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Antithrombin activity as a significant predictor of early mortality in pulmonary embolism patients

Antitrombinska aktivnost kao značajan prediktor ranog mortaliteta kod bolesnika sa embolijom pluća

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Abstract

Background/Aim. The role of antithrombin (AT) activity in predicting early mortality in patients with pulmonary embolism (PE), measured at an early stage of the disease, has not yet been investigated. Therefore, the aim of the study was to examine the predictive value of AT activity for all-cause 30-day mortality, measured in consecutive PE patients on admission to the hospital. **Methods**. This single-center clinical retrospective cross-sectional study followed consecutive patients with acute PE from 2014 to 2021. On admission to the hospital, venous blood was taken from patients for laboratory analyses including determination of AT activity. The basic parameters of the patients were recorded on admission, and through the univariate analysis, their connection with 30-day mortality was tested. The predictive significance of AT values for 30-day mortality was tested through quartile values by comparing the first quartile with all others together. Cox regression model analysis was used in the multivariate analysis where one parameter, marked as significant in the univariate analysis, was added to the basic model (AT, age, and risk affiliation in two groups). **Results**. A total of 378 PE patients were included in the study. The total all-cause 30-day mortality was 7.9% (30 patients). Patients with AT activity in the first quartile had significantly higher early mortality compared with those having AT activity in the other quartiles combined (log-rank $p = 0.001$). AT retained a significant predictive value for early mortality in the multivariate analysis despite the comorbidity present, which also significantly affected mortality. **Conclusion**. Low AT activity measured on admission in PE patients is a significant and independent predictor of 30-day mortality.

Key words:
antithrombins; mortality; prognosis; pulmonary embolism.

Apstrakt

Uvod/Cilj. Uloga aktivnosti antitrombina (AT) u predviđanju rane smrtnosti kod bolesnika sa plućnom embolijom (PE), merena u ranoj fazi bolesti, još uvek nije istražena. Cilj rada bio je da se ispita prediktivna vrednost aktivnosti AT za 30-dnevni mortalitet, merena na prijemu, kod bolesnika sa PE. **Metode**. Retrospektivnom studijom preseka, praćeni su svi bolesnici sa akutnom PE, lečeni u našoj Klinici u periodu od 2014. do 2021. godine. Bolesnicima je na prijemu uzimana venska krv za laboratorijske analize uključujući i merenje aktivnosti AT. Osnovni podaci o bolesnicima beleženi su na prijemu, a primenom univarijantne analize testirana je njihova povezanost sa 30-dnevnim mortalitetom. Prediktivni značaj vrednosti AT za 30-dnevni mortalitet testiran je kroz kvartilne vrednosti tako što je prvi kvartil poređen sa svim ostalima zajedno. *Cox*-regresiona analiza korišćena je u multivarijantnoj analizi, gde je osnovnom modelu (AT, godine i pripadnost riziku u dve grupe) dodavan po jedan parametar, označen kao značajan u univarijantnoj analizi. **Rezultati**. U studiju je bilo uključeno ukupno 378 bolesnika sa PE. Ukupan 30-dnevni mortalitet iznosio je 7.9% (30 bolesnika). Bolesnici sa aktivnošću AT u prvom kvartilu imali su značajno veći rani mortalitet u poređenju sa onima koji su tu aktivnost imali u ostalim kvartilima zajedno (*log rank* $p = 0{,}001$). Varijabla AT je zadržala značajnu prediktivnu vrednost za rani mortalitet i u multivarijantnoj analizi bez obzira na prisutni komorbiditet, koji je takođe značajno uticao na mortalitet. **Zaključak**. Niska aktivnost AT izmerena na prijemu kod bolesnika sa PE je značajan i nezavisan prediktor 30-dnevnog mortaliteta.

Ključne reči:
antitrombini; mortalitet; prognoza; pluća, embolija.

