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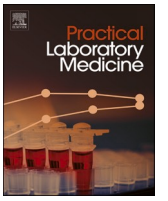

Beyond the fractures: A comprehensive Comparative analysis of Affordable and Accessible laboratory parameters and their coefficients for prediction and Swift confirmation of pulmonary embolism in high-risk orthopedic patients

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ABSTRACT

Background: Pulmonary embolism (PE) poses a significant challenge in diagnosis and treatment, particularly in high-risk patient populations such as those hospitalized for orthopedic reasons. This study explores the predictive and diagnostic potential of laboratory parameters in identifying PE among orthopedic patients.

Objectives: The purpose of this study was to determine whether selected (inexpensive and readily available) laboratory parameters and their coefficients can be used to diagnose pulmonary embolism and whether they are applicable in predicting its occurrence.

Material and methods: Selected laboratory parameters were determined twice in 276 hospitalized orthopedic patients with suspected PE: PLT, MPV, NEU, LYM, D-dimer, troponin I, age-adjusted D-dimer and their coefficients. Depending on the angio-CT results, patients were divided into groups. Selected popular laboratory coefficients were calculated and statistically analyzed. Optimal cutoff points were determined for the above laboratory tests and ROC curves were plotted.

Results: D-dimer/troponin I [$p = 0.008$], D-dimer [$p = 0.001$], age-adjusted D-dimer [$p = 0.007$], NLR/D-dimer [$p = 0.005$] and PLR [$p = 0.021$] are statistically significant predictors of PE. D-dimer/troponin I [$p < 0.001$], troponin I [$p = 0.005$] and age-adjusted D-dimer [$p = 0.001$] correlated with the diagnosis of PE after the onset of clinical symptoms.

Conclusions: In the context of orthopedic patients, cost-effective laboratory parameters, particularly the D-dimer/troponin I ratio and age-adjusted D-dimer, exhibit considerable potential in predicting and diagnosing PE. These findings suggest that combining readily available laboratory tests with clinical observation can offer a viable and cost-effective diagnostic alternative, especially in resource-constrained settings. Further studies with larger and diverse patient populations are recommended to validate these results.

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1. Introduction

Pulmonary embolism (PE) denotes the occlusion or constriction of a pulmonary artery or its branches due to embolic material, constituting a crucial aspect of venous thromboembolism (VTE). The counterpart in this thromboembolic dyad is deep vein thrombosis (DVT). These entities share similar risk factors and may impact identical high-risk patient cohorts, such as those hospitalized for orthopedic reasons. However, DVT is notably more prevalent than PE, the primary focus of our current investigation.

Within the spectrum of high-risk orthopedic patients, instances of PE may manifest without concurrent clinical suspicion of DVT [1–4]. This phenomenon is particularly observed in post-traumatic cases involving fractures of the spine, pelvis, and lower limbs, frequently occurring subsequent to total arthroplasty in major joints. The subsequent Figs. 1 and 2 encapsulate computed tomography (CT) and computed tomography pulmonary angiography (CTPA) images of select orthopedic patients participating in our retrospective study, illustrating cases of post-traumatic pulmonary embolism.

The patients showcased in the examples include a 58-year-old female with a right femoral neck fracture and a 64-year-old male with a compression fracture of the vertebral body of the L4 vertebra, along with fractures of the right ischium and right pubic bone. These clinical scenarios exemplify the nuanced manifestations of pulmonary embolism in the context of orthopedic trauma, underscoring the complexity and diversity of this critical medical condition.

The classic symptoms of pulmonary embolism are widely recognized and extensively documented; nevertheless, the clinical presentation often deviates from the typical. The diagnostic and therapeutic challenges posed by PE are encountered routinely by clinicians, with numerous patient groups exhibiting an elevated risk of the condition. Predominantly, individuals with distinct personal characteristics and specific clinical conditions, along with those undergoing various surgical, therapeutic, diagnostic, or prophylactic interventions, fall into this heightened risk category. Notably, patients hospitalized for orthopedic reasons form a unique subset, frequently meeting the criteria for a "high-risk patient for PE."

This particular patient cohort, deemed "exceptionally difficult" for the purposes of our study, stands out due to the confluence of multiple risk factors for PE frequently present simultaneously. It is imperative to acknowledge that utilizing D-dimer as an auxiliary predictor in this population proves highly unproductive, given its low specificity as a laboratory parameter. Furthermore, the indiscriminate ordering of D-dimer tests by clinicians contributes to unnecessary healthcare costs.

In light of these considerations, there is a pressing need to explore alternative, readily available, cost-effective, and universally applicable laboratory parameters that can facilitate the prediction and/or confirmation of PE. Table 1 outlines some of the risk factors contributing to venous thromboembolic events (VTE) and specifically delineates the risk factors prevalent in orthopedic patients. This information aligns with the 2019 European Society of Cardiology Guidelines for the diagnosis and management of acute pulmonary embolism, developed in collaboration with the European Respiratory Society [5]. The pursuit of such predictive parameters aligns with the overarching goal of refining diagnostic strategies and optimizing patient care in this complex and high-risk demographic.

Unraveling the diagnostic intricacies of this insidious ailment remains a formidable task, even in the face of the dynamic evolution of auxiliary methodologies. The fiscal repercussions associated with diagnosing, treating, and rehabilitating individuals grappling with pulmonary embolism (PE) undeniably place a substantial burden on hospital budgets and the overarching healthcare sector. Currently, the utilization of two scales—the Wells scale and the modified Geneva scale - aims to quantify the clinical probability of PE [6]. However, the diagnostic landscape often relies on imperfect laboratory measurements and imaging techniques, albeit with computed tomography pulmonary angiography standing out as the gold standard, distinguished by its commendable sensitivity and specificity [7].

Despite the efficacy of this gold standard, the associated expenses and the considerable X-ray burden it imposes on patients necessitate careful consideration. Furthermore, it is imperative to highlight that, notwithstanding ongoing strides in high-quality imaging and laboratory diagnostics, access to these advanced tests remains constrained, particularly in economically challenged regions and smaller healthcare facilities.

