Can INR on admission be a new prognostic parameter in patients with acute pulmonary embolism?

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Abstract: Pulmonary embolism (PE) is one of the leading causes of cardiovascular mortality, therefore new parameters regarding risk stratification are sought after. In patients admitted for acute PE we investigated associations between the initial coagulation impairment, expressed by prothrombin time international normalised ratio (INR), and parameters reflecting PE severity. Furthermore, in-hospital, 30-day and long-term mortality were also evaluated. The analysis included 848 patients who were divided into two groups: with normal INR≤1.2, and elevated INR>1.2 (252 patients, 29.7%). The group with elevated INR presented higher incidence of tachycardia and lower systolic blood pressure, higher CRP, d-dimer, and NT-proBNP. This group presented higher estimated systolic pulmonary artery pressure (49 IQR39-62mmHg vs 43 IQR32-53mmHg, p<0.001) and shorter pulmonary artery acceleration time (65 IQR55-85ms vs 81 IQR63-102ms; p<0.001). Patients with elevated INR had more often a sPESI of 1 or higher (78%vs60%, p=0.003). Cox regression model revealed that age, leukocyte level, SBP, neoplasm, and INR are associated with higher risk of death (p<0.001). Finally, elevated INR was associated with higher in-hospital (13%vs3%; p<0.001), 30-day (19%vs6%; p<0.001), and long-term mortality (p<0.001). Summing up, elevated INR on admission is frequent in patients with PE, reflects worse clinical condition and is related to PE severity and prognosis.

Keywords: coagulation impairment, international normalised ratio, mortality, pulmonary embolism, thrombosis

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1. Background

Pulmonary embolism (PE) is one of the most common cardiovascular causes of death. About 10% of patients with PE belonging to the high-risk group present clinical picture of the acute heart failure (AHF), require hemodynamic support and prompt reperfusion therapy, usually thrombolysis [1]. However most of the PE patients are normotensive, non-high risk, but constitute a very heterogeneous group with subpopulation of subjects who during following hours or days may abruptly become hemodynamically unstable, develop cardiogenic shock and die due to acute right ventricular (RV) failure. The identification of the early prognostic factors of deterioration is crucial for such patients' assessment and optimal therapy [1-4]. Previous research have shown the parameters reflecting RV dysfunction, like RV to left ventricular diameter ratio and tricuspid annular plane systolic excursion (TAPSE), contributing to the worse clinical presentation [5, 6]. Moreover, we and others have shown the association between PE severity and supraventricular arrhythmias [7, 8].

In patients with acute heart failure (AHF) profound disorders in haemostasis have been described in the form of activation of coagulation as well as activation of fibrinolysis with elevated D-dimer levels [9, 10]. They are thought to be caused by inflammation and neurohormonal activation [11, 12]. On the other hand in critically ill patients including patients with AHF a potentially reversible decrease in concentration of plasma coagulation factors, thrombocytopenia has been observed as a manifestation of disseminated intravascular coagulation (DIC) or a DIC-like consumptive coagulopathy [13, 14]. Among various not fully understood causes of which acute liver failure and hemodilution have been reported [13]. It is worthy to highlight, that there are many data confirming the value of hemostasis related parameters in prognostic assessment of ICU patients [15].

Prothrombin time international normalised ratio (INR), a surrogate of prothrombin time (PT), was initially designed for patients on warfarin to estimate therapeutic range. In

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clinical practice INR is also applied as a sensitive marker of coagulation abnormalities and as the indicator of severe liver dysfunction [16, 17]. In PE patients acute RV failure results in systemic congestions and multiorgan failure encompassing an acute liver insufficiency which can lead to the impairment of coagulation factors synthesis [16, 17]. Data concerning a prognostic value of an increased INR in patients with PE are scarce but available results seem to confirm its value in predicting poor short-term outcome [13, 18, 19]. Futhermore, there is lack of data on relation of INR with long-term mortality after acute PE.

2. Objectives

Aim of our study was to investigate associations between the coagulation impairment, expressed by INR and clinical, laboratory and echocardiographic parameters of PE severity as well as its predictive power for poor outcome assessment expressed as in-hospital, 30-day, and one-year mortality.