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Introduction

Pulmonary embolism (PE) is the third cause of cardiovascular mortality, just behind acute myocardial infarction and stroke. The mortality risk from PE is highest in the first 30 days and gradually decreases over time, reaching the mortality rate of a normal population. The overall mortality rate from PE is around 9.7% but could vary significantly depending on associated comorbidity. For instance, the mortality rate of PE patients with malignancy is 19.1%, but only 3.6% in those without malignancy [1]. The current guideline suggests the assessment of early mortality risk prior to choosing the optimal treatment strategy [2]. According to the newest guideline, patients who are hypotensive or in shock should be treated with reperfusion therapy, such as fibrinolysis, or catheter-guided and surgical thrombectomy. PE patients who are not hypotensive, even with imaging or laboratory signs of increased right ventricular (RV) load, should be anticoagulated and closely monitored, and reperfusion therapy should be used only if clinical deterioration occurs. Previous studies reported higher survival of such PE patients (with intermediate-high risk PE) who were treated initially with fibrinolysis but with higher cost because of increased major bleeding [3–5]. Therefore, additional parameters for assessing early mortality in PE are warranted in order to identify PE patients who are at risk of sudden deterioration and who would benefit from immediate reperfusion therapy.

Antithrombin (AT) is a main natural anticoagulant, and its acquired deficiency has already been reported in published data of patients with massive PE [6]. However, the predictive value for early mortality in PE of such acquired AT deficiency has not been investigated so far. The aim of the study was to test the predictive value of AT for 30-day mortality in consecutive PE patients through univariate and multivariate analyses, including the most present comorbidities.

Methods

A single-center retrospective cross-section study included all consecutive PE patients admitted to the Clinic for Emergency Internal Medicine at the Military Medical Academy in Belgrade, the Republic of Serbia, from November 2014 to May 2021. The study was approved by the institutional Ethics Committee (No 160/2019, from December 26, 2019). Diagnosis of PE was confirmed with multi-detector CT pulmonary angiography in all patients. All patients were treated with the highest regard as per current guidelines [2]. Using 30-day mortality risk as a baseline, PE patients were classified as high-risk (presenting with shock or hypotension where systolic pressure was below 90 mmHg, or normotensive patients with signs of RV dysfunction on transthoracic echocardiography or increased troponin in laboratory analysis) or low-risk (normotensive PE patients with no signs of RV dysfunction). Patients' baseline characteristics were obtained on admission. Antecubital venipuncture was used to collect blood samples for full blood count and laboratory analysis of troponin I (TnI), C-reactive protein (CRP) levels, and activity of AT. Blood samples were collected after the initial *iv* bolus of unfractionated heparin and prior to eventual thrombolytic treatment. Except for the initial anticoagulation with heparin, all patients were not on anticoagulant treatment before admission. The initial dose of heparin was 80 U/kg but did not exceed 5,000 U, as per protocol for the treatment of PE. The glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault equation. Laboratory analyses for AT activity were performed using an automatic coagulometer, type BCS-XP Siemens Healthcare Diagnostics Products GmbH (Marburg, Germany). All baseline characteristics were compared in univariate analysis between the group of PE patients who died in the first 30 days and those who survived. When a significant association with early mortality was identified among tested characteristics, a Cox regression model analysis was used in a multivariate analysis of AT predictive value. AT, age, and risk stratification were used in a baseline model of a Cox regression analysis, and other co-factors were added separately, building different models that represented different associated comorbidity. When AT activity values were assessed as a predictor of early mortality, a quartile with values associated with increased frequency of the observed outcome was compared with other quartiles together.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, and continuous variables as means with standard deviations. For values without normal distribution, the nonparametric Mann-Whitney *U* or Kruskal-Wallis H tests were used, with the results expressed as the median of the interquartile range. A Hazard Ratio (HR) was calculated for the observed outcome using multivariable Cox regression model analysis. Optimal cut-off values and their sensitivity and specificity, along with positive and negative predictive values, for the prediction of 30-day mortality were calculated in MedCalc for Windows version 12.7.0.0 (MedCalc Software, Acacialaan, Belgium). Comparisons of nonparametric variables and frequencies of categorical data between survivors and deceased patients were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Differences with a *p*-value of ≤ 0.05 were considered significant.