The gravity of the challenge in achieving accurate PE diagnoses reverberates through statistical trends. Annual incidence rates for PE exhibit a fluctuation between 39 and 115 cases per 100,000 individuals, with a discernible upward trajectory. In 2004, six European countries recorded a staggering 370,000 deaths attributed to venous thromboembolism (VTE). Poignantly, 34 % of patients succumbed to complications within hours of diagnosis, while acute PE claimed the lives of the remaining individuals—diagnosed posthumously in

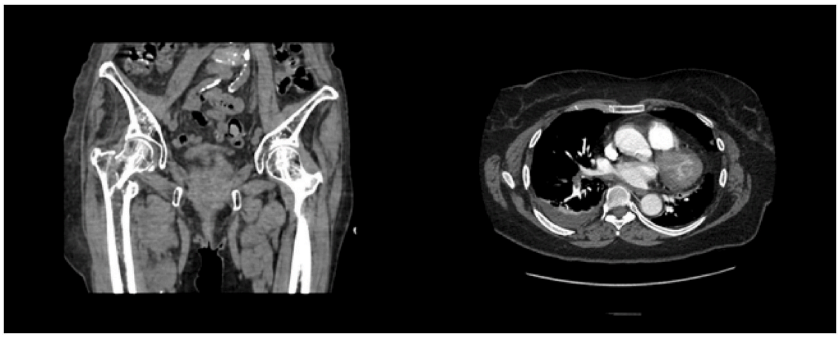

Fig. 1. CT scan of a 58-year-old female patient with a fractured right femoral neck and CTPA of developed pulmonary embolism of the same patient.

59 % of cases. Disturbingly, correct pre-mortem diagnoses materialized in a mere 7 % of cases, underscoring the dire need for enhanced diagnostic strategies and broader accessibility to advanced medical technologies [4]. This imperative becomes increasingly evident as we strive to navigate the evolving landscape of PE diagnosis and treatment.

Diagnosis and treatment of PE carry substantial costs, which range from USD 3889 to USD 13,748 per patient [8]. Our own experience and an in-depth analysis of the literature became the motivation for the search for a "universal", i.e., readily available, fast and inexpensive solution in the diagnosis of PE, initially in a strictly selected group of patients: patients hospitalized for orthopedic reasons. To the best of the authors' knowledge, the presented study and its results are the first of its kind. In the presented retrospective study, the following goals were set.

a) To conduct an analysis of specific laboratory parameters in peripheral venous blood to identify potential predictors of pulmonary embolism (PE) in a designated patient population.
b) To identify the most significant, specific, and sensitive predictors of pulmonary embolism occurrence in a cohort of patients hospitalized for orthopedic reasons.
c) To determine the most significant, specific, and sensitive factors for confirming the diagnosis of pulmonary embolism in a patient population hospitalized for orthopedic reasons.

The following theses were put forward for the study.

a) It is feasible to predict an increased risk of pulmonary embolism in a selected high-risk group (patients hospitalized for orthopedic reasons) based on the analysis of selected laboratory parameters of peripheral venous blood.
b) It is possible to diagnose pulmonary embolism in patients of a selected high-risk group (hospitalized for orthopedic reasons) through the analysis of selected laboratory parameters of peripheral venous blood.

2. Materials and methods

2.1. Study design and participants

The research endeavor involved a meticulous and thorough retrospective examination of a cohort characterized by individuals admitted for orthopedic reasons - individuals who inherently embody a multitude of risk factors predisposing them to pulmonary embolism. This high-risk group, comprising orthopedic and trauma patients, was subjected to an intricate analysis that spanned the spectrum of laboratory assessments, CTPA imaging studies, and an evaluation of clinical parameters.

The comprehensive scrutiny extended to the clinical data of 276 patients, admitted to the hospital between the years 2012 and 2020. The patient selection process involved qualification from the pre-clinical outpatient department or direct admission from the Emergency Department, contingent upon the established diagnosis. Notably, the meticulousness of this retrospective analysis sought to illuminate intricate connections between the clinical, imaging, and laboratory dimensions, shedding light on the diagnostic landscape of pulmonary embolism within this specific patient demographic.

2.2. Groups and Variables

Patients were stratified into two distinct cohorts based on the results of computed tomography pulmonary angiography (CTPA) and the diagnosis of pulmonary embolism (PE). The study group (n = 116) comprised individuals with confirmed PE, while the control group (n = 160) consisted of patients in whom PE was conclusively ruled out. In the research protocol, all patients underwent dual assessments of laboratory parameters, first upon admission to the ward, and subsequently at the onset of clinical suspicion of pulmonary embolism, immediately preceding the pulmonary artery angiography-CT examination.

The dual measurement strategy, as delineated in the research design, facilitated the evaluation of parameter dynamics and the

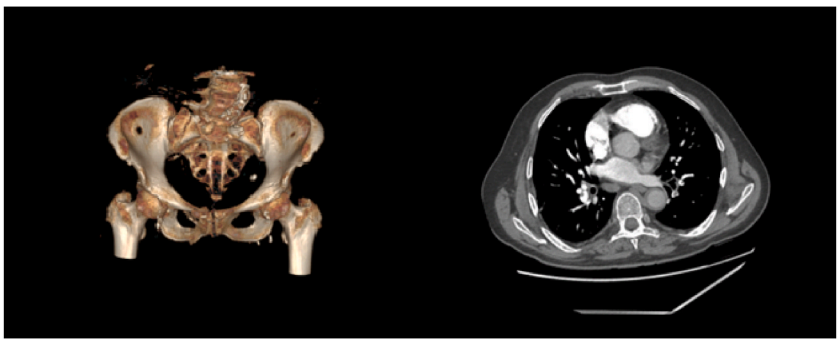

Fig. 2. Compression fracture of the vertebral body of the L4 vertebra, fracture of the right ischium and the right pubic bone in a 64-year-old man (3D reconstruction computed tomography) and CT of developed pulmonary embolism of the same patient.

identification of factors correlating with the anticipation or confirmation of pulmonary embolism. Venous blood, collected from the upper extremities, was drawn into tubes containing sodium citrate. Within a 30-min timeframe from sample acquisition, automated counting analyzers were utilized for the comprehensive assessment of blood parameters. The intricate process of forming the study and control groups is depicted in Fig. 3, providing a visual representation of the meticulous approach employed in patient stratification and subsequent analysis. Remaining biological materials were disposed of in accordance with typical and basic hospital laboratory rules. The analyzed laboratory parameters and their respective coefficients are presented in Table 2.

