Heliyon 10 (2024) e25317

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

A new nomogram prediction model for pulmonary embolism in older hospitalized patients

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ARTICLE INFO

Keywords:
Pulmonary embolism
Older adults
Hospitalized
Nomogram
Predictive model

ABSTRACT

Purpose: Diagnosing pulmonary embolism (PE) in older adults is relatively difficult because of the atypical clinical symptoms of PE in older adults accompanied by multiple complications. This study aimed to establish a nomogram model to better predict the occurrence of PE in older adults.
Methods: Data were collected from older patients (≥65 years old) with suspected PE who were hospitalized between January 2012 and July 2021 and received confirmatory tests (computed tomographic pulmonary angiography or ventilation/perfusion scanning). The PE group and non-PE (control) group were compared using univariable and multivariable analyses to identify independent risk factors. A nomogram prediction model was constructed with independent risk factors and verified internally. The effectiveness of the nomogram model, Wells score, and revised Geneva score was assessed using the area under the receiver operating characteristic curve (AUC).
Results: In total, 447 eligible older patients (290 PE patients and 157 non-PE patients) were enrolled. Logistic regression analysis revealed nine independent risk factors: smoking, inflammation, dyspnea, syncope, mean corpuscular hemoglobin concentration, indirect bilirubin, uric acid, left atrial diameter, and internal diameter of the pulmonary artery. The AUC, sensitivity, and specificity of the nomogram prediction model were 0.763 (95 % confidence interval, 0.721–0.802), 74.48 %, and 67.52 %, respectively. The nomogram showed superior AUC compared to the Wells score (0.763 vs. 0.539, $P < 0.0001$) and the revised Geneva score (0.763 vs. 0.605, $P < 0.0001$).
Conclusions: This novel nomogram may be a useful tool to better recognize PE in hospitalized older adults.

1. Introduction

Pulmonary embolism (PE) is a clinical and pathophysiological syndrome of pulmonary circulatory dysfunction caused by endogenous or exogenous emboli blocking the pulmonary artery. The annual incidence of PE is approximately 5–10 % and increases

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https://doi.org/10.1016/j.heliyon.2024.e25317
Received 27 January 2023; Received in revised form 22 December 2023; Accepted 24 January 2024
Available online 1 February 2024

with age [1]. Common symptoms of PE include dyspnea, shortness of breath, chest pain, and syncope. These symptoms are nonspecific, especially in older adults, and may overlap with various cardiopulmonary conditions, easily leading to delayed diagnosis or misdiagnosis. As the chest pain is often related to cardiac disease, it attracts patients' attention easily and prompts them to seek medical attention as soon as possible. In contrast, dyspnea can be related to various diseases, lowering the patient's alertness and leading to delayed medical treatment or diagnosis. Notably, approximately 12–75 % of patients with PE [2–7] have a delayed diagnosis. Another study found that less than 25 % of patients were diagnosed within 1 day, whereas nearly 25 % had symptoms the week before diagnosis [8]. A few tools were developed to assist in diagnosing PE in some clinical settings. For example, a novel electrocardiography parameter, based on the longer RS time (the elapsed time from the beginning of QRS to the peak of the S-wave), can identify acute PE in patients admitted to the emergency department with a sensitivity of 85.3 % and a specificity of 79.4 % [9].

To improve the predictive accuracy of PE, previous studies have summarized the predictive scoring tools such as Wells [10], the revised Geneva [11], the Charlotte criteria [12], the PERC rule [13], and Wicki (Geneva score) [14]. Among these instruments, the Wells score and the revised Geneva score are currently widely used, but their performance is not satisfactory in some clinical scenarios.

Some studies have compared the Wells and Wicki scores for hospitalized patients and found that the predictive power of these two scoring systems was significantly better in outpatients and emergency patients than in hospitalized patients (the area under the receiver operating characteristic (ROC) curve (AUC) 0.76 vs 0.65, 0.7 vs 0.6, $P < 0.05$). This may be related to the more complex clinical situation of hospitalized patients, which affects the scoring accuracy, and the predictive power is the poorest in the surgical ward (AUC, 0.58 and 0.52, respectively) [15]. Therefore, these scoring systems may not be appropriate for hospitalized patients. In another multicenter study, the Wells score and the revised Geneva score were used to assess the predictive accuracy of PE in an outpatient older adult population. The AUC does not differ significantly (0.632 vs 0.610, $p = 0.441$), suggesting that the predictive efficacy of the two scoring systems is similar. However, the AUC of these two scores was low [16] and may not have good predictive power.

Considering the unsatisfactory predictive power for hospitalized and aging patients, we attempted to use the nomogram to create a predictive model for PE in older hospitalized patients. The nomogram integrates multiple predictors and draws a graph with a reference line. The length of the line on the graph represents the relative importance of the predictor variables. The nomogram is commonly used in tumor and medical prognosis analyses that estimate individual risk based on patient and disease characteristics [17]. A nomogram is often used to predict the risk of a single disease because of its visual prediction of the occurrence of clinical events in a single individual and its clear understanding of the risk of a single disease. To better identify PE in older patients suspected of PE, according to the European Respiratory Society (ERS) in 2019 [18], computed tomographic pulmonary angiography (CTPA) and ventilation/perfusion (V/Q) scanning were used as diagnostic methods for PE, and a nomogram prediction model for the risk of PE in older adults was created.

2. Materials and methods

In our study, the comprehensive clinical data of patients with suspected PE were retrospectively collected, including demographic characteristics, symptoms and signs, laboratory tests, and imaging studies. The patients were scored according to the Wells score and the revised Geneva score (Table 1) [19].

2.1. Data collection

Clinical data were collected from older patients hospitalized in a university-affiliated hospital between January 2012 and July 2021. Enrolled patients met the following criteria. Inclusion criteria: (1) Older patients ≥65 years old; (2) Suspected pulmonary embolism, which was defined as a condition with symptoms such as dyspnea, chest pain, syncope, or hemoptysis without obvious explanation after clinical examination; (3) Patients who received the CTPA or V/Q scan examination. Exclusion criteria: patients with heart failure, renal failure, or incomplete data.

Based on the final diagnosis, enrolled patients were divided into the PE and control groups. Inflammation was defined as infectious

Table 1
Wells score and revised Geneva score.