Results

During the follow-up period, 378 PE patients overall entered the analysis. Among them, 191 (50.5%) were men, and 187 (49.5%) were women. All-cause 30-day mortality was 30 patients (7.9%). Increased mortality was noticed in patients with unprovoked PE, chronic heart failure, coronary artery disease, and atrial fibrillation. Additionally, PE patients with diabetes mellitus (DM), chronic kidney disease, and malignancy had also increased early mortality. Other patients' characteristics on admission to the hospital and their relation to the 30-day mortality rate are shown in Table 1.

The median value of AT activity, measured on admission, in PE patients who died in the first 30 days was significantly lower than the value in patients who survived [0.73

(0.60–0.96) vs. 0.89 (0.78–0.99), respectively; $p = 0.002$]. Additionally, PE patients with AT activity values within the first quartile had significantly lower survival as compared with the patients who had AT activity values within other quartiles (Figure 1).

A cut-off value of AT activity for increased early mortality rate was ≤ 0.8 U/L (AUC = 0.670, $p = 0.008$) with 66.7% sensitivity and 70.7% specificity. The positive predictive value was 16.4%, and the negative predictive value was 96.1% (Figure 2).

Table 1

Baseline characteristics of the pulmonary embolism (PE) patients and 30-day mortality

Characteristic	30-day mortality		*p*
	yes n = 30	no n = 348	
Age (years), mean ± SD	69 ± 15	60 ± 16	**0.003**
Sex, n (%)			0.257
men	12 (40.0)	179 (51.4)	
women	18 (60.0)	169 (48.6)	
Factors that provoked PE, n (%)			**< 0.001**
unprovoked PE	9 (30.0)	189 (54.3)	
major transient	4 (13.3)	61 (17.5)	
minor persistent	9 (30.0)	36 (10.3)	
minor transient	1 (3.3)	35 (10.1)	
major persistent	7 (23.3)	27 (7.8)	
COPD, n (%)	1 (3.3)	24 (6.9)	0.708
CHF, n (%)			**< 0.001**
HFrEF	3 (10.0)	5 (1.4)	
HFmrEF	4 (13.3)	14 (4.0)	
HFpEF	4 (13.3)	21 (6.0)	
Smokers, n (%)	3 (10.0)	65 (18.7)	0.272
Obesity (BMI > 30 kg/m^2), n (%)	5 (16.6)	102 (29.3)	0.278
Localization of DVT, n (%)			0.964
distal	13 (44.4)	181 (52.0)	
proximal	17 (56.6)	162 (46.6)	
Arterial hypertension, n (%)	21 (70.0)	187 (53.7)	0,125
Coronary artery disease, n (%)	7 (23.3)	28 (8.0)	**0.013**
Diabetes mellitus, n (%)	9 (30.0)	51 (14.7)	**0.037**
Atrial fibrillation, n (%)			**< 0.001**
paroxysmal	10 (33.3)	26 (7.5)	
permanent	2 (6.7)	15 (4.3)	
Creatinine clearance < 30 mL/min, n (%)	5 (16.7)	16 (4.6)	**0.019**
Creatinine clearance < 60 mL/min, n (%)	15 (50.0)	79 (22,7)	**0.003**
Malignancy, n (%)	9 (30.0)	40(11.5)	**0.007**
CRP (mg/L), median (IQR)	95.9 (59.5–161.1)	44.7 (19.0–108.0)	**< 0.001**
Total leukocyte count (×10^9), median (IQR)	12.7 (10.3–15.6)	9.7 (7.6–12.5)	**< 0.001**
Fibrinolysis, n (%)	13 (43.3)	168 (48.3)	0.704

COPD – chronic obstructive pulmonary disease; CHF – chronic heart failure; HFrEF – heart failure with reduced ejection fraction (EF); HFmrEF – heart failure with mid-range EF; HFpEF – heart failure with preserved EF; BMI – body mass index; CRP – C-reactive protein; IQR – interquartile range; SD – standard deviation.
Statistically significant values are bolded.

