

Plasma N-terminal pro-brain natriuretic peptide concentrations may help to identify patients with very low-risk acute pulmonary embolism: A preliminary study

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Abstract

Background. Patients with an acute pulmonary embolism (APE) are a heterogeneous group, and some of them may benefit from early discharge and an ambulatory care referral. We aimed to evaluate the use of N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma level assessment in patients with low-risk APE based on clinical findings (0 points on the simplified Pulmonary Embolism Severity Index (sPESI)).

Materials and methods. Preliminary analysis of an ongoing prospective study including 1,151 normotensive patients with at least a segmental APE. In the final analysis, 348 patients with a 0-point sPESI were included. Blood samples were collected within the first 24 h of admission. The clinical endpoint (CE) included APE-related mortality and/or rescue thrombolysis in patients with clinical deterioration.

Results. Clinical endpoints occurred in 3 patients who had higher plasma NT-proBNP levels than study participants with a favorable clinical course (164 [64–650] pg/mL compared to 2,930 [2,285.5–13,965] pg/mL; $p = 0.01$). Receiver operating characteristic (ROC) analysis showed that the area under the curve (AUC) for NT-proBNP for the prediction of the CEs was 0.918 (95% confidence interval [95% CI]: 0.831–1.00; $p = 0.013$). We defined the cutoff value of NT-proBNP at $\geq 1,641$ pg/mL.

Conclusions. Among subjects with 0 points on the sPESI, those with concentrations of NT-proBNP exceeding 1,641 pg/mL might require closer attention; remaining patients could be considered candidates for outpatient treatment. However, these findings warrant further investigation in a large, prospective group of patients.

Key words: N-terminal pro-brain natriuretic peptide, pulmonary embolism, outcome prediction

Cite as

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Background

Acute pulmonary embolism (APE) occurs frequently, with an estimated incidence rate reaching up to 200 cases a year per 100,000 people worldwide.^{1,2} The prevalence of APE increases with age; therefore, in aging populations, such as in Europe, this number is likely to rise. Furthermore, among cardiovascular diseases, APE is the 3rd most common cause of death, behind myocardial and cerebral infarctions.^{1,3} Taking these data into consideration, in the foreseeable future, APE management is going to remain an important challenge for healthcare professionals. Multiple risk factors increasing chances of developing APE have been described, such as trauma, postoperative state, malignancy, inflammatory diseases, COVID-19, congenital coagulation disorders, and many others.

The course of the disease depends on the thromboembolic material burden as well as individual features such as age, comorbidities, etc. Small thrombi may dissolve spontaneously and remain clinically irrelevant. Conversely, rapid occlusion of the pulmonary arteries can lead to substantial increase in pulmonary vessel resistance. As a result, high heart rate and increased right ventricular contractility are required to provide flow through the pulmonary circulatory system. In this case, RV oxygen demand significantly rises, and its insufficient supply may cause myocardial injury. Acute RV volume overload leads to N-terminal pro-brain natriuretic peptide (NT-proBNP) release and may be visualized in imaging studies (e.g., echocardiography and computed tomography (CT)), while plasma cardiac troponin concentration assessments are used to detect myocardial damage.^{3,4}

The clinical spectrum of APE is wide, ranging from asymptomatic to cardiogenic shock. In patients with no signs of RV overload or myocardial damage, the mortality during the acute phase does not exceed 1%, while in cases associated with hemodynamic instability, it can reach up to 60%.⁵ Even though the majority of APE patients do not present with shock or sustained hypotension on admission, some of them are at substantial risk of clinical deterioration; therefore, each individual may require a different approach. Thus, proper initial risk stratification is crucial, as it indicates further optimal management strategies. Recent guidelines issued by the European Society of Cardiology (ESC) suggest that each patient should be categorized into low, low-intermediate, high-intermediate, or high-risk group, based on clinical findings, biomarker assessment and imaging studies.³

Objectives

In the past, when vitamin K antagonists (VKA) were the standard of care, treatment initiation was difficult due to the need for individual dose adjustments. Currently, new oral anticoagulants (NOACs) are available,

and the treatment in a simple dosing scheme can be implemented immediately after diagnosis. Selected individuals may benefit from early discharge and ambulatory treatment; however, identifying them among patients not presenting with hemodynamic instability on admission can be challenging, especially if a properly trained echocardiographer is not immediately available.⁶ Therefore, this study aimed to evaluate the use of NT-proBNP level assessments, which are usually available in any emergency department, in patients with 0 points on the simplified Pulmonary Embolism Severity Index (sPESI).