In adherence to the 2019 ESC guidelines on anticoagulant treatment for pulmonary embolism, some patients received anticoagulant prophylaxis as outlined in Table 3. Others were excluded either due to the absence of indications for anticoagulant prophylaxis or for other specific reasons.

2.3. Statistical analysis

To ascertain the utility of laboratory indicators in diagnosing PE, statistical analysis was conducted using TIBCO Statistica 13.3 software. This encompassed Student's t-test for independent samples, frequency analysis using the Chi-square test, and ROC curve analysis. A significance level of $\alpha = 0.05$ was applied. Coefficients significantly correlated with PE were identified through analysis of areas under the curve (AUC), and cutoff points were determined using the Youden index, where sensitivity and specificity were 100 %.

2.4. Ethical approval and literature review

The study design received ethical consent of the Bioethics Committee of the local Medical University, ensuring compliance with stringent ethical standards in medical research.

Notably, 90 % of the literature referenced in this manuscript was sourced from the last 7–8 years, reflecting the incorporation of the latest advancements and findings in the field. This approach underscores the contemporary relevance and currency of the scholarly foundation underpinning the study.

3. Results

3.1. Predicting the occurrence of pulmonary embolism

Of the total 276 patients, 138 patients were female and 138 patients were male. In the study group, there were 54 women and 62 men. Due to the need for the universality of the laboratory parameter, a retrospective study was conducted on a wide group of patients. The age range was 26–98 years, with a mean age of 71.6 years of age. The control group consisted of 84 females and 76 males. The age range was 22–100 years, with a mean age of 69.85 years.

Analysis of the ROC curves showed that the following laboratory parameters may be important in predicting pulmonary embolism (the order was determined by AUC values).

1. D-dimer;
2. D-dimer/troponin I ratio;
3. Age-adjusted D-dimer;
4. NLR/D-dimer ratio;
5. PLR.

The results are presented in Table 4.

For the above-presented laboratory tests, the optimal cutoff points were determined (using the Youden index) as the cutoff points at which 100 % sensitivity and specificity were observed. The results are shown in Table 5 and Figs. 4–8.

Table 1
The presentation of risk factors for VTE episodes and the risk factors already existing in orthopedic patients.

Strong risk factors for VTE (S)	Moderate risk factors for VTE (M)	Weak risk factors for VTE (L)	The Risk Factors of VTE Present in Orthopedic Patients (research group)
Fracture of lower limb	Arthroscopic knee surgery	Bed rest >3 days	Fracture of lower limb (S)
Knee or hip replacement	Autoimmune diseases	Diabetes mellitus	Knee or hip replacement (S)
Major trauma	Blood transfusion	Arterial hypertension	Major trauma (S)
Myocardial infarction	Central venous lines	Immobility	Arthroscopic knee surgery (M)
Previous VTE	Intravenous catheters and leads	Increasing age	Intravenous catheters and leads (M)
Spinal cord injury	Chemotherapy	Laparoscopic surgery	Immobility (W)
Hospitalization for heart failure	Cancer	Obesity	
	Thrombophilia	Pregnancy	
	Hormone replacement therapy	Varicose veins	
	Paralytic stroke		
	Infection		

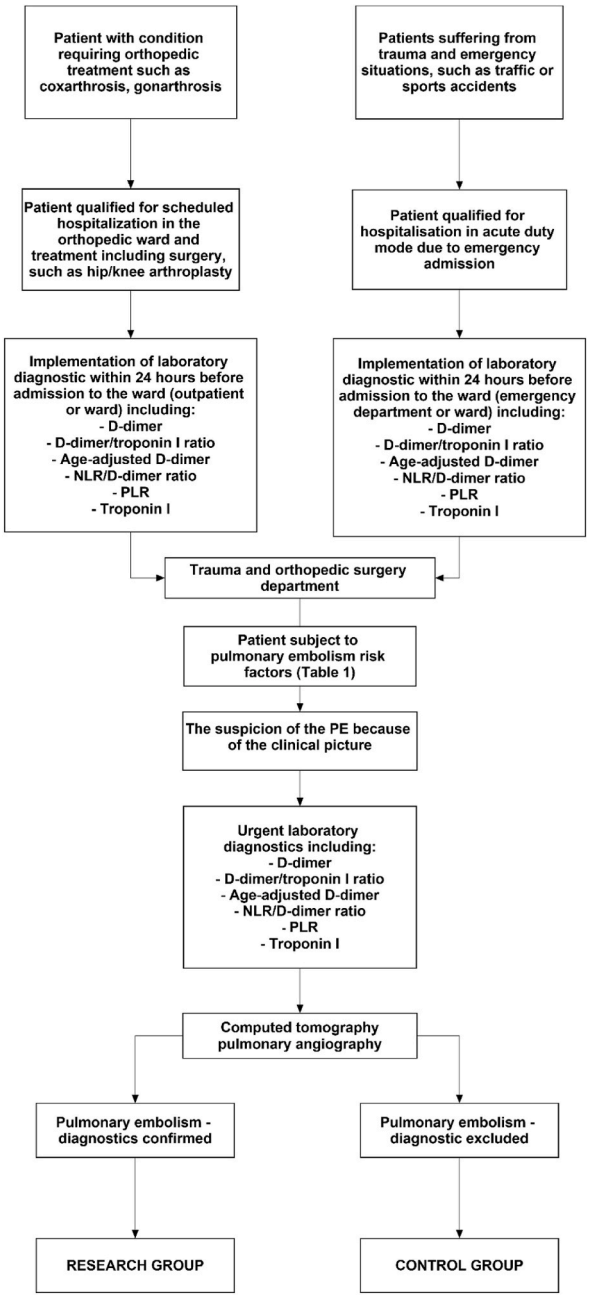

Fig. 3. The scheme of patient qualification for the study.