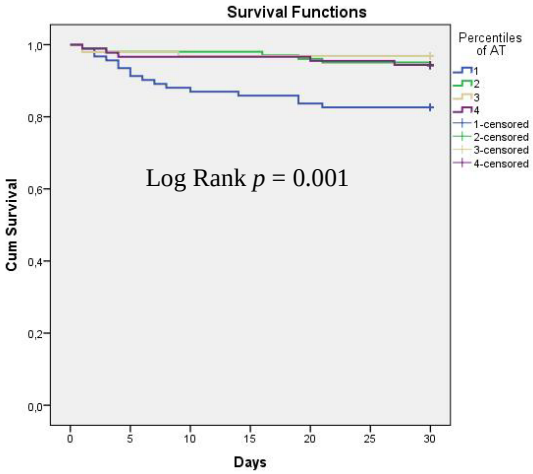


Fig. 1 – Kaplan-Meier survival curve regarding quartiles of antithrombin (AT).

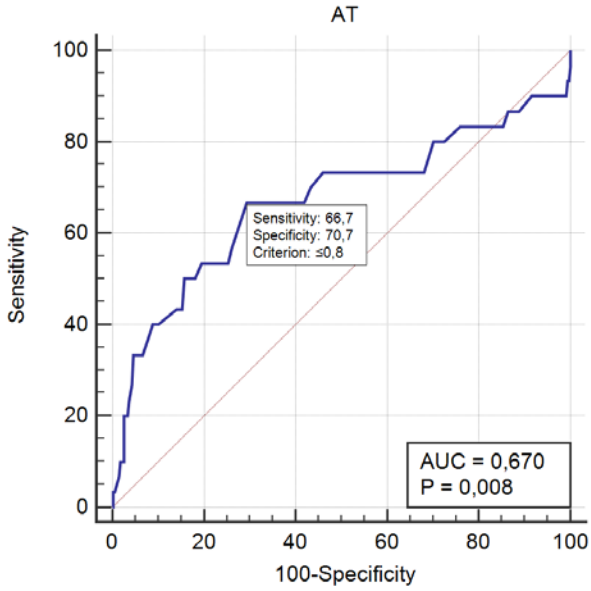


Fig. 2 – Receiver operating characteristic (ROC) curve depicting the cut-off value of antithrombin (AT) activity for increased early mortality. AUC – area under curve.

Table 2

Predictive value of antithrombin (AT) and adjusted hazard ratio (HR) for 30-day mortality

Adjusted to	HR (95% CI) of AT as a 30-day mortality predictor	*p*
Malignancy, age, and risk in two groups	2.75 (1.25–6.06)	0.012
Diabetes mellitus, age, and risk in two groups	2.75 (1.33–5.68)	0.006
HFrEF, age, and risk in two groups	2.58 (1.16–5.70)	0.020
Coronary artery disease, age, and risk in two groups	2.80 (1.36–5.79)	0.005
Atrial fibrillation, age, and risk in two groups	2.50 (1.21–5.18)	0.013
Chronic kidney disease (CrCl < 60 mL/min), age, and risk in two groups	2.43 (1.15–5.14)	0.006
Inflammation (CRP and TLC), age, and risk in two groups	2.45 (1.15–5.18)	0.020
Fibrinolysis and age	3.36 (1.61–6.99)	0.001

HFrEF – heart failure with reduced ejection fraction; CrCl – creatinine clearance; CRP – C-reactive protein; TLC – total leukocyte count; CI – confidence interval.

Cox proportional hazards model showed that AT was a significant predictor of early mortality when adjusted to age and risk in two groups as co-factors. When different comorbidities, shown to be significantly associated with early mortality, were included in this basic model, AT remained a significant and independent predictor of this outcome. When the patients who received fibrinolysis were included in the Cox proportional hazard model (without the risk in two groups as a co-factor due to possible bias), AT remained a significant predictor of 30-day mortality (Table 2).

Discussion

The results of this study have shown that AT activity, measured in PE patients on admission to the hospital, can serve as a reliable early mortality predictor in addition to other conventional predictors of 30-day mortality in PE, already recommended in the current guidelines.