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3. Patients and Methods

The study cohort consisted of 1004 consecutive patients with primary diagnosis of acute PE. Patients were aged 18 years or older and were hospitalized in the Department of Cardiology at University Hospital in Bialystok, Poland, from January 1st, 2004, to December 31st, 2018 or at Department of Internal Medicine and Cardiology in Warsaw, from January 1st, 2015, to December 31st, 2017. Their medical records were retrospectively analyzed. In all patients, the diagnosis of PE was established by computed tomography pulmonary angiography

The standard biochemical parameters were analyzed at index hospitalization, including INR assessment at the time of hospital admission, and we found that this parameter was not evaluated at admission in 156 cases. Therefore study group consisted of 848 patients with available INR test. On this basis, two groups were distinguished:

1) with the correct INR value ≤ 1.2 (596 patients), and

2) with elevated INR value > 1.2 (252 patients).

Because of the incomplete history of oral anticoagulation, the effect of this treatment was not taken into consideration in the analysis.

The analysis included demographic and clinical characteristics, including symptoms, hemodynamic profile, oxygen saturation, length of hospital stay, risk factors for PE, and comorbidities. The Simplified Pulmonary Embolism Severity Index (sPESI) was calculated retrospectively [1],. The following laboratory parameters were measured at admission: complete blood count, D-dimer, and estimated glomerular filtration rate (eGFR, using the Modification of Diet in Renal Disease formula). Transthoracic echocardiography was performed within 24 hours of admission, and the following parameters were analyzed: left ventricular ejection fraction (LVEF) estimated by visual assessment, left atrial dimensions, presence of RV

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contractility disturbances, systolic pulmonary artery pressure estimated using the simplified Bernoulli equation (SPAP = 4*V*maxTR2 +RAP, where*V*maxTR is the maximal velocity of tricuspid regurgitant jet and RAP is the estimated right atrial pressure on the basis of inferior vena cava diameter and diameter respiratory changes), pulmonary artery acceleration time, and presence of thrombi in the right heart cavities or in the pulmonary artery. As a standard procedure during index hospitalization, color duplex ultrasound of the lower extremity was performed to assess the presence of deep vein thrombosis (DVT).

Moreover, on admission a standard 12-lead electrocardiogram was performed to analyze the leading rhythm and the presence of significant tachycardia (>110 beats/min). Furthermore, electrocardiogram was analyzed to detect intraventricular conduction disturbances and signs of right ventricular overload.

- Study Outcomes

All-cause mortality was the primary outcome. Data on all-cause in-hospital mortality were obtained from medical records. The long-term outcome of the study cohort that was prevoiusly hospitalized at the Department of Cardiology in Bialystok, was retrieved from a national death registry database provided by the Polish Ministry of Home Affairs. A censored date of April 30th, 2019, was determined to allow a minimum follow-up of 4 months for living patients (ranged from 4 to 148 months).

- Statistical Analysis

The normality of distribution was assessed with use of the Kolmogorov-Smirnov test with the Lilliefors correction and the Shapiro-Wilk test. The distribution of continuous variables was other than normal. The quantitative parameters were presented by a median and interquartile range and the nominal parameters with the use of percentages.

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The nonparametric U Mann-Whitney test was used to compare quantitative variables without normal distribution between the groups. The statistical analysis of categorical variables was done using the chi-square test of independence. The analysis of the parameters affecting survival was performed with the use of Cox proportional hazards model. Furthermore, the Kaplan-Meyer method was used to estimate long-term survival for each INR group [15]. Differences between survival curves in the two groups were evaluated using the long-rank test.

For all tests, a p value of less than 0.05 was considered as statistically significant. Statistical analysis was performed using the Statistica 13.3 software (TIBCO Software Inc., Palo Alto, CA, USA) and STATA 15.1 software (StataCorp, College Station, Texas, USA).

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4. Results

The data regarding clinical characteristics, outcome, laboratory parameters and risk score profiles of the study population classified according to INR value are shown in Tables 1–3.

The groups did not differ in age, sex or in clinical symptoms on admission between groups (Tables 1, 2).

Table 1. Characteristics and outcome of the patients with pulmonary embolism stratified for the INR value: normal INR (≤ 1.2) group and elevated INR (> 1.2).