Materials and methods

Study population

We performed an analysis of an ongoing prospective observational study, “PE-Aware”, registered at ClinicalTrials.gov (unique identifier NCT03916302). The study population consisted of 1,151 adult patients (517 men, 634 women, median age = 67 years [51; 79]), hospitalized in a single referral center for APE between January 2006 and December 2019. None of the participants presented with hemodynamic instability, defined as a systolic blood pressure (SBP) below 90 mm Hg and signs of peripheral hypoperfusion. Diagnostic criteria for APE included the presence of thromboembolic material, visualized on computed tomography pulmonary angiography (CTPA), in at least 1 segmental pulmonary artery with a duration of symptoms not exceeding 14 days before diagnosis. Each individual was managed in accordance with the current guidelines by a physician having unlimited access to the medical records.

Risk stratification was performed as described in the current ESC guidelines. Among subjects with neither signs of RV distress nor cardiac troponin elevation, those with 0 points on the sPESI formed low risk group, while those with sPESI ≥ 1 were classified to intermediate-low risk category. Patients with both signs of RV distress on imaging (echocardiography or CTPA) and elevated myocardial injury markers were included to the intermediate-high risk category, while those meeting only 1 of the 2 criteria mentioned above were classified into the intermediate-low-risk category.³ Patients diagnosed with chronic thromboembolic pulmonary hypertension and participants in therapeutic clinical trials were not included in this study.

An echocardiographic examination was performed within the first 24 h of admission, and the results were digitally recorded. Patients were examined in the left lateral position. The dimensions of the right and left ventricles were measured using the 4-chamber RV-focused view at the level of the mitral and tricuspid valve tips in late diastole, as defined by the R wave of continuous electrocardiographic (ECG) tracing. After recording the tricuspid valve peak systolic velocity with continuous-wave Doppler echocardiography, the tricuspid regurgitation peak

gradient (TRPG) was calculated using the simplified Bernoulli equation. Right ventricular dysfunction was defined as a RV/left ventricle (RV/LV) ratio in the apical 4-chamber view ≥ 1.0 and/or a TRPG ≥ 31 mm Hg.

Biochemical analysis

Blood samples were collected from patients within the first 24 h of admission. The NT-proBNP plasma concentrations were measured quantitatively using an automated sandwich electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). Based on current guidelines and other available scientific data, results above 600 pg/mL were considered elevated.^{3,7,8} Serum cardiac troponin I (cTnI) and high-sensitivity cardiac troponin T (cTnT-hs) levels were measured quantitatively using an automated sandwich electrochemiluminescence (ECL) immunoassay (Roche Diagnostics GmbH). Levels above 0.014 ng/mL for cTnT-hs and 0.1 ng/mL for cTnI were considered elevated.

The clinical endpoint of the study

The clinical endpoint (CE) of the study was designed to reflect fatal and possibly fatal complications if advanced medical care procedures had not been implemented immediately. They were defined as 1) in-hospital, APE-related death and/or 2) rescue thrombolysis performed due to hemodynamic collapse, which was defined as the occurrence of at least 1 of the following: 1) need for advanced life support; 2) SBP below 90 mm Hg for at least 15 min with signs of end-organ hypoperfusion; or 3) need for intravenous catecholamines in vasopressor doses. The CEs analysis concerned the patient's hospital stay.

Statistical analyses

The Shapiro–Wilk test was used to verify the statistical distribution of the analyzed parameters. Parameters characterized by a non-normal distribution were expressed as median followed by interquartile range (IQR). The Mann–Whitney U test was used to compare parameters between the study groups. Categorical variables were compared using Fisher's exact t-test. Youden's index from a receiver-operating curve (ROC) was calculated to identify the optimal cutoff value for NT-proBNP concentration for the prediction of the CEs. Diagnostic performance markers (sensitivity and specificity) were calculated for the chosen cutoff value.