The patients diagnosed with PE may have additional comorbidity that can impact survival. Some of those comorbidities are included in the Pulmonary Embolism Severity Index (PESI) score, which is involved in the assessment of early mortality risk together with imaging and laboratory signs of an increased RV load [2]. However, the results of this study showed that some other comorbidity, not included in the PESI score, may exist in PE patients but still be associated with early mortality, such as DM, chronic kidney disease, atrial fibrillation, coronary artery disease, or markers of inflammation. When adjusted to age and affiliation to one of the two risk groups for early mortality (determined by the presence of clinical and laboratory signs of an increased RV load), AT was a significant predictor of early mortality. When added independently to this Cox proportional hazard model, whether it was malignancy, diabetes, chronic kidney disease, atrial fibrillation, coronary artery disease, or markers of inflammation (CRP and total leukocyte count), AT remained an independent and significant predictor. Furthermore, some of the patients received fibrinolysis in their treatment, which probably had an impact on their survival. Nevertheless, when adjusted to age and fibrinolysis, AT was

still a significant predictor of early mortality. Hence, AT activity measured early in the course of PE can indicate the increased risk of early mortality, independently of other predictors recommended in the guidelines, and thus may influence the decision for optimal therapy. That is especially important in patients with intermediate-high risk PE where routine administration of fibrinolysis is not advised. According to the current guideline, it is advised that patients' subgroup with intermediate-high risk PE be carefully monitored and fibrinolysis be administered only in case of clinical deterioration [2]. According to the results of this study, PE patients with AT activity in the first quartile had a significantly increased 30-day mortality rate. Given that the values of AT in the first quartile are relatively rare, we determined the cut-off value of AT activity for increased mortality rate, which was ≤ 0.8 U/L and could be useful for the clinician when assessing the mortality risk. Hence, low AT activity may indicate increased early mortality risk in intermediate-high risk PE and, therefore, facilitate early administration of fibrinolysis in such patients.

Low AT activity in massive PE could be due to the consumption of AT during the excessive thrombus formation leading to an acquired AT deficiency. Such theory was first implicated by Leitner et al. [6], who have demonstrated that patients with massive PE requiring cardiopulmonary resuscitation have reduced AT levels as compared with PE patients not requiring cardiopulmonary resuscitation. Furthermore, PE patients resuscitated for reasons other than PE (i.e., resuscitation as a result of primary cardiac causes) have a markedly less intense activation of coagulation than patients with PE. Hence, a pulmonary clot itself may likely contribute to coagulopathy. AT has the role of scavenger because it can inhibit free thrombin and free factor Xa more efficiently than it inhibits thrombin and factor Xa located on activated surfaces and in fibrin clots [7]. That may be because this function of AT blocks coagulation and thrombin non-coagulant functions in remote and uninjured areas. The clearance of AT from the circulation by the liver is more rapid when it is in the form of thrombin–AT (TAT) complex [7]. Therefore, in clinically severe thrombosis and thromboembolism, more TAT complexes are formed. The more TAT complexes are formed, the more rapidly AT is cleared from circulation by the liver.

In this study, PE patients with malignancy and low AT activity had also increased early mortality. Earlier studies demonstrated the bidirectional interaction of AT and malignant cells. It was noticed that patients with malignancy have lower AT activity. Furthermore, AT was found to be an inhibitor of metastasis of particular tumors, and some of the tumors can even secrete inhibitors of AT [8–11]. Therefore, decreased AT in malignancy is not only due to consumption but as a consequence of direct AT-tumor interaction.

Cardiovascular comorbidities are the most frequent comorbidities in PE patients [12]. In our study, the most frequent were heart failure, in particular heart failure with reduced ejection fraction (HFrEF), atrial fibrillation, and coronary artery disease. Low values of AT were significant predictors in PE patients with these comorbidities. Interestingly, the low value of AT was also recognized as a significant predictor of cardiovascular mortality.