	INR ≤ 1.2 (n = 596), Me (Q1-Q3) or %	**INR > 1.2 (n = 252), Me (Q1-Q3) or %**	**P value**
Age, years	68 (55 – 79)	70 (52 – 78)	0.5
Males	47%	48%	0.77
Current smoker	13%	13%	0.93
Ex-smoker	38%	25%	*0.046*
Length of hospital stay, days	7 (5-10)	9 (5-12)	*0.009*
Comorbidities			
Cardiovascular disease	11%	17%	0.2

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Arterial hypertension	59%	60%	0.86
Diabetes	13%	20%	*0.04*
Chronic obstructive pulmonary disease	10%	10%	0.99
History of stroke	5%	11%	*0.01*
Mortality			
In-hospital mortality	3%	13%	*<0.001*
30-day mortality	6%	19%	*<0.001*

Me (Q1-Q3) or % - data presented as a median and interquartile range or a percent of the group

Abbreviations: INR - international normalized ratio

Table 2. Comparison of the PE risk score parameters, and sPESI score values in the investigated population stratified for the INR value: normal INR (≤ 1.2) group and elevated INR (> 1.2).

	INR ≤ 1.2 (n = 596), **Me (Q1-Q3) or %**	**INR > 1.2** **(n = 252),** **Me (Q1-Q3) or %**	**P value**

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PE associated with DVT	62%	58%	0.43
Risk factors			
Immobilization	19%	19%	0.89
Malignancy	21%	19%	0.71
Pregnancy/Delivery	3%	1%	0.76
Recurrent PE	6%	9%	0.62
sPESI score ≥ 1	60%	78%	*0.003*
Hemodynamic profile on admission			
Heart rate, beats per minute	86 (74 – 100)	90 (77 – 109)	*<0.001*
Tachycardia (> 110 beats/minute)	14%	29%	*0.006*
Systolic blood pressure <100mmHg	4%	12%	*<0.001*
Systolic blood pressure, mmHg	130 (120 – 145)	125 (112 – 140)	*<0.001*

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Oxygen saturation, %	95 (92 – 97)	95 (91 – 98)	0.54

Me (Q1-Q3) or % - data presented as a median and interquartile range or a percent of the group

Abbreviations: DVT - deep vein thrombosis, INR - international normalized ratio, PE - pulmonary embolism

Furthermore, the groups did not differ according to the established PE risk factors, including co-existing deep vein thrombosis (Table 2).

The analysis of comorbidities shown significantly higher prevalence of diabetes and history of stroke in patients with elevated INR (Table 1).

The hemodynamic profile on admission revealed a higher incidence of significant tachycardia (>110 beats/min) in patients with elevated INR (Table 2). Patients with normal INR value had lower heart rate and higher systolic blood pressure, while saturation did not differ between groups (Table 2). The analysis of sPESI showed that patients with elevated INR had more often the sPESI of ≥1 compared to patients with normal INR (Table 2).

The analysis of laboratory parameters showed several differences between groups. The group with elevated INR presented higher level of inflammatory markers, such as C-reactive protein or leukocyte level (Table 3). This group had higher concentration of d-dimer, while fibrinogen level was lower (Table 3). Furthermore, patients with elevated INR had higher concentrations of NT-proBNP (Table 3). On the other hand these patients had lower levels of total cholesterol, LDL, HDL and triglycerides (Table 3).

Among echocardiographic parameters in patients with elevated INR higher estimated systolic pulmonary artery pressure and shorter median pulmonary artery acceleration time were found, as well as significantly lower left ventricular ejection fraction and higher left

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atrial dimension (Table 3). Furthermore patients with elevated INR had higher frequency of a thrombus observed within right heart (Table 3). The analysis of the heart rhythm did not revealed differences, however patients with elevated INR had more often ECG changes revealing righ ventricular overload (Table 3).

Table 3. Comparison of the baseline laboratory, echocardiographic, and electrocardiographic parameters in patients with pulmonary embolism stratified for the INR value: normal INR (≤ 1.2) group and elevated INR (> 1.2).