Wells score		Revised Geneva score	
Previous PE or DVT	1.5	Previous PE or DVT	3
Surgery or immobilization within the past four weeks	1.5	Surgery or fracture within the past month	2
Active cancer	1	Active cancer	2
Heart rate ≥100 b.p.m.	1.5	Heart rate 75–94 b.p.m.	3
Hemoptysis	1	Heart rate ≥95 b.p.m.	5
Clinical signs of DVT	3	Hemoptysis	2
Alternative diagnosis less likely than PE	3	Unilateral lower limb pain	3
		Pain on lower limb deep venous palpation and unilateral edema	4
		Age >65 years	1
Two-level score		Two-level score	
PE unlikely	0–4	PE unlikely	0–5
PE likely	≥5	PE likely	≥6

Abbreviations: b.p.m., beats per minute; DVT, deep vein thrombosis; PE, pulmonary embolism.

inflammation, including pneumonia, urinary tract infection, acute exacerbation of chronic obstructive pulmonary disease, bronchiectasis with complicated infection, acute appendicitis, and skin infections. Smoking was defined as a continuous or cumulative smoking experience of six months or more [20], regardless of current smoking status. This retrospective clinical study was approved by the Medical Ethics Committee of the Second Hospital of Tianjin Medical University (No.KY2022032), and the need for informed consent was waived.

2.2. Statistical analysis

The statistical analysis of the data was performed using SPSS 19, R software 4.1.0 and MedCalc version. Continuous variables were expressed as the mean ± standard deviation or median (interquartile range). When comparing two groups, a *t*-test was used if the data had a normal distribution; otherwise, a non-parametric test was used. Categorical data were described as the number of cases (constituent ratio), and comparisons between the two groups were performed with the chi-square test. $P < 0.05$ was considered statistically significant.

Variables associated with PE were screened by comparison between the two groups. Variables with $P < 0.1$ and non-linear relationships were included in the logistic regression analysis. The nomogram prediction model was established using the R software, according to independent risk factors revealed by the regression analysis. Internal validation of the nomogram was performed using bootstrap validation. The calibration of the nomogram model was evaluated by the calibration curve. Finally, AUC was calculated to assess the effectiveness of the nomogram model, Wells score, and the revised Geneva.

3. Results

Overall, 290 patients with PE and 157 patients without PE were included. Among all patients, 215 (48.1 %) were men and 232 (51.9 %) were women.

3.1. Comparison of suspected PE patients with and without PE

In the PE group (n = 290), 270 (93.1 %) were diagnosed with CTPA and 20 (6.9 %) with V/Q scan. Significant differences in smoking (34.8 % vs. 22.9 %, P = 0.009), tumor history (2.1 % vs. 5.7 %, P = 0.04), and inflammation (38.3 % vs. 22.3 %, P = 0.001)) were observed, whereas no significant differences in sex, diabetes, hypertension, coronary artery disease, deep vein thrombosis (DVT), or pulmonary disease history between the PE and control groups were observed (Table 2).

Among these clinical symptoms, the prevalence of dyspnea (76.6 % vs. 56.1 %, P < 0.001), syncope (12.1 % vs. 5.7 %, P = 0.032), and hemoptysis (5.2 % vs. 0 %, P = 0.004) was significantly higher in the PE group than those in the control group, whereas the prevalence of chest pain (15.2 % vs. 16 %, P = 0.812) showed no statistical difference. Only three patients in the PE group had the typical triad of PE (Table 3a).

Heart rate (84.38 ± 15.50 vs 77.64 ± 16.63, P < 0.001) and diastolic pressure (79.37 ± 13.36 vs 76.01 ± 12.60, P = 0.01) were higher in the PE group than those in the control group, but there were no significant differences in systolic pressure and temperature (Table 3b).

Table 2
Comparisons of sex and clinical history between the two groups [n (%)].

		PE	Control group	$\chi^2(t)$	*P*
Age		76.32 ± 6.62	76.04 ± 6.43	−0.425	0.671
Male		143 (49.3 %)	72 (45.9 %)	0.486	0.486
Female		147 (50.7 %)	85 (54.1 %)		
Smoking	yes	101 (34.8 %)	36 (22.9 %)	6.783	0.009
	no	189 (65.2 %)	121 (77.1 %)		
Diabetes	yes	50 (17.2 %)	37 (23.6 %)	2.600	0.107
	no	240 (82.8 %)	120 (76.4 %)		
Hypertension	yes	182 (62.8 %)	101 (64.3 %)	1.108	0.742
	no	108 (37.2 %)	56 (35.7 %)		
Coronary heart disease	yes	126 (43.4 %)	81 (51.6 %)	2.717	0.099
	no	164 (56.6 %)	76 (48.4 %)		
History of DVT	yes	27 (9.3 %)	10 (6.4 %)	1.160	0.281
	no	263 (90.7 %)	147 (93.6 %)		
History of lung disease	yes	58 (20.0 %)	21 (13.4 %)	3.072	0.080
	no	232 (80.0 %)	136 (86.6 %)		
Past tumor history	yes	6 (2.1 %)	9 (5.7 %)	4.215	0.04
	no	284 (97.9 %)	148 (94.3 %)		
Active tumor	yes	24 (8.3 %)	19 (12.1 %)	1.715	0.19
	no	266 (91.7 %)	138 (87.9 %)		
Inflammation	yes	111 (38.3 %)	35 (22.3 %)	11.830	0.001
	no	179 (61.7 %)	122 (77.7 %)		

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Blood tests showed that thrombocytocrit (PCT), percentage of prothrombin time activity (PTA), albumin (ALB), high-density cholesterol (HDLc), creatine kinase (CK), C-reactive protein (CRP), and temperature-corrected CO_2 partial pressure (PCO_2T) were significantly lower in the PE group than in the control group, whereas white blood cell (WBC), neutrophil (N), monocyte (M), red blood cell (RBC), hemoglobin (Hb), specific red blood cell volume (HCT), mean corpuscular hemoglobin concentration (MCHC), prothrombin time (PT), total bilirubin (TBIL), indirect bilirubin (IBIL), creatinine (Cr), uric acid (UA), N-terminal pro-B-natriuretic peptide (NT -proBNP), temperature-corrected hydrogen potential (PH (T)), and the O_2 pressure difference between alveolar gas and arterial blood (PO_2 (A-a)) were significantly higher than those in the control group ($P < 0.05$). Color Doppler ultrasonography of the heart showed that left ventricular end-diastolic diameter (LVEDD) (44.69 ± 7.48 vs 47.35 ± 4.94, $P < 0.001$) and left atrial diameter (LAD) (38.12 ± 6.82 vs 41.36 ± 8.68, $P = 0.001$) were significantly lower in the PE group than those in the control group. Internal diameter of the pulmonary artery (PAID) was significantly higher in the PE group than that in the control group (23.57 ± 4.72 vs 22.34 ± 3.50, $P = 0.026$), whereas no significant differences were observed in left ventricular end-systolic diameter (LVESD), right ventricular end-diastolic diameter (RVEDD), and pulmonary artery systolic pressure (PASP) (Table 4).

3.2. Comparison of D-dimer in patients with suspected PE

Among the D-dimer negative patients, 41 cases of PE, and with statistical differences between the two groups were observed ($P = 0.008$) (Table 5). The sensitivity and specificity of the D-dimer measurement were 85.86 % and 24.2 %, respectively; therefore, D-dimer was mainly used to exclude PE. We did not include it in the nomogram-related predictors.