3.2. Confirming suspicion of pulmonary embolism

In the next stage of the study, it was examined whether it was possible to use laboratory test results to confirm the diagnosis of PE. For this purpose, a series of ROC curve analyses were performed for individual laboratory test results. The analysis revealed that the D-dimer/troponin I ratio (AUC = 0.771) was the most significant for confirming PE, followed by the ratio of the age-adjusted D-dimer level (AUC = 0.752). Laboratory parameters relevant to PE confirmation are listed below (order is set based on AUC values).

1. D-dimer/troponin I ratio;
2. Age-adjusted D-dimer;
3. Troponin I.

Table 2
Determined laboratory parameters and coefficients of peripheral venous blood.

Parameter	Unit
PLT	μL
MPV	fL
NEU	$\times 10^9$/L
NEU%	%
LYM	$\times 10^9$/L
LYM%	%
D-dimer	ng/mL
Troponin I	ng/mL
Age-adjusted D-dimer	ng/mL
D-dimer/troponin I	–
MPV/PLT	–
PLR	–
NLR	–
NLR/D-dimer	–

PLT – platelets, MPV – mean platelet volume, NEU – neutrophils, LYM – lymphocytes, PLR – platelet to lymphocyte ratio, NLR – neutrophil to lymphocyte ratio, NLR/D-dimer – NLR to D-Dimer ratio.

Table 3
Anticoagulant treatment in patients with pulmonary embolism.

	Dose of the Drug	Route of Drug Administration
Unfractionated heparin	80 IU/kg	i.v.
Dalteparin (LMWH)	100 IU/kg/12 h	s.c.
Enoxaparin (LMWH)	1 mg/kg/12 h	s.c.
Nadroparin (LMWH)	85 IU/kg/12 h	s.c.
Fondaparinux	7.5 mg/24 h	s.c.
Rivaroxaban	15 mg 2 × per day for 3 weeks	p.o.
Apixaban	10 mg 2 × per day for 7 days	p.o.
Endoxaban	60 mg once a day (after 5 days of using LMWH)	p.o
Dabigatran	150 mg 2 × per day (after 5 days of using LMWH)	p.o

LMWH—Low-molecular-weight heparin.

Table 4
Parameters of ROC curves on the possibility of predicting pulmonary embolism on the basis of selected laboratory results.

	AUC	SE	95 % CI LL	95 % CI UL	z	p
PLT (μL)	0.558	0.035	0.489	0.627	1.65	0.099
MPV (fL)	0.505	0.035	0.565	0.426	0.14	0.892
NEU ($\times 10^9$/L)	0.506	0.036	0.564	0.424	0.18	0.858
NEU%	0.536	0.035	0.468	0.605	1.04	0.300
LYM ($\times 10^9$/L)	0.559	0.035	0.510	0.373	1.67	0.094
LYM%	0.533	0.035	0.464	0.603	0.95	0.343
D-dimer (ng/mL)	0.666	0.035	0.598	0.734	4.75	<0.001
D-dimer/troponin I	0.648	0.056	0.539	0.758	2.65	0.008
Troponin I (ng/mL)	0.556	0.048	0.462	0.649	1.17	0.243
MPV/PLT	0.558	0.036	0.512	0.373	1.63	0.104
PLR	0.580	0.035	0.512	0.647	2.30	0.021
NLR	0.533	0.035	0.464	0.602	0.93	0.355
NLR/D-dimer	0.601	0.036	0.530	0.671	2.79	0.005
Age-adjusted D-dimer (ng/mL)	0.640	0.052	0.537	0.743	2.68	0.007

AUC—area under the curve,. SE—standard error,. 95 % CI—confidence interval for area under the curve,. LL and UL—lower and upper limits of the confidence interval,. z—test statistics,. p—significance, PLT – platelets, MPV – mean platelet volume, NEU – neutrophils, LYM – lym-phocytes, PLR – platelet to lymphocyte ratio, NLR – neutrophil to lymphocyte ratio, NLR/D-dimer – NLR to D-Dimer ratio.

The results of all studied parameters in terms of the possibility of confirming PE are shown in Table 6.

Next, the optimal cutoff point was determined for the above laboratory parameters (using the Youden index) as the cutoff point at which 100 % sensitivity and specificity were observed. The results are shown in Table 7 and Figs. 9–11.

Table 5
Proposed cutoff points for laboratory tests that may be relevant in predicting pulmonary embolism.

	CP	YI	S	Sp.
D-dimer (ng/mL)	6717.40	0.28	58.10 %	70.20 %
	64,684.00	0.03	2.90 %	100.00 %
	394.76	0.00	100.00 %	0.00 %
Age-adjusted D-dimer (ng/mL)	23.96	0.27	87.00 %	39.70 %
	7274.89	0.06	5.60 %	100.00 %
	0.01	0.03	100.00 %	3.40 %
NLR/D-dimer	0.002	0.16	88.60 %	27.70 %
	0.038	0.01	100.00 %	0.70 %
	0.000	0.14	37.10 %	77.60 %
PLR	252.87	0.15	56.90 %	57.90 %
	1120.00	0.03	2.60 %	100.00 %
	52.26	0.02	100.00 %	1.90 %
D-dimer/troponin I	95962.86	0.28	63.0 %	80.40 %
	2,130,780.00	0.02	0.2 %	100.00 %
	9.14	0.04	100.0 %	0.04 %

CP—cut-off point,. YI—Youden index,. S—sensitivity,. Sp,.—specificity,. PLT – platelets, NLR/D-dimer – NLR to D-Dimer ratio.

