonary Embolism. *Clin. Appl. Thromb.* 2020;26:1076029619900549.
 26. Zurauskaite G, et al. Biological pathways underlying the association of red cell distribution width and adverse clinical outcome: Results of a prospective cohort study. *PLoS One.* 2018;13:e0191280.
 27. Lippi G, Buonocore R, Cervellin G. Value of Red Blood Cell Distribution Width on Emergency Department Admission in Patients With Venous Thrombosis. *Am. J. Cardiol.* 2016;117:670-675.
 28. Weiss G, Goodnough LT. Anemia of chronic disease. *N. Engl. J. Med.* 2005;352:1011-1023.
 29. Jones PD, Moll S, Dellon ES. Pulmonary embolism in a patient with eosinophilic esophagitis: causal or coincidental? *Case Rep. Gastroenterol.* 2013;7:82-88.
 30. Li D, et al. Acute pulmonary embolism and deep vein thrombosis secondary to idiopathic hypereosinophilic syndrome. *Respir. Med. Case Reports.* 2018;25:213-215.
 31. Bontekoe E, et al. Upregulation of Inflammatory Cytokines in Pulmonary Embolism Using Biochip-Array Profiling. *Clin. Appl. Thromb. Off. J. Int. Acad. Clin. Appl. Thromb.* 2021;27:10760296211013108.
 32. Coutance G, Le Page O, Lo T, Hamon M. Prognostic value of brain natriuretic peptide in acute pulmonary embolism. *Crit. Care.* 2008;12:R109-R109.
 33. Santos AR, et al. Risk stratification in normotensive acute pulmonary embolism patients: focus on the intermediate-high risk subgroup. *Eur. Hear. J. Acute Cardiovasc. Care.* 2019;2048872619846506. doi:10.1177/2048872619846506