3.3. Screening of independent predictors and establishment of the nomogram

For variables with $P < 0.1$, a collinearity test was performed, and the logistic regression model was established if there were no collinear variables. The glm function of the R software and the MASS package were used to perform a two-way stepwise regression to screen the variables. Finally, an optimal Akaike information criterion of 522.92 was used as the basis for including the variables (Fig. 1; Table 6).

Based on the independent variables with $P < 0.05$ in the logistic regression model, a prediction model of the nomogram for the risk of PE in older adults was established. The nomogram model included nine indicators: smoking, inflammation, dyspnea, syncope, MCHC, IBIL, UA, LAD, and PAID (Fig. 2).

A calibration curve was used to evaluate the degree of calibration of the model. In Fig. 3, the results showed that the calibration curve was close to the ideal standard curve, indicating that the nomogram had better calibration ability. The accuracy of the nomogram model was evaluated via AUC. The results showed that the AUC, Youden index, sensitivity, specificity, and corresponding risks of the nomogram were 0.763 (0.721–0.802), 0.42, 74.48 %, 67.52 %, and 0.629 and 138.4 points, respectively. Furthermore, comparing the predictive performance of the nomogram, the Wells score, and the revised Geneva score, the result showed that the AUC of the nomogram was higher than that of the Wells score (0.763 vs 0.539, $P < 0.0001$) and the revised Geneva score (0.763 vs 0.605, $P < 0.0001$) (Fig. 4).

4. Discussion

PE is a relatively common clinical condition. Older adults are often a high-risk group for PE owing to many underlying diseases. The symptoms of PE are atypical, and specificity is low. Definitive diagnosis requires a long time from the onset of symptoms, and the diagnosis is often delayed by more than 7 days [3], which can easily lead to misdiagnosis and missed diagnosis, and the prognosis is abysmal. Of the patients who underwent autopsy, 3.9 % died of PE, including 80.0 % of patients aged >60 years [21]. Some researchers have shown that 3.8 % of older patients with PE die within 30 days [22].

D-dimer is elevated during thrombosis and is often used to rule out PE because of its higher sensitivity. Since D-dimer levels increase with aging, it is recommended that D-dimer levels be corrected for age (age × 10 ng/ml) in patients aged >50 years to reduce the false positive rate [23]. In this data group, D-dimer showed a sensitivity of 85.86 % and a specificity of 24.2 %. Therefore, it is

Table 3a
Comparison of clinical symptoms between the two groups [n (%)].

		PE	Control group	χ^2	*P*
Dyspnea	yes	222 (76.6 %)	88 (56.1 %)	20.140	<0.001
	no	68 (23.4 %)	69 (43.9 %)		
Chest pain	yes	44 (15.2 %)	25 (16.0 %)	0.056	0.812
	no	246 (84.8 %)	131 (84.0 %)		
Syncope	yes	35 (12.1 %)	9 (5.7 %)	4.608	0.032
	no	255 (87.9 %)	148 (94.3 %)		
Hemoptysis	yes	15 (5.2 %)	0 (0.0 %)	8.432	0.004
	no	274 (94.8 %)	157 (100.0 %)		
Typical triad of PE	yes	3 (1.0 %)	0 (0.0 %)	1.647	0.199
	no	285 (99.0 %)	157 (100.0 %)		

Abbreviations: PE, pulmonary embolism.

Table 3b
Comparison of vital signs between the two groups.

	PE	Control group	*t/Z*	*P*
Temperature (°C)	36.50 ± 0.42	36.51 ± 0.45	−0.341	0.733
Heart rate (b.p.m.)	84.38 ± 15.50	77.64 ± 16.63	4.267	<0.001
Systolic pressure (mmHg)	133.56 ± 23.89	134.65 ± 19.55	−0.488	0.625
Diastolic pressure (mmHg)	79.37 ± 13.36	76.01 ± 12.60	2.586	0.010

Abbreviations: PE, pulmonary embolism.

feasible to rule out PE by a negative D-dimer in older adults. Since D-dimer can also be elevated in infections, postoperative status, malignancies, etc., it was not included as a predictor in the nomogram.

Many risk factors for PE in older patients, include major trauma, lower extremity fractures, atrial fibrillation or atrial flutter, myocardial infarction, tumors, central venous catheterization, infections, and bed rest. Analyzing the clinical data on suspected PE, we found that the proportions of smoking and inflammation were significantly higher in the PE group. However, the proportion of history of patients with a tumors was significantly lower in the PE group, but there was no significant difference in the proportion of active tumors between the two groups. Currently, the risk of thrombosis is thought to be increased by tumors through several pathways that differ from our assumptions. Some studies have found that older patients with PE have more concomitant diseases, although the typical triad is uncommon. The main symptoms of PE are cough, hemoptysis, and chest pain with a low incidence [3]. In our data, the proportions of dyspnea, syncope, and hemoptysis were higher in the PE group (76.6 %, 12.1 %, and 5.2 %, respectively) than in the control group (56.1 %, 5.7 %, and 0 %, respectively; $P < 0.05$), whereas only three patients had a typical PE triad. Notably, the proportion of dyspnea was highest in the total population, the proportion of syncope and hemoptysis was low, and dyspnea was related to various cardiopulmonary conditions, which may affect the diagnosis of the disease. In laboratory and ancillary investigations, PCT, PTA, ALB, HDLc, CK, CRP, PCO2T, LVEDD, and LAD were significantly lower, whereas heart rate, diastolic pressure (DBP), WBC, N, M, RBC, Hb, HCT, MCHC, PT, TBIL, IBIL, Cr, UA, NT-proBNP, PH, PO2(A-a), and PAID were higher in the PE group ($P < 0.05$), indicating that older patients may be more likely to have cardiorenal insufficiency, inflammation, or possible hemoconcentration. Although the low serum albumin level was not found to be an independent risk factor for the occurrence of PE in this study, it has well predicted long-term mortality in patients with acute PE [24].

After comparing the PE and the control group, the variables with $P < 0.1$ and without collinearity were used to establish a logistic regression model. The glm function of the R software and the MASS package were used to perform stepwise two-way regression for the screening variables. Finally, smoking, inflammation, dyspnea, syncope, MCHC, IBIL, UA, LAD, and PAID were associated with the risk of PE in older adults. Smoking, inflammation, dyspnea, syncope, IBIL, and UA were risk factors, whereas MCHC and LAD were protective factors. Therefore, when MCHC $\leq$316 g/L, MCHC $\geq$354 g/L, and LAD decrease, the risk of PE will increase. Interestingly, tumor and heart rate were not associated with PE, which was different from previous scores; this may be related to comorbidities and polypharmacy common in older adults. For example, the proportion of coronary heart disease in this date set is close to 50 %. The application of beta-blockers and aspirin may weaken the correlation between tumor, heart rate, and PE.