	INR ≤ 1.2 (n = 596), **Me (Q1-Q3) or %**	**INR > 1.2** **(n = 252),** **Me (Q1-Q3) or %**	**P value**
Biochemical parameters			
eGFR, ml/min/1.73m^2	75 (59 – 92)	71 (46 – 88)	*0.004*
D-dimer, ng/ml	5.3 (2.5 – 12)	9 (3.4 – 18.2)	*0.026*
Hemoglobin, g/dl	13 (11.7 – 14.3)	12.6 (11.3 – 14.1)	0.095
Leukocytes, 10^3/ul	9.1 (7.1 – 11.8)	10 (7.5 – 13.6)	*0.007*
Platelets,	218 (177 – 277)	207 (143 – 267)	*0.014*
C-reactive protein,	26.6 (10.3 – 76.5)	56 (18.6 – 100.3)	*<0.001*
Fibrinogen	433 (353 – 544)	394 (259 – 471)	*0.003*
Iron	43 (26 – 65)	23 (15 – 51)	*0.011*

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NT-proBNP, pg/ml	463 (142 – 2513)	1411 (142 – 6214)	*0.046*
Total cholesterol	174 (151 – 200)	149 (127 – 188)	*<0.001*
Low-density lipoprotein	116 (94 – 138)	98 (76 – 125)	*<0.001*
High-density lipoprotein	37 (30 - 45)	34 (24 – 41)	*<0.001*
Triglycerides,	113 (91 – 149)	109 (81 – 136)	*0.001*
Alanine aminotransferase, IU/l	22 (17 – 35)	25 (17 – 59)	*0.004*
Aspartate aminotransferase, IU/l	23 (17 – 34)	29 (18 – 55)	*0.001*
Echocardiography			
LVEF, %	60 (55 – 60)	55 (50 – 60)	*<0.001*
Left atrium, cm	3.8 (3.4 – 4.1)	3.9 (3.5 – 4.5)	*0.02*
eSPAP, mmHg	43 (32 – 53)	49 (39 – 62)	*<0.001*
ACT, ms	81 (63 – 102)	65 (55 – 85)	*<0.001*
Right ventricular wall contractility disturbances	44%	69%	*<0.001*

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McConnell's sign	13%	21%	*<0.001*
Inferior vena cava, mm	17 (14 – 20)	18 (15 – 23)	*0.04*
Thrombus within right heart	3%	7%	*0.016*
Electrocardiogram			
Rhythm			0.18
Sinus rhythm	83%	87%	
Atrial fibrillation persistent	7%	12%	
Atrial fibrillation paroxysmal	10%	1%	
SIQIIITIII sign	23%	31%	*0.027*
dekstrogram	3%	11%	*<0.001*
Right bundle branch block	10%	13%	0.3

Me (Q1-Q3) or % - data presented as a median and interquartile range or a percent of the group

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Abbreviations: ACT- acceleration time; eGFR – estimated glomerular filtration rate; eSPAP- estimated systolic pulmonary artery pressure; INR - international normalized ratio; LVEF - left ventricular ejection fraction; NT-proBNP - n-terminal pro-brain natriuretic peptide.

The Cox regression model revealed that standard parameters on admission, including age, leukocyte level, systolic blood pressure, and history of neoplasm (present or within 5 years), combined with INR are associated with higher risk of death after acute PE ($p<0.001$) (Table 4). Among these parameters neoplasm history had the highest negative impact on survival (HR 4.17) (Table 4).

Table 4. COX regression model for risk of death after acute PE in investigated population ($p<0.001$).

	Hazard ratio	**Standard error**	**Z**	**P**	**95% Confidence interval**
INR	1.62	0.256	3.06	0.002	1.19 - 2.21
Age	1.05	0.007	7.04	0.000	1.03 - 1.06
White blood cells	1.02	0.007	2.84	0.005	1.01-1.03
Systolic blood pressure	0.988	0.003	-3.34	0.001	0.982-0.995
Neoplasm	4.17	0.676	8.82	0.000	3.04 – 5.73