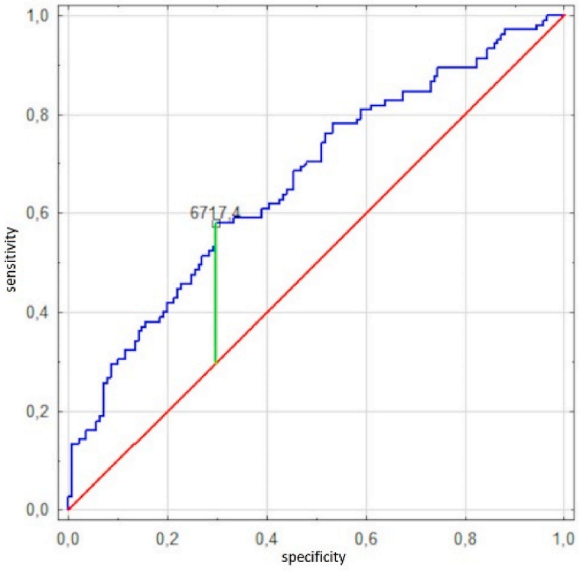

Fig. 4. ROC curve evaluating the potential of using D-dimer levels to predict the occurrence of pulmonary embolism.

4. Discussion

The obtained results showed that the following laboratory parameters may have prognostic significance for the diagnosis of PE in patients hospitalized for orthopedic reasons: D-dimer, the ratio of D-dimer levels to the age standard, the NLR/D-dimer ratio, the D-dimer/troponin I ratio and PLR. The D-dimer/troponin I ratio was found to be most useful in confirming PE. Determination of serum D-dimer levels is an inexpensive test helpful for the diagnosis of PE among patients, as confirmed by other authors [9–11]. A D-dimer value of <500 μg/L was taken as the reference point. Below this value, an episode of PE or DVT was excluded [12]. However, high D-dimer levels are not used to confirm these diagnoses, as elevated levels can be observed in various clinical situations and in groups of elderly patients [13]. Unfortunately, in a group of orthopedic patients, which is a group characterized by a high risk of developing VTE [14], the predictive and diagnostic value of D-dimers has been assessed less well than in the general population.

In the settings of trauma and orthopedic departments, D-dimer values of less than 500 μg/L are rarely observed. Much more common are results representing multiples of this number that may reach over 100,000 μg/L in asymptomatic patients, which translates into a decrease in the specificity of this laboratory test. Glober et al. took a similar view when they examined the sensitivity and specificity of D-dimers in a group of 3523 patients from a hospital emergency department. Their study showed that despite the high sensitivity of D-dimers, their specificity for PE did not exceed 40 % [15]. Due to the low specificity of D-dimers, a more useful laboratory parameter is the ratio of D-dimer levels to the patient's age norm. Similar conclusions were reached by Harper et al. in their study "D-dimer concentration increases with age reducing the clinical value of the D-dimer assay in the elderly", conducted on a group of 6631 patients. The specificity of D-dimers in the group of patients over 80 years of age did not exceed 5 %, while the highest

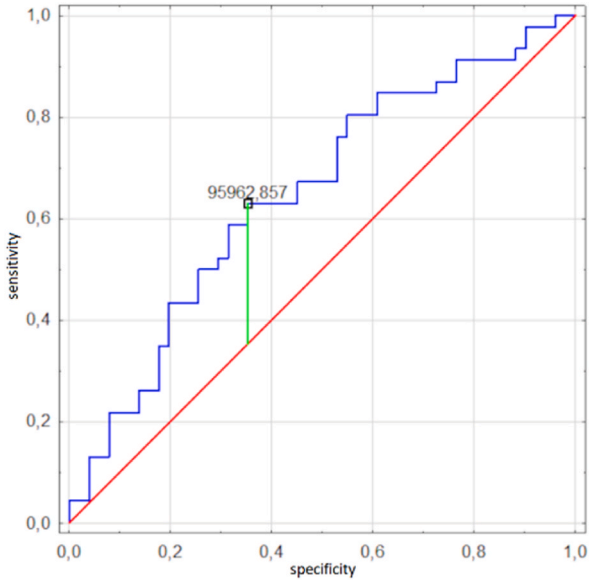

Fig. 5. ROC curve evaluating the potential of using the ratio of D-dimer to troponin I to predict pulmonary embolism.

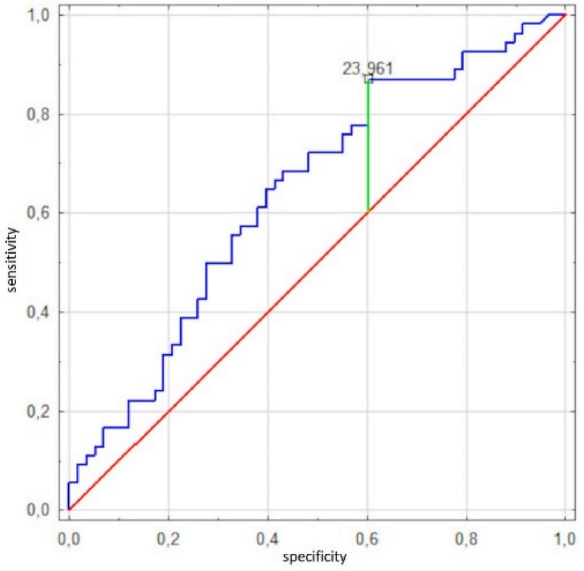

Fig. 6. ROC curve evaluating the potential of using the ratio of age-adjusted D-dimer for predicting the occurrence of pulmonary embolism.

specificity occurred in the group of patients under 40 years of age and reached up to 70 % [16]. Due to the described limitations in the use of D-dimers, the researchers implemented efforts to improve the utility of this test. A cutoff point for D-dimer levels was established. A negative D-dimer result <500 μg/L can rule out PE in 60 % of patients aged <40 years, but only in 5 % of patients aged >80 years. The optimal correlation between age and D-dimer levels has been established as ten times the patient's age in patients over 50 (patient age × 10 ng/mL). Other authors also agree that the ratio of D-dimer level to age norm is more useful than the patient's serum D-dimer level alone, especially in the absence of imaging studies [9,17,18]. In addition, the implementation of an age-correlated cutoff point for D-dimers may be associated with measurable benefits, such as a reduction in the number of CTPA procedures performed, which is associated with less radiation exposure to patients. Dubin et al., in their publication "Multi-center implementation of automated age-adjusted D-dimer results reduces unnecessary PE imaging", showed that the number of CT scans performed can be reduced by 4.4 % [19].