Active smokers have significantly higher levels of tissue factor pathway inhibitors, factor XII, soluble fibrinogen, and fibrinogen, whereas thrombomodulin, vWF, FXII, FVIII, and FVII are all significantly decreased, leading to the development of thrombosis [25]. Some researchers believe that infection is an independent risk factor for venous thromboembolism (VTE); 39.4 % of patients with venous thrombosis have an infection, and the incidence of VTE caused by infection at any site is 2.4 times that of patients without infection [26]. Meanwhile, pneumococcal pneumonia is also considered a risk factor for VTE. After the adjustment of age, sex, and comorbidities, the risk of VTE was significantly increased in patients with pneumonia, and the incidence was significantly higher after pneumonia within four weeks [27]. Hyperuricemia is an established cardiovascular risk factor. UA can cause vascular damage through a variety of mechanisms, and elevated UA levels are associated with endothelial dysfunction, inflammation, and a prothrombotic state. Therefore, UA can be used as a biomarker for the prothrombotic state [28]. Proximal pulmonary artery dilatation was observed on echocardiography PE, suggesting possible pulmonary hypertension or high right ventricular overload. The researchers summarized six studies published between 2012 and 2019 and found that the severity of acute PE increased with decreasing left atrial volume (LA), and the index of pulmonary artery obstruction correlated significantly negatively with area LA. A decrease in LA should be considered a marker of severe hemodynamic compromise [29]. The results of these previous studies support this study.

In data analysis, we found that the levels of bilirubin and IBIL were within the normal range but significantly higher in the PE group than in the control group, and regression analysis revealed that IBIL was an independent predictor of PE. Some researchers have suggested that the risk of PE was increased by 73 % in patients with reduced total bilirubin concentrations, which may be considered a potential risk factor for PE [30]. Another study found that bilirubin decreased significantly in the VTE group, independent of VTE. The cut-off value for bilirubin was 8.9 mmol/L, and the AUC was 0.659, with a sensitivity and specificity of 55 % and 74 %, respectively [31]. These results differ from ours, possibly due to the compensatory mechanism after PE in older adults, resulting in a compensatory increase in bilirubin levels. Poor nutrition and low albumin levels in older adults lead to a decrease in direct bilirubin levels. Whether this affects the antioxidant capacity of bilirubin requires further research. The relationship between hemoglobin levels and PE is controversial. Previous studies have suggested that the decrease in hemoglobin levels is not related to PE. However, some case reports state that megaloblastic anemia is susceptible to PE, which may be related to elevated homocysteine levels caused by vitamin B12 deficiency [32]. Our results show that the levels of Hb, HCT, and MCHC were significantly higher in the PE group. Furthermore, regression analysis showed that MCHC between 316 and 354 g/L was a protective factor; regardless of the increase or decrease in the

Table 4
Comparisons of laboratory examinations and auxiliary examinations between the two groups.

	PE	Control group	*t/Z*	*P*
WBC (10^9/L)	8.24 ± 3.71	7.14 ± 3.11	3.139	0.002
N (10^9/L)	5.4 (4.13, 7.5)	4.63 (3.3, 6.33)	−3.577	<0.001
L (10^9/L)	1.23 (0.92, 1.71)	1.21 (0.81, 1.69)	−0.995	0.320
M (10^9/L)	0.46 (0.34, 0.62)	0.39 (0.29, 0.55)	−3.295	0.001
E (10^9/L)	0.07 (0.03, 0.14)	0.07 (0.03, 0.14)	−0.593	0.553
B (10^9/L)	0.02 (0.01, 0.03)	0.02 (0.02, 0.03)	−1.113	0.265
RBC (10^12/L)	4.18 (3.74, 4.58)	4.07 (3.73, 4.39)	−2.171	0.030
Hb (g/L)	126.6 ± 21.97	121.46 ± 22.63	2.327	0.020
HCT (%)	38.55 ± 6.7	36.66 ± 6.44	2.867	0.004
MCV (fL)	92.43 ± 7.09	92.69 ± 6.92	−0.371	0.711
MCH (pg)	30.60 ± 2.67	31.48 ± 8.12	−1.321	0.188
RDW-CV (%)	13.59 ± 1.85	14.40 ± 6.85	−1.443	0.151
MCHC (g/L)	327.02 ± 36.69	312.84 ± 69.50	2.373	0.019
PLT (10^9/L)	203.24 ± 79.34	206.76 ± 82.77	−0.439	0.661
PCT	0.18 (0.14, 0.22)	0.19 (0.15, 0.24)	−2.105	0.035
MPV (fL)	9.3 (8.6,10.1)	9.4 (8.7,10.4)	−1.130	0.258
RDW (fL)	41.72 ± 9.21	42.43 ± 16.29	−0.479	0.632
PDW (%)	16.27 ± 3.12	16.23 ± 5.01	0.119	0.905
PDW-SD (fL)	10.7 (9.7, 12.4)	10.8 (9.5, 12.38)	−0.416	0.677
P-LCC (10^9/L)	43.06 ± 15.22	44.61 ± 16.62	−0.896	0.371
P-LCR (%)	23.33 ± 8.19	23.13 ± 7.58	0.227	0.821
PT (s)	11.6 (10.9, 12.6)	11.1 (10.5, 12.2)	−3.225	0.001
PTA (%)	90.11 ± 24.73	97.41 ± 29.59	−2.457	0.015
PTR	1.03 ± 0.29	1.01 ± 0.19	0.681	0.496
INR	1.03 ± 0.29	1.01 ± 0.20	0.654	0.513
PTT (s)	28.63 ± 12.39	27.59 ± 7.92	0.945	0.345
Fbg (g/L)	3.41 ± 1.13	3.53 ± 1.23	−1.014	0.311
TT (s)	17.8 (16.9, 18.8)	17.6 (16.7, 18.9)	−1.062	0.288
TP (g/L)	62.22 ± 7.09	63.53 ± 7.60	−1.787	0.075
ALB (g/L)	36.43 ± 5.07	37.66 ± 5.55	−2.338	0.020
ALT (U/L)	17.8 (11.8, 26.65)	15.35 (11.38, 26.68)	−1.075	0.282
AST (U/L)	18.9 (15.05, 28.85)	17.95 (14.08, 23.7)	−1.856	0.063
ALP (U/L)	70.2 (58.62, 92.5)	74 (65.15, 92.23)	−1.67	0.095
GGT (U/L)	27.35 (19.3, 44.13)	25.8 (17.45, 47.45)	−0.795	0.427
TBIL (μmol/L)	12.2 (8.8, 18.75)	11.4 (7.4, 15.05)	−2.43	0.015
IBIL (μmol/L)	7.7 (5.05, 11.1)	6.5 (4.4, 9.8)	−2.59	0.010
BUN (mmol/L)	6.6 (5, 8.9)	6.25 (5, 7.8)	−1.261	0.207
Cr (μmol/L)	77.25 (64.7, 101.63)	70.35 (59.5, 86.33)	−3.28	0.001
UA (μmol/L)	357.90 ± 140.25	316.62 ± 115.66	3.308	0.001
TC (mmol/L)	4.66 ± 1.48	4.52 ± 1.02	0.832	0.406
TG (mmol/L)	1.18 (0.95, 1.57)	1.11 (0.87, 1.54)	−1.019	0.308
LDLc (mmol/L)	2.99 ± 1.18	2.78 ± 0.78	1.721	0.086
HDLc (mmol/L)	1.09 ± 0.33	1.24 ± 0.40	−3.308	0.001
CK (U/L)	64.4 (42.05, 95.6)	76.3 (51, 117.3)	−2.012	0.044
CK-Mb (U/L)	11.4 (8, 15.55)	11 (8.4, 16)	−0.335	0.737
K (mmol/L)	4 (3.6, 4.4)	4.1 (3.8, 4.4)	−1.915	0.055
Na (mmol/L)	139.66 ± 9.18	139.37 ± 12.04	0.283	0.777
CI (mmol/L)	104.00 ± 4.86	104.04 ± 4.88	−0.068	0.946
CO_2cp (mmol/L)	25.68 ± 3.90	25.99 ± 3.77	−0.808	0.419
Ca (mmol/L)	2.23 ± 0.18	2.24 ± 0.16	−0.188	0.852
P (mmol/L)	1.12 (0.96, 1.45)	1.28 (1.04, 1.34)	−0.103	0.918
Mg (mmol/L)	0.92 ± 0.14	0.91 ± 0.09	0.156	0.877
GLU (mmol/L)	6.22 (5.32, 7.87)	6.42 (5.36, 8.31)	−1.053	0.292
Troponin I (ng/mL)	0.02 (0.01, 0.06)	0.01 (0, 0.03)	−3.282	0.001
NT-proBNP (ng/L)	1094.8 (222.5, 4303.5)	410.5 (110.5, 1803.25)	−3.442	0.001
CRP (mg/dL)	1.71 (0.58, 5.04)	5.85 (1.69, 11.17)	−2.55	0.011
PH(T)	7.44 ± 0.06	7.42 ± 0.06	2.121	0.035
PCO2T (mmHg)	36.22 ± 8.63	38.86 ± 8.77	−2.451	0.015
PO_2T (mmHg)	72.28 ± 25.48	73.11 ± 22.45	−0.273	0.785
HCO3 (mmol/L)	24.62 ± 3.66	24.75 ± 3.13	−0.312	0.755
SBE (mmol/L)	0.2 (−2.1, 2.7)	0.5 (−1.6, 2.7)	−0.433	0.665
PO_2 (A-a) (mmHg)	56.6 (41.1, 124.55)	48.2 (30.5, 107.65)	−2.209	0.027
P50 (T) e (mmHg)	25.62 ± 2.88	25.20 ± 1.97	1.433	0.153
LVEDD (mm)	44.69 ± 7.48	47.35 ± 4.94	−3.788	<0.001
LVESD (mm)	28.74 ± 7.92	27.38 ± 6.19	1.533	0.126
LAD (mm)	38.12 ± 6.82	41.36 ± 8.68	−3.42	0.001
RVEDD (mm)	23.45 ± 5.89	22.50 ± 4.95	1.524	0.129
PAID (mm)	23.57 ± 4.72	22.34 ± 3.50	2.234	0.026
PASP (mmHg)	48.05 ± 19.47	43.29 ± 16.12	1.653	0.100