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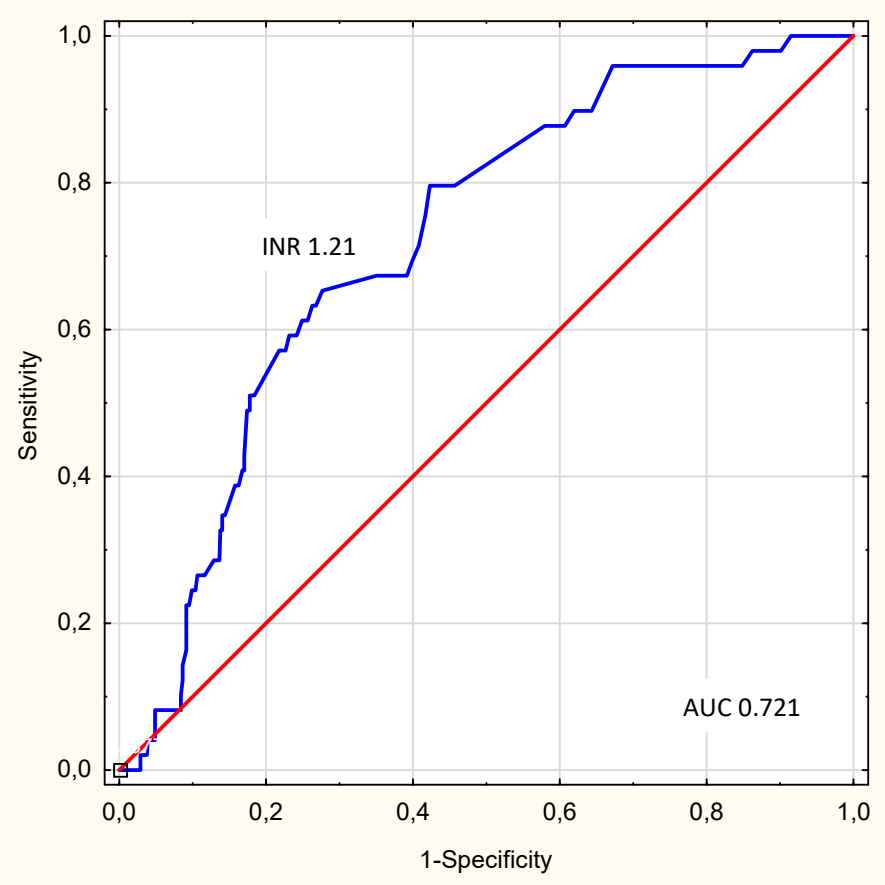
Finally, it was observed, that elevated INR value was associated with higher in-hospital and 30-day mortality (Table 1). Moreover, this trend continued in long-term observation. The ROC analysis revealed the predictive cut-off value for the risk of in-hospital mortality for INR higher than 1.21 (sensitivity 0.653, specificity 0.723; AUC 0.721; confidence interval - CI – 0.66 – 0.79) (Figure 1) and 30-day mortality for INR higher than 1.13 (sensitivity 0.761, specificity 0.599; AUC 0.718; confidence interval - CI - 0.66 – 0.78) (Figure 2). The Kaplan-Meier analysis showed a significantly worse survival in patients with elevated INR in comparison with patients with normal INR ($p< 0.001$) (Figure 3).

Figure 1. ROC curve showing the INR predictive value for the risk of in-hospital death.



Abbreviations: AUC, area under curve; INR, international normalized ratio; ROC, receiver operating characteristic.

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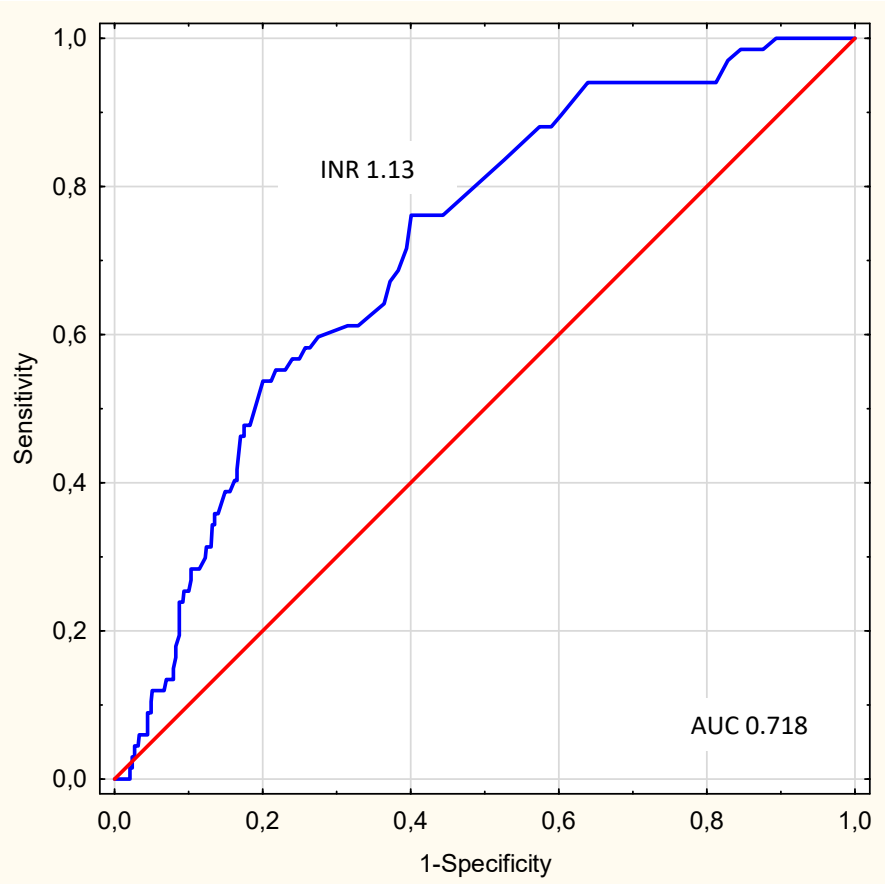
Figure 2. ROC curve showing the INR predictive value for the risk of 30-day death.