In contrast, a study conducted by Freudyn et al. on a group of 1414 patients compared a conventional method of VTE exclusion using CTPA with a method that relies on a combination of the YEARS algorithm and age-dependent D-dimer levels in patients meeting PE exclusion criteria (PERC-positive). The results showed that the method based on the YEARS algorithm and age-dependent D-dimer

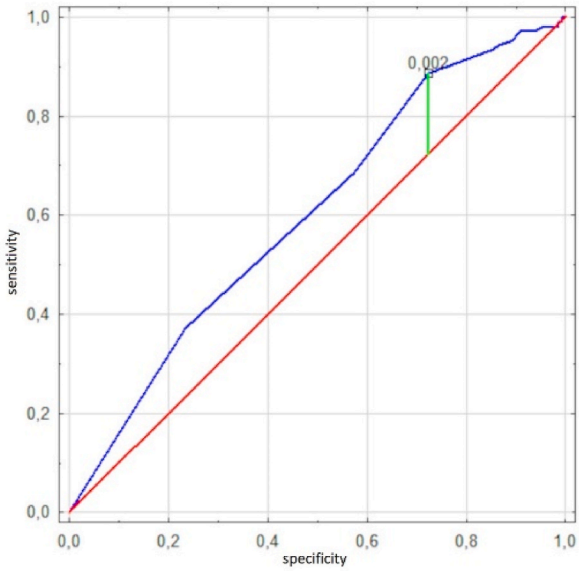

Fig. 7. ROC curve evaluating the potential of using the NLR/D-dimer ratio to predict the occurrence of pulmonary embolism.

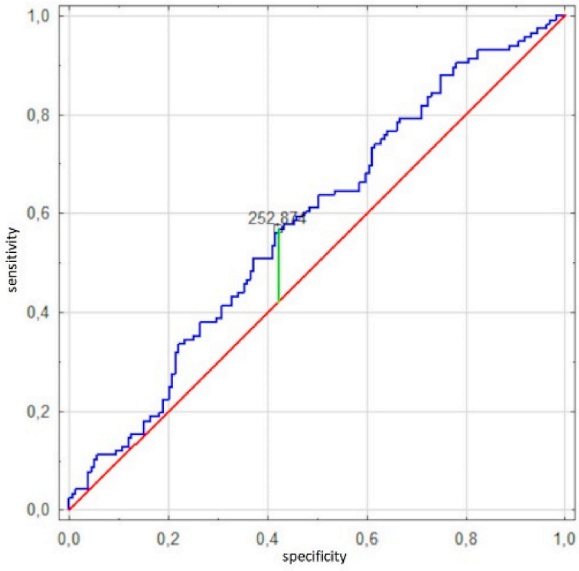

Fig. 8. ROC curve evaluating the potential of using PLR to predict the incidence of pulmonary embolism.

levels did not lead to a lower rate of diagnoses of thromboembolic events relative to the conventional method, and resulted in a 10 % reduction in the number of CTPAs performed [20]. Drescher et al. showed that by using the Wells criteria, PERC criteria and D-dimer testing, it is possible to reduce the number of CTPAs performed [21]. A similar view is held by Zhang Y. et al., who, in their work, showed that a diagnostic strategy based on D-dimers and another expensive test like CTPA is more cost-effective than using CTPA alone [22].

Reducing the number of tests performed and simplifying diagnosis is also associated with reduced expenses. In the article "Age-adjusted D-dimer cutoff for the diagnosis of pulmonary embolism: A cost-effectiveness analysis", Blondon M. et al. estimated that the savings in the United States could exceed USD 80 million [23].

Some of the other coefficients whose predictive value was tested in this study are NLR and PLR. The neutrophil/lymphocyte ratio (NLR), or the ratio of neutrophils to lymphocytes, increases when inflammation develops in the body. Neutrophils secrete inflammatory mediators that damage the vascular endothelium, predisposing the organism to thrombotic complications [24–26]. High values of these ratios can be observed in all conditions with neutrophilia (NLR) or thrombocytosis (PLR), as well as in conditions with

Table 6
Parameters of ROC curves for the possibility of confirming pulmonary embolism on the basis of selected laboratory results.

	AUC	SE	95 % CI LL	95 % CI UL	z	p
PLT (μL)	0.515	0.036	0.445	0.585	0.42	0.673
MPV (fL)	0.545	0.037	0.473	0.617	1.24	0.217
NEU ($\times 10^9$/L)	0.512	0.036	0.558	0.418	0.33	0.738
NEU%	0.515	0.036	0.445	0.586	0.43	0.668
LYM ($\times 10^9$/L)	0.534	0.036	0.463	0.606	0.95	0.342
LYM%	0.530	0.036	0.46	0.6	0.83	0.405
D-dimer (ng/mL)	0.538	0.048	0.556	0.369	0.79	0.431
MPV/PLT	0.543	0.035	0.474	0.613	1.22	0.222
PLR	0.545	0.036	0.475	0.615	1.26	0.209
NLR	0.518	0.036	0.448	0.588	0.50	0.615
NLR/D-dimer	0.523	0.048	0.571	0.383	0.48	0.633
Age-adjusted D-dimer (ng/mL)	0.752	0.079	0.597	0.907	3.18	0.001
D-dimer/troponin I	0.771	0.075	0.623	0.918	3.59	<0.001
troponin I (ng/mL)	0.691	0.067	0.559	0.823	2.83	0.005

AUC—area under the curve,. SE–standard error. 95 % CI—confidence interval for the area under the curve,. LL and UL—lower and upper limits of the confidence interval,. z—test statistics,. p—significance, PLT – platelets, MPV – mean platelet volume, NEU – neutrophils, LYM – lym-phocytes, PLR – platelet to lymphocyte ratio, NLR – neutrophil to lymphocyte ratio, NLR/D-dimer – NLR to D-Dimer ratio.

Table 7
Proposed cutoff points for laboratory tests that may be relevant in confirming pulmonary embolism.