Abbreviations: WBC, white blood cell; N, Neutrophil; L, lymphocyte; M, monocyte; E.
eosinophil; B, basophil; RBC, red blood cell; Hb, hemoglobin; HCT, Red blood cell specific.
volume; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW-CV, Red blood cell distribution width-CV; MCHC, mean corpuscular hemoglobin concentration; PLT,platelet; PCT, thrombocytocrit; MPV, mean platelet volume; RDW, erythrocyte hemoglobin distribution width; PDW, Platelet volume distribution width; PDW-SD, platelet distribution width-SD; P-LCC, Number of large platelets; P-LCR, platelet-larger cell ratio.
PT, prothrombin time; PTA, prothrombin time activity percentage; PTR, Proto-ratio of thrombin; INR, international normalized ratio; PTT, activated partial thromboplastin time; Fbg, Fibrinogen; TT, thrombin time; TP, total Protein; ALB, albumin; ALT.
glutamic pyruvic transaminase; AST, glutamicoxaloacetic transaminase; ALP.
alkaline phosphatase; GGT, gamma-glutamyltransferase; TBIL, total bilirubin.
IBIL, indirect Bilirubin; Cr, creatinine; UA, uric acid; TC, serum total cholesterol.
TG, triglyceride; LDLc, Low-Density Lipoprotein Cholesterol; HDLc, high density lipoprotein cholesterol; CK, creatine kinase; CO_2cp, carbon dioxide combining power; GLU, blood glucose; NT-proBNP, N-terminal pro B-type natriuretic peptide; CRP, c-reactive. Protein; PH(T), Body temperature-corrected potential of hydrogen; PCO_2T, temperature-corrected CO_2 partial pressure; PO_2T, temperature-corrected oxygen partial pressure; SBE, standard base deficit; PO_2 (A-a), O_2 Pressure Difference Between Alveolar Gas and Arterial Blood; LVEDD, the left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrial diameter; RVEDD, right ventricular end-diastolic diameter; PAID, Internal diameter of pulmonary artery; PASP, pulmonary artery systolic pressure.

Table 5
Comparison of D-dimer level in patients with suspected PE between two groups (n = 447).

D-dimer	PE		Sum	χ^2	*P*
	(+)	(−)			
(−)	41	38	79	7.093	0.008
(+)	249	119	368		
	290	157	447		

D-dimer: age × 10 ng/mL was used as the correction value. D-dimer < corrected value was defined as negative, while D-dimer ≥ corrected value was defined as positive.
Abbreviations: PE, pulmonary embolism.

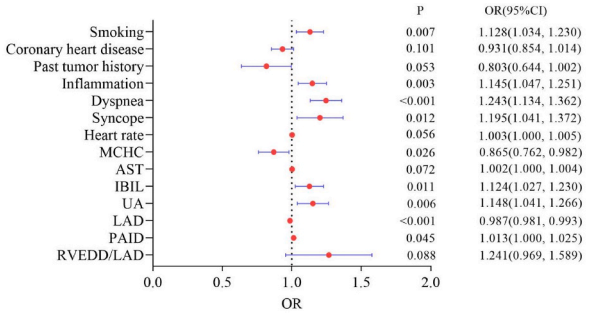

Fig. 1. Logistic regression analysis of suspected pulmonary embolism in older adults (n = 447) Abbreviations: MCHC, mean corpuscular hemoglobin concentration; AST, glutamic oxaloacetic transaminase; IBIL, Indirect Bilirubin; UA, uric Acid; LAD, left atrial diameter; PAID, Internal diameter of pulmonary artery; RVEDD, right ventricular end-diastolic diameter.

value, the risk of PE increases in older adults. The MCHC value represents the average hemoglobin concentration per liter of blood and is mainly used to identify the type of anemia. The mechanism of its effect on PE needs further exploration.