Abbreviations: AUC, area under curve; INR, international normalized ratio; ROC, receiver operating characteristic.

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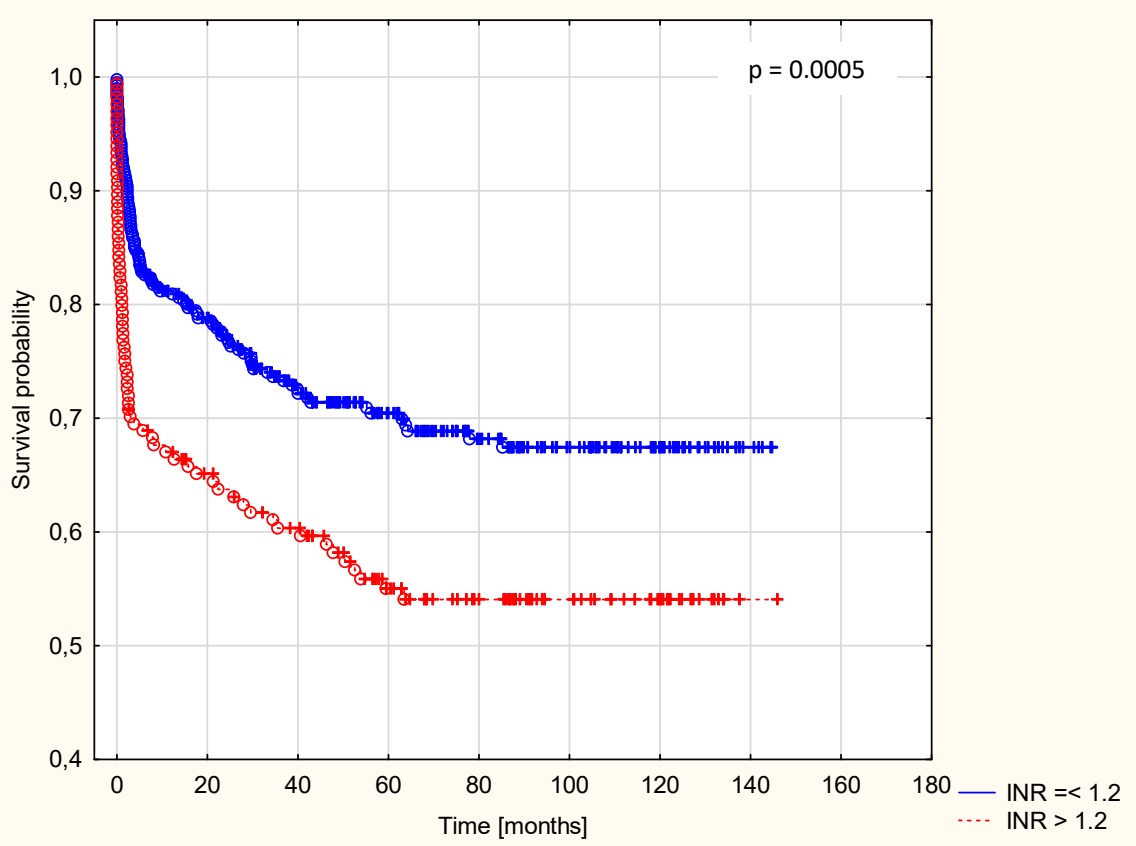
Figure 3. The Kaplan-Meyer survival curves in PE patients comparing survival between two groups according to INR value: normal INR (≤ 1.2) group and elevated INR (> 1.2) group.