DM is another frequent comorbidity in PE patients. Scherz et al. [13] stated in their research on over 13,000 PE patients that DM was an independent predictor of early mortality. In fact, they found that stress hyperglycemia was a more precise parameter for mortality assessment and that this glycemic increase measured on admission was more indicative of early mortality in non-diabetics than in diabetics. The existence of DM or chronic hyperglycemia, as well as acute (stress) hyperglycemia, is a known prothrombotic factor that may increase the incidence of venous thromboembolism (VTE) [14, 15]. Numerous published studies have shown that AT activity was decreased both in DM type 1 and 2 [16–18]. The state of hyperglycemia has a strong impact on AT, decreasing its activity. In addition, these studies have shown that normalization of glycemic levels can reverse AT activity. One of the main inhibitors of AT activity identified in hyperglycemia is methylglyoxal. Therefore, in our PE patients with DM, stress hyperglycemia may be one of the mechanisms for acquired AT deficiency and increased mortality.

Various published studies demonstrated an increased risk of PE in patients with chronic kidney disease [19, 20]. In our study, 50% of patients with PE who died in the first 30 days had creatinine clearance below 60 mL/min. Kumar et al. [20] reported that the mortality rate of PE patients with chronic kidney disease was 57% higher than in PE patients without chronic kidney disease. The main mechanism of hypercoagulability in chronic kidney disease is through the increase of tissue factor, coagulation factor VII, XII, and fibrinogen, and decrease of tissue plasminogen inhibitor [21–23]. With a progression of kidney failure toward the terminal phase, there is a larger increase of fibrinogen, thrombin–AT complexes, and acquired protein C (PC) deficiency [24, 25]. In chronic kidney disease with nephrotic syndrome, increased daily loss of AT is the main reason for hypercoagulability [26].

In the last decade, there have been a lot of published data regarding the increased coagulability in inflammation. The baseline mechanism lies in the activation of endothelial cells, platelets, and leukocytes, which leads to the increased formation of tissue factor-rich microvesicles. Furthermore, when inflammation is present, fibrinogen increases, thrombomodulin decreases, and there is an increase in plasminogen activator inhibitor-1 (PAI-1) (leading to decreased fibrinolysis). The consequence of such a process is a hypercoagulable state and a decrement of thrombus resolution [27–29]. The role of neutrophils in thrombosis is also important. When activated, neutrophils can release their decondensed chromatin to extracellular space, forming traps (neutrophil extracellular traps – NETs) for microorganisms, but also promoting thrombosis through activation of platelets and coagulation [30, 31]. In our study, CRP and leukocyte count were used as markers of inflammation and so used in a multivariant analysis of mortality prediction. AT was a significant predictor of early mortality in such a multivariant model. Low activity of AT in inflammation is due to increased removal of AT from the circulation by activated neutrophils. They secret neutrophil elastase and matrix metalloproteinases that cleave

the active loop on AT molecule, which inactivates AT [7]. Therefore, in PE and inflammation, more mechanisms are involved in the occurrence of an acquired AT deficiency.

The clinical implication of the results from this study could be in better understanding of the role of AT in mortality prediction in acute PE where different comorbidities are present. Low AT activity represents a higher mortality risk in PE patients and improves the decision-making process for optimal therapy. A new question, whether AT substitution would make a better survival, arises. So far, there are no published studies with AT substitution in patients with PE without known hereditary AT deficiency. Substitution with recombinant AT was also reported in septic conditions with disseminated intravascular coagulation [31]. The effectiveness was debatable, but the safety profile was encouraging because no significant increase in major bleeding was reported.

Limitations of the study

All patients received an intravenous bolus of unfractionated heparin immediately prior to admission. Taking a blood sample before receiving heparin was virtually impossible, as this anticoagulant was generally given immediately before admission to the intensive care unit since it is recommended not to wait with the initial heparin bolus while a diagnosis was made. The results of a recently published study show that the same intravenous bolus dose of unfractionated heparin in patients with acute myocardial infarction has a significantly smaller effect on AT activity compared to patients with PE in this study [32]. That is evidence that in addition to the known effect of heparin, massive thrombosis has an additional effect on AT activity.

It is unknown whether some patients had congenital AT deficiency, but this is a very rare thrombophilia and would not affect the overall outcome.

Conclusion

PE patients with low AT activity measured on hospital admission have increased 30-day mortality risk. The measurement of AT activity in the early phase of PE could be used in everyday clinical practice when assessing mortality risk prior to the decision for optimal therapy.

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