A nomogram is a visual graph of the results of multivariate regression analysis that makes the results more readable, allows intuitive and easy evaluation of patients, and generates individual probabilities of clinical events by integrating different prognostic or determining variables. On this basis, a nomogram prediction model for the risk of PE in older adults was established for independent variables, including smoking, inflammation, dyspnea, syncope, MCHC, IBIL, UA, LAD, and PAID. The probability of PE in older patients can be predicted individually using this nomogram model. The nomogram showed that LAD and PAID had higher scores. The calibration of the nomogram model is evaluated by the calibration curve. As the calibration curve was almost consistent with the ideal standard curve, the nomogram showed good calibration ability. In addition, the AUC was used to indicate the effect of the prediction PE. The AUC of the nomogram was 0.763 (0.721–0.802), and the best cut-off points were 0.629 and 138.4. Based on our nomogram, patients with more than 138.4 points indicate a high occurrence probability of PE. Therefore, confirmatory tests should be initiated on time, and early anticoagulation therapy could be recommended for such high-risk patients in the absence of anticoagulation contraindications.

ROC curves are widely used in medicine to assess whether a particular factor is valuable for diagnosing a particular disease and can be used to evaluate the probability of disease occurrence before diagnosis. In this study population, the AUC values of the nomogram

Table 6
Logistic regression analysis of suspected pulmonary embolism in older adults (n = 447).

Variable	*B*	*SE*	*Wald*	*P*	*OR* (95 % CI)
Intercept	0.249	0.21	–	–	–
Smoking	0.12	0.044	7.419	0.007	1.128 (1.034, 1.230)
Coronary heart disease	−0.072	0.044	2.696	0.101	0.931 (0.854, 1.014)
Past tumor history	−0.219	0.113	3.767	0.053	0.803 (0.644, 1.002)
Inflammation	0.135	0.045	8.91	0.003	1.145 (1.047, 1.251)
Dyspnea	0.218	0.047	21.661	<0.001	1.243 (1.134, 1.362)
Syncope	0.178	0.07	6.407	0.012	1.195 (1.041, 1.372)
Heart rate	0.003	0.001	3.659	0.056	1.003 (1.000, 1.005)
MCHC	−0.145	0.065	5.024	0.026	0.865 (0.762, 0.982)
AST	0.002	0.001	3.262	0.072	1.002 (1.000, 1.004)
IBIL	0.117	0.046	6.503	0.011	1.124 (1.027, 1.230)
UA	0.138	0.050	7.648	0.006	1.148 (1.041, 1.266)
LAD	−0.013	0.003	16.094	<0.001	0.987 (0.981, 0.993)
PAID	0.012	0.006	4.028	0.045	1.013 (1.000, 1.025)
RVEDD/LAD	0.216	0.126	2.923	0.088	1.241 (0.969, 1.589)

Past tumor history (0 = no, 1 = yes), MCHC (0 = 316–354 g/L, 1 = <316 g/L, >354 g/L, IBIL (0 = 1.7–10.2 μmol/L, 1 ≤ 1.7 μmol/L, >10.2 μmol/L, UA (0 = male <414 μmol/L, female <390 μmol/L, 1 = male >414 μmol/L, female >390 μmol/L).
Abbreviations: MCHC, mean corpuscular hemoglobin concentration; AST, glutamic oxaloacetic transaminase; IBIL, indirect bilirubin; UA, uric acid; LAD, left atrial diameter; PAID, internal diameter of pulmonary artery; RVEDD, right ventricular end-diastolic diameter.

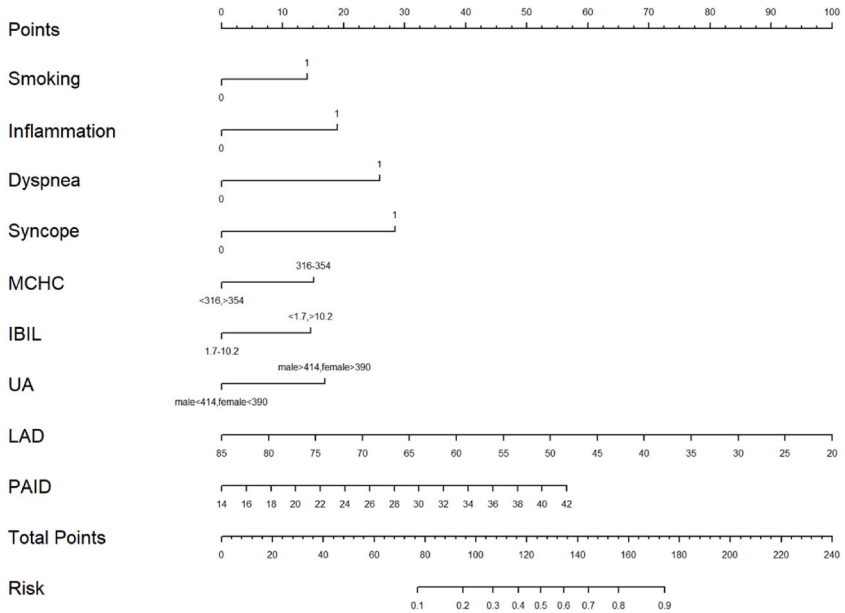

Fig. 2. Nomogram prediction model for the risk of pulmonary embolism in older adults Abbreviations: MCHC, mean corpuscular hemoglobin concentration; IBIL, Indirect Bilirubin; UA, uric Acid; LAD, left atrial diameter; PAID, Internal diameter of the pulmonary artery.

model were higher than those of the Wells score and the revised Geneva score, indicating that the nomogram model was better than the Wells score and the revised Geneva score. Evidently, the nomogram model has good predictive power for PE risk in older patients with suspected PE.

This study had some limitations. First, this is a single-center retrospective study. Therefore, selection bias might not be completely excluded. Second, although we collected all hospitalized older patients who met the inclusion criteria during the study period, the sample size was limited. Third, further external validation is important for this nomogram model.

5. Conclusions

This novel nomogram may be a useful tool to better recognize PE in hospitalized older adults.