Abbreviations: INR, international normalized ratio;

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Discussion

Our study revealed for the first time that in patients hospitalized with acute PE, INR > 1.2 is related to substantially increase in hospital, 6-month as well as long-term mortality. The cut-off value of 1.2 for INR was determined on the basis of the norm adopted from above for this indicator [20, 21].

Moreover, not all patients had information about previous anticoagulation, therefore the impact of this treatment on INR value can not be investigated. The increase of INR in our investigated population may be a result of overlaping organ impairment including heart failure, liver dysfunction and secondary to neoplasm abnormalities rather than the effect of anticoagulant treatment [13, 14, 18, 19]. The mechanism of INR increase is not fully understood and in our population the data regarding anticoagulation are lacking, therefore this issue requires further research.

The case reports as well as large group studies show, how difficult is to establish exact mechanism of clot formation and the treatment targets in patients developing PE with known coagulation impairment [22-24]. However, this abnormality may be explained by decrease of generation of clotting factors in liver malfunction or injury or secondary impairment due to congestion or disseminated intravascular coagulation, that may be observed in patients with massive PE [13, 14, 25, 26]. Therefore, the elevated INR value, that is followed by occurrence of PE, may itself reflect the severity of coagulation system abnormalities irrespective the oral anticoagulation is taken or not. The thrombus formation reflects the hypercoagulable state and confirms the impairment of patient's homeostasis resulting in clot formation [26-28]. These findings may be indirectly confirmed in our study group by echocardiographic results: more frequent occurrence of thrombi in the right heart and a echocardiographic signs of right heart, impairment (which may lead to the liver congestion) in patients with elevated INR. Another aspect is that the effect of anticoagulation is related to patient's compliance, which seems to

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be uncertain in the face of PE event. Previously researchers analyzed the adherence to anticoagulation at the time of acute PE diagnosis and shown that subtherapeutic anticoagulation in the weeks before PE onset were common [29].

Our study revealed that 29.7% of patients with known INR at admission had increased value of this parameter. This finding was also shown in other study, in which authors have found approximately 9% of patients admitted to hospital with acute PE, had an elevated INR without known anticoagulation [16, 17]. Further, these patients were significantly more likely to have a higher sPESI score, as well as prolonged hospital stay [16, 17], which observation is similar to observed in our research. In our analysis Cox regression model revealed that standard parameters on admission, including age, leukocytes, systolic blood pressure, and neoplasm, combined with INR are associated with higher risk of death after acute PE. Among these parameters the highest HR was observed for neoplasm.

We have shown for the first time that elevated INR was associated with higher in-hospital, 30-day as well as long term mortality, therefore INR is the marker contributing to short as well as long term prognosis. This finding was further confirmed in retrospective calculation of sPESI, that predicts 30-day mortality of PE patients [1]. Therefore, this study is consistent with previous that confirmed INR as parameter helpful in reclassification of PE patients into more appropriate risk groups [13, 18, 19], that should translate into more careful in-hospital as well as long-term outpatient care, that might result in an improvement of post-PE patients survival.

Conclusions: Abnormal INR value on admission was a frequent phenomenon in patients with acute PE. Elevated INR seems to reflect worse clinical and haemodynamic status and may be related to PE severity. Furthermore elevated INR is associated with higher short and long-term mortality after acute PE.

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Author Contributions

Conceptualization, methodology, resources, software, writing—original draft, K.P.K, E.S., M.C., R.M, I.K, A.K., U.K., M.S., M.P., A.F., K.K., P.P., W.J.M., K.K., B.S.; data curation, visualisation K.P.K, E.S., R.M, I.K, A.K., U.K., M.S., M.P., A.F., K.K.; formal analysis, investigation, supervision, writing—review and editing, validation, K.P.K, E.S., M.C., R.M, I.K, A.K., U.K., M.S., M.P., A.F., K.K., P.P., W.J.M., K.K., B.S.; project administration, K.P.K. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Medical University of Bialystok (R-I-002-116-2015).

Informed Consent Statement

Patient consent was waived due to retrospective study.

Data Availability Statement: Data supporting reported results on request.

Conflicts of Interest: The authors declare no conflicts of interest.

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