	CP	YI	S	Sp.
Age-adjusted D-dimer (ng/mL)	168.650	0.52	72.0 %	80.0 %
	21,044.870	−0.05	0.0 %	95.0 %
	0.040	0.05	100.0 %	5.0 %
D-dimer/troponin I	184,238.000	0.52	68.0 %	84.2 %
	1,821,170.000	0.12	12.0 %	100.0 %
	26.850	0.05	100.0 %	5.3 %
Troponin I (ng/mL)	0.046	0.40	71.4 %	69.0 %
	182.000	0.03	100.0 %	3.4 %
	0.001	0.13	20.0 %	93.1 %

CP—cutoff point; YI—Youden index; S—sensitivity; Sp.—specificity.

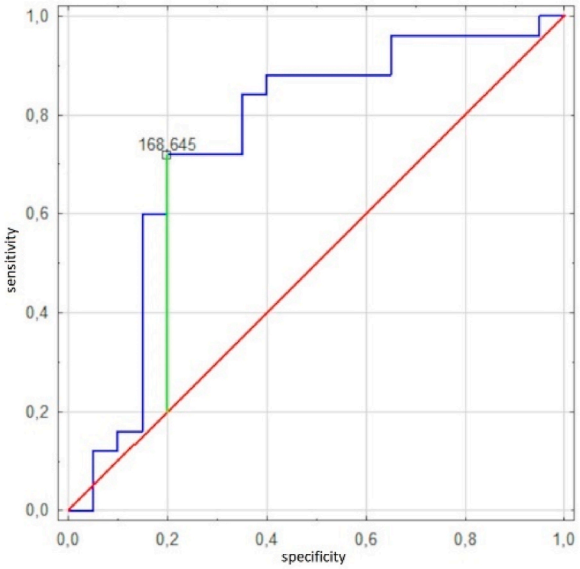

Fig. 9. ROC curve evaluating the feasibility of using the ratio of age-adjusted D-dimer to confirm the presence of pulmonary embolism.

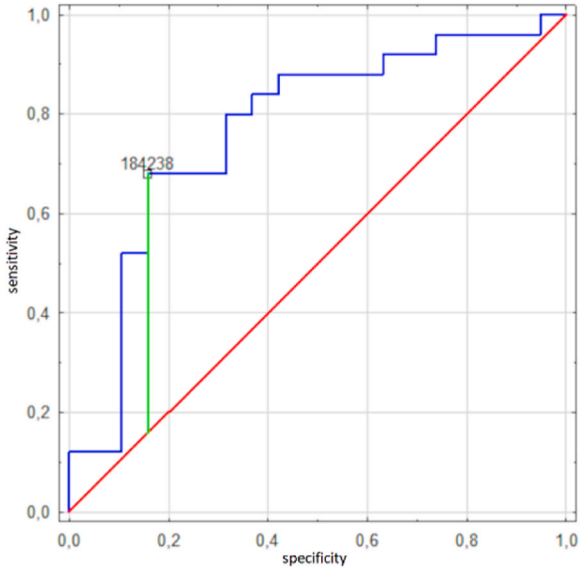

Fig. 10. ROC curve evaluating the feasibility of using the ratio of D-dimer to troponin I to confirm the presence of pulmonary embolism.

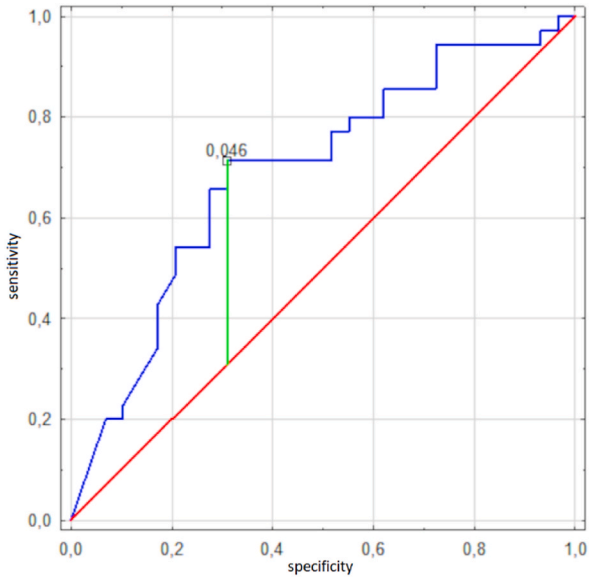

Fig. 11. ROC curve evaluating the possibility of using troponin I to confirm the presence of pulmonary embolism.

lymphopenia (NLR and PLR). Determination of these ratios is becoming increasingly popular, with numerous studies proving their value in the prognosis of conditions such as myocardial infarction [27], neoplastic proliferations [28–32], acute inflammation [33] or other vascular incidents [34].

Studies show that increased NLR correlates with increased mortality in patients with PE [24,35]. This suggests that this indicator can be used for assessing the risk of death of PE patients. Similar conclusions have been drawn about the usefulness of the PLR index. In their study, Phan et al. indicated that a higher level of this index correlated with higher mortality in patients diagnosed with PE [36]. It is worth mentioning, however, that according to the statistical analysis performed in this study, a higher diagnostic value for suspected PE than the NLR and PLR coefficients was demonstrated by the ratio of D-dimers to the age-specific D-dimer standard.

Another laboratory test worth performing when acute pulmonary embolism is suspected is the mean thrombocyte volume (MPV). This study tested whether this test can be used to diagnose PE, and based on statistical analysis, it may not speak for or against the diagnosis of pulmonary embolism. However, like NLR or PLR, it is useful for predicting the severity of the course of the disease among patients, which is also confirmed by other scientific studies [37–39].

It is worth mentioning that in order to calculate the aforementioned coefficients, it is not necessary to perform additional laboratory

tests beyond a basic peripheral blood count, which is a cheap and widely available test.

Another factor studied was the ratio of NLR to D-dimers. Literature reports on the usefulness of this laboratory parameter in the diagnosis of PE are scarce. In their publication, Ates H. et al. evaluated the relationship between the parameter in question and the incidence of PE and extramedullary pneumonia, as well as its usefulness in the differential diagnosis of these diseases in comparison with other laboratory results. They proved that NRL/D-dimer is the most sensitive and specific test for the differential diagnosis of PE and extramedullary pneumonia (sensitivity 91.7 %, specificity 85.3 %) [40].