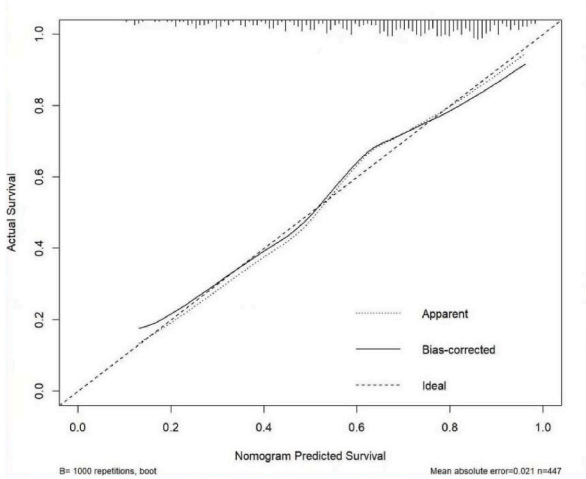

Fig. 3. Calibration curve of the nomogram model for predicting the risk of pulmonary embolism in older adults.

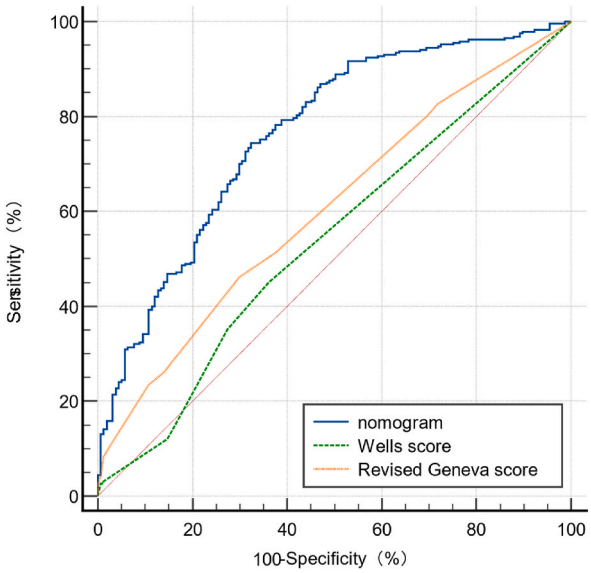

Fig. 4. Receiver operating characteristic (ROC) analysis of the nomogram (area under the ROC curve (AUC) = 0.763, 95 % confidence interval (CI) = 0.721–0.802), Wells score (AUC = 0.539, 95 % CI = 0.491–0.585) and revised Geneva score (AUC = 0.605, 95 % CI = 0.558–0.65) in patients aged 65 or older.

Date availability

Data will be made available on request.

CRediT authorship contribution statement

Qingjun Liu: Writing – original draft, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Jichen Xiao:** Writing – original draft, Validation, Formal analysis. **Le Liu:** Investigation, Data curation. **Jiaolei Liu:** Investigation, Data curation. **Hong Zhu:** Software, Methodology. **Yanping Lai:** Methodology. **Lin Wang:** Methodology. **Xin Li:** Methodology. **Yubao Wang:** Writing – review & editing, Methodology, Formal analysis. **Jing Feng:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank all the colleagues who helped and participated in this study.