The results presented here are most likely the first available data evaluating the usefulness of the NLR/D-dimer parameter in the prediction and confirmation of PE as an isolated parameter. Analysis of the above laboratory parameters showed a correlation between the NLR/D-dimer value before admission to the clinic and the subsequent occurrence of pulmonary embolism. This means that the NLR/D-dimer ratio may be important for predicting the occurrence of pulmonary embolism.

The next of the laboratory factors tested in this retrospective study in terms of its ability to confirm PE is troponin I (cTnI). Studies show that elevated levels of cardiac troponins, including cTnI, depending on the extent of pulmonary embolism, were present in 80 % of patients with extensive pulmonary embolism, 56 % of patients with moderately extensive embolism and 38 % of patients with non-extensive pulmonary embolism. In their study, Yousuf et al. confirmed that cTnI determination is statistically significant in the diagnosis of PE, although not every patient will have an elevated rate [41].

Determination of troponin I levels, as well as D-dimers, increases the sensitivity and specificity of laboratory tests relative to the determination of only one of these parameters [42]. For this reason, in this study, we decided to test the usefulness of the D-dimer/troponin I ratio for its ability to predict and confirm an episode of PE in patients hospitalized for orthopedic reasons. As a result of statistical analysis, it turned out that the aforementioned ratio was the best laboratory parameter among all those tested in this retrospective study for confirming an episode of PE and the second-best for predicting an episode of PE.

Troponin I, together with troponins C and T, form the cardiac troponin complex, the concentration of which is increased in conditions that damage the myocardium [43]. In the case of PE, the pathomechanism of troponin release is due to right ventricular overload [44]. Their utility is mainly in the diagnosis of acute coronary syndromes, but troponin I has also found use in patients with PE, as studies show that higher levels of troponin I correlate with increased mortality in patients with pulmonary embolism [45]. As a result, the aforementioned coefficient is used in differentiating acute pulmonary embolism from non-ST-segment elevation myocardial infarction (NSTEMI) (sensitivity 93.3 %, specificity 86.6 %), where the finding of its elevation may lead to the abandonment of unnecessary coronary angiography [46].

According to a 2021 Canadian study, the most commonly used test for diagnosing PE among clinicians was nevertheless CTPA, which was often ordered without prior venous blood laboratory tests and therefore without the determination of the coefficients mentioned earlier in this paper [47]. Wang et al. argue that the ability to image the pulmonary arteries during this test makes it possible to assess the severity and threat to life of PE patients [48]. However, this imaging has limitations. A significant problem is its cost. It is also important to remember the harmful effects on the body caused by the ionizing radiation emitted during this examination. In addition, not all health care facilities have a CT scanner among their equipment, and the severe condition of a PE patient may preclude transport to a unit that would allow CTPA. Determination of D-dimer levels or ratios such as NLR or PLR, on the other hand, is an inexpensive, widely available and feasible test.

This retrospective study had some limitations. The main one was the relatively small study group. In order to further analyze the usefulness of the studied diagnostic coefficients in diagnosing and predicting the course of PE, further studies should be performed in the future, conducted on a larger and more diverse study group of patients.

5. Limitations of the study

The study's interpretative scope is constrained by several limitations, including its small cohort size, potentially impacting the results' representativeness and generalizability. The absence of predefined exclusion criteria, considering all orthopedic patients with complete lab results and CTPA, further limits its broad applicability.

A conscious choice was made to not extensively analyze pharmacotherapeutic interventions and comorbidities, aiming to extract universal insights from the targeted group. This exclusion, particularly in the assessment of D-dimers, may affect the depth of clinical understanding and implications for interpreting outcomes. The variance in physicians' approaches to suspecting pulmonary embolism also introduces a challenge to standardization, potentially affecting the results.

Despite these constraints, the study offers valuable insights. Nonetheless, further research on larger, diverse cohorts is essential to conclusively affirm the utility of the parameters in diagnosing and prognosing pulmonary embolism.

6. Conclusions

There are inexpensive and readily available laboratory parameters and their coefficients that can be used to predict the occurrence of PE and confirm it in a select group of patients. After thorough consideration, it turns out that only some of these present adequate sensitivity and specificity at the current cut-off points. The most advantageous are age-adjusted D-dimer, D-dimer/troponin I and NLR/D-dimer. D-dimer/troponin I [$p = 0.008$], D-dimer [$p < 0.001$], age-standardized D-dimer [$p = 0.007$], NLR/D-dimer [$p = 0.005$] and PLR [$p = 0.021$] may prove to be helpful parameters in predicting the occurrence of PE in patients before any clinical symptoms are presented. D-dimer/troponin I [$p < 0.001$], troponin I [$p = 0.005$] and age-adjusted D-dimer level [$p = 0.001$] can be used to rapidly diagnose PE after clinical suspicion has been raised, especially in the absence of other diagnostic tools.

Particularly noteworthy is the D-dimer/troponin I ratio, which, in a selected group of patients, has high sensitivity and specificity

for both the possibility of predicting the occurrence of PE as well as its confirmation. An important parameter is also the age-adjusted D-dimer in both groups. The role of overused D-dimers in the diagnosis of a selected group is strictly limited.

The potential practical use of low-cost and readily available parameters in specific groups of patients, especially when combined with clinical observation and physical examination, may be a viable and less expensive diagnostic alternative—especially when access to other methods is limited.

Institutional review board statement

On January 31, 2019, the draft of the study received a positive opinion of the Bioethics Committee of the Medical University of Lublin (Poland), number KE-0254/17/2019.

The study was conducted in accordance with the principles of the Declaration of Helsinki.

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CRediT authorship contribution statement

Piotr Piech: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mateusz Haratym:** Writing – original draft, Visualization, Validation, Resources, Data curation. **Bartosz Borowski:** Writing – original draft, Resources, Investigation, Data curation. **Robert Węgłowski:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Formal analysis. **Grzegorz Staśkiewicz:** Writing – review & editing, Supervision, Project administration, Conceptualization.

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.

Data availability

Data will be made available on request.

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