References

[1] L.C. García Gómez, L. Castilla Guerra, M. Gandullo Moro, R. Cano Alba, M. Paniagua García, M.Á. Colmenero Camacho, Pulmonary embolism in very elderly patients. A diagnostic challenge, Rev. Clin. Esp. 219 (2019) 310–314, https://doi.org/10.1016/j.rce.2018.09.016.
[2] J.A. Kline, J. Hernandez-Nino, A.E. Jones, G.A. Rose, H.J. Norton, C.A. Camargo Jr., Prospective study of the clinical features and outcomes of emergency department patients with delayed diagnosis of pulmonary embolism, Acad. Emerg. Med. 14 (2007) 592–598, https://doi.org/10.1197/j.aem.2007.03.1356.
[3] J.M. Hendriksen, M. Koster-van Ree, M.J. Morgenstern, R. Oudega, R.E. Schutgens, K.G. Moons, G.J. Geersing, Clinical characteristics associated with diagnostic delay of pulmonary embolism in primary care: a retrospective observational study, BMJ Open 7 (2017) e12789, https://doi.org/10.1136/bmjopen-2016-012789.
[4] J. Torres-Macho, A.B. Mancebo-Plaza, A. Crespo-Gimenez, M.R. Sanz de Barros, C. Bibiano-Guillén, R. Fallos-Martí, J. Calderón-Parra, J.M. de Miguel-Yanes, Clinical features of patients inappropriately undiagnosed of pulmonary embolism, Am. J. Emerg. Med. 31 (2013) 1646–1650, https://doi.org/10.1016/j.ajem.2013.08.037.
[5] S.B. Smith, J.B. Geske, T.I. Morgenthaler, Risk factors associated with delayed diagnosis of acute pulmonary embolism, J. Emerg. Med. 42 (2012) 1–6, https://doi.org/10.1016/j.jemermed.2011.06.004.
[6] J.L. Alonso-Martinez, F.J. Sanchez, M.A. Echezarreta, Delay and misdiagnosis in sub-massive and non-massive acute pulmonary embolism, Eur. J. Intern. Med. 21 (2010) 278–282, https://doi.org/10.1016/j.ejim.2010.04.005.
[7] Y. Jenab, M.J. Alemzadeh-Ansari, S.A. Fehri, N. Ghaffari-Marandi, A. Jalali, Effect of delay in hospital presentation on clinical and imaging findings in acute pulmonary thromboembolism, J. Emerg. Med. 46 (2014) 465–471, https://doi.org/10.1016/j.jemermed.2013.09.014.
[8] S. Walen, R.A. Damoiseaux, S.M. Uil, J.W. van den Berg, Diagnostic delay of pulmonary embolism in primary and secondary care: a retrospective cohort study, Br. J. Gen. Pract. 66 (2016) e444–e450, https://doi.org/10.3399/bjgp16x685201.
[9] I. Rencuzogullari, M. Çağdaş, Y. Karabağ, S. Karakoyun, H. Çiftçi, M.O. Gürsoy, S. Karayol, T. Çinar, O. Tanik, Hamideyin S, A novel ECG parameter for diagnosis of acute pulmonary embolism: RS time: RS time in acute pulmonary embolism, Am. J. Emerg. Med. 37 (2019) 1230–1236, https://doi.org/10.1016/j.ajem.2018.09.010.
[10] P.S. Wells, D.R. Anderson, M. Rodger, J.S. Ginsberg, C. Kearon, M. Gent, A.G. Turpie, J. Bormanis, J. Weitz, M. Chamberlain, D. Bowie, D. Barnes, J. Hirsh, Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer, Thromb. Haemostasis 83 (2000) 416–420, https://doi.org/10.1055/s-0037-1613830.
[11] G. Le Gal, M. Righini, P.M. Roy, Prediction of pulmonary embolism in the emergency department: the revised Geneva score, Ann. Intern. Med. 144 (2006) 165–171, https://doi.org/10.7326/0003-4819-144-3-200602070-00004.
[12] J.A. Kline, R.D. Nelson, R.E. Jackson, D.M. Courtney, Criteria for the safe use of D-dimer testing in emergency department patients with suspected pulmonary embolism: a multicenter US study, Ann. Emerg. Med. 39 (2002) 144–152, https://doi.org/10.1067/mem.2002.121398.
[13] J.A. Kline, A.M. Mitchell, C. Kabrhel, P.B. Richman, D.M. Courtney, Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism, J. Thromb. Haemostasis 2 (2004) 1247–1255, https://doi.org/10.1111/j.1538-7836.2004.00790.x.
[14] J. Wicki, T.V. Perneger, A.F. Junod, H. Bounameaux, A. Perrier, Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score, Arch. Intern. Med. 161 (2001) 92–97, https://doi.org/10.1001/archinte.161.1.92.
[15] G.P. Ollenberger, D.F. Worsley, Effect of patient location on the performance of clinical models to predict pulmonary embolism, Thromb. Res. 118 (2006) 685–690, https://doi.org/10.1016/j.thromres.2005.11.011.
[16] J. Coelho, M. Divernet-Queriaud, P.M. Roy, A. Penaloza, G. Le Gal, A. Trinh-Duc, Comparison of the Wells score and the revised Geneva score as a tool to predict pulmonary embolism in outpatients over age 65, Thromb. Res. 196 (2020) 120–126, https://doi.org/10.1016/j.thromres.2020.07.026.
[17] V.P. Balachandran, M. Gonen, J.J. Smith, R.P. DeMatteo, Nomograms in oncology: more than meets the eye, Lancet Oncol. 16 (2015) e173–e180, https://doi.org/10.1016/s1470-2045(14)71116-7.
[18] S.V. Konstantinides, G. Meyer, C. Becattini, H. Bueno, G.J. Geersing, V.P. Harjola, M.V. Huisman, M. Humbert, C.S. Jennings, D. Jiménez, N. Kucher, I.M. Lang, M. Lankeit, R. Lorusso, L. Mazzolai, N. Meneveau, F. Ní Áinle, P. Prandoni, P. Pruszczyk, M. Righini, A. Torbicki, E. Van Belle, J.L. Zamorano, 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS), Eur. Heart J. 41 (2020) 543–603, https://doi.org/10.1183/13993003.01647-2019.
[19] S.V. Konstantinides, A. Torbicki, G. Agnelli, S.V. Konstantinides, A. Torbicki, G. Agnelli, N. Danchin, D. Fitzmaurice, N. Galiè, J.S. Gibbs, M.V. Huisman, M. Humbert, N. Kucher, I. Lang, M. Lankeit, J. Lekakis, C. Maack, E. Mayer, N. Meneveau, A. Perrier, P. Pruszczyk, L.H. Rasmussen, T.H. Schindler, P. Svitil, A. Vonk Noordegraaf, J.L. Zamorano, M. Zompatori, 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism, Eur. Heart J. 35 (2014) 3033–3069, https://doi.org/10.5603/kp.2014.0211, 3069a–3069k.
[20] World Health Organization, Guidelines for Controlling and Monitoring the Tobacco Epidemic, Tobacco or Health Programme, WHO, Geneva, 1997.
[21] R. Alikhan, F. Peters, R. Wilmott, A.T. Cohen, Fatal pulmonary embolism in hospitalised patients: a necropsy review, J. Clin. Pathol. 57 (2004) 1254–1257, https://doi.org/10.1136/jcp.2003.013581.
[22] D. Zwierzina, A. Limacher, M. Mean, M. Righini, K. Jaeger, H.J. Beer, B. Frauchiger, J. Osterwalder, N. Kucher, C.M. Matter, M. Banyai, A. Angelillo-Scherrer, B. Lämmle, M. Egloff, M. Aschwanden, L. Mazzolai, O. Hugli, M. Husmann, H. Bounameaux, J. Cornuz, N. Rodondi, D. Aujesky, Prospective comparison of clinical prognostic scores in elder patients with a pulmonary embolism, J. Thromb. Haemostasis 10 (2012) 2270–2276, https://doi.org/10.1111/j.1538-7836.2012.04929.x.
[23] E.O. Essien, P. Rali, S.C. Mathai, Pulmonary embolism, Med. Clin. 103 (2019) 549–564, https://doi.org/10.1016/j.mcna.2018.12.013.
[24] V.O. Tanık, T. Çınar, Y. Karabağ, B. Şimşek, C. Burak, M. Çağdaş, İ. Rencüzoğulları, The prognostic value of the serum albumin level for long-term prognosis in patients with acute pulmonary embolism, Clin. Res. J 14 (2020) 578–585, https://doi.org/10.1111/crj.13176.
[25] G. Delgado, R. Siekmeier, T.B. Grammer, B.O. Boehm, W. März, M.E. Kleber, Alterations in the coagulation system of active smokers from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, Adv. Exp. Med. Biol. 832 (2015) 9–14, https://doi.org/10.1007/5584_2014_5.
[26] K.P. Cohoon, A.A. Ashrani, D.J. Crusan, T.M. Petterson, K.R. Bailey, J.A. Heit, Is infection an independent risk factor for venous thromboembolism? A population-based, case-control study, Am. J. Med. 131 (2018) 307–316, https://doi.org/10.1016/j.amjmed.2017.09.015.
[27] Y.G. Chen, T.Y. Lin, W.Y. Huang, C.L. Lin, M.S. Dai, C.H. Kao, Association between pneumococcal pneumonia and venous thromboembolism in hospitalized patients: a nationwide population-based study, Respirology 20 (2015) 799–804, https://doi.org/10.1111/resp.12501.
[28] L. Tapoi, D.L. Salaru, R. Sascau, C. Stătescu, Uric Acid-an emergent risk marker for thrombosis? J. Clin. Med. 10 (2021) 2062, https://doi.org/10.3390/jcm10102062.
[29] M. Zuin, G. Rigatelli, S. Turchetta, P. Zonzin, G. Zuliani, L. Roncon, Left atrial size measured on CT pulmonary angiography: another parameter of pulmonary embolism severity? A systematic review, J. Thromb. Thrombolysis 50 (2020) 181–189, https://doi.org/10.1007/s11239-019-01994-8.
[30] G. Cervellin, R. Buonocore, F. Sanchis-Gomar, G. Lippi, Low serum bilirubin values are associated with pulmonary embolism in a case-control study, Clin. Chem. Lab. Med. 54 (2016) e229–e230, https://doi.org/10.1515/cclm-2015-1156.
[31] H. Duman, S. Ozyurt, T. Erdogan, B.Y. Kara, M.E. Durakoğlugil, The role of serum bilirubin levels in determining venous thromboembolism, J Vasc Surg Venous Lymphat Disord 7 (2019) 635–639, https://doi.org/10.1016/j.jvsv.2019.02.002.
[32] G.I. Raymundo-Martinez, R. Gopar-Nieto, G. Carazo-Vargas, Pulmonary embolism and megaloblastic anemia: is there a link? A case report and literature review, Radiol Case Rep 13 (2018) 1212–1215, https://doi.org/10.1016/j.radcr.2018.07.018.