Results

Overall, 410 study participants were classified into the sPESI 0-point group. Subsequently, 62 patients were excluded: 61 due to unknown NT-proBNP concentrations

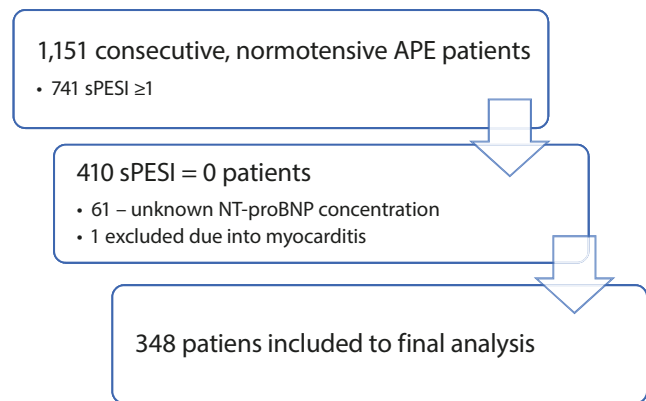


Fig. 1. The flow of patients

APE – acute pulmonary embolism; sPESI – simplified Pulmonary Embolism Severity Index.

and 1 due to myocarditis (diagnosed with the use of cardiac magnetic resonance imaging), as this comorbidity most probably would significantly impact the biochemical test results. In each patient, treatment was initiated with rivaroxaban (15 mg twice/day), apixaban (10 mg twice/day), low molecular weight heparin (LMWH), or unfractionated heparin (UFH). Low molecular weight heparin was administered subcutaneously, in doses adjusted for body weights and glomerular filtration rates (GFRs), and UFH was administered intravenously in doses modified based on the activated partial thromboplastin time. The flow of patients is presented in Fig. 1.

The final analysis included 348 (179 M, 169 F, age median = 52 (39; 66)) sPESI 0-point patients. In this group, rescue thrombolysis was performed due to hemodynamic collapse in 3 (0.86%) patients, and 2 of them survived. The in-hospital APE-related mortality was 0.29% (1 patient). The CEs, which included APE-related death (1 study participant, 0.29%) and/or thrombolysis (3 study participants, 0.86%), occurred in 3 (0.86%) patients.

Patients with a complicated course of the disease had significantly higher plasma NT-proBNP concentrations than those who did not experience the CE. No significant differences between the studied groups for creatinine and D-dimer concentrations were noted. The clinical characteristics of acute pulmonary embolism (APE) study participants are provided in Table 1.

We carefully analyzed the data of patients who experienced the CE and presented them in Table 2. The first patient to reach the CE was a 76-year-old man with a history of stage G4 chronic kidney disease and type 2 diabetes. After several hours, a significant blood pressure drop was observed, which required thrombolytic treatment. Immediate echocardiography revealed RV overload and no signs of LV dysfunction. Similarly, the 2nd patient was a 30-year-old man with a history of ulcerative colitis, who received thrombolytic treatment due to hypotension on the 2nd day of hospitalization. The 3rd patient was a 79-year-old woman

Table 1. Clinical characteristics of APE patients. Data are presented as median followed by interquartile range (IQR) or range in the CE column

Parameter	Non-CE patients (n = 345)	CE patients (n = 3)	All sPESI = 0 patients (n = 348)	p-value
Female/male	168/177	1/2	169/179	–
Age [years]	52 (39–66)	76 (30–79)	52 (39–66)	0.27
HR [bpm]	80 (70–90)	105 (80–105)	80 (70–90)	0.06
SBP [mm Hg]	130 (120–140)	140 (110–160)	130 (120–140)	0.9
NT-proBNP [pg/mL]	164 (64–650)*	2,930 (1,641–25,001)	166 (64–660)	0.01
Elevated NT-proBNP, n (%)	89/345 (26)	3/3 (100)	92/348 (26.4)	0.02
Creatinine [mg/dL]	0.87 (0.73–1.02)	1 (0.8–2.3)	0.88 (0.73–1.02)	0.25
D-dimer [ng/mL]	4,157 (1,784–6,577)	20,680 (4,480–36,880)	4,174 (1,795–6,069)	0.19
ESC risk group, low/intermediate-low/intermediate-high	166/103/76	0/0/3	166/103/79	–

CE – clinical endpoint; HR – heart rate; SBP – systolic blood pressure; ESC – European Society of Cardiology; sPESI – simplified Pulmonary Embolism Severity Index; NT-proBNP – N-terminal pro-brain natriuretic peptide; p-values were calculated using the Mann–Whitney U test or Fisher’s exact test comparing CE (+) to CE (–) patients.

Table 2. The clinical characteristics of patients reaching CEs

Patient No.	Age [years]	Sex	HR [bpm]	SBP [mm Hg]	NT-proBNP [pg/mL]	Creatinine [mg/dL]	D-dimer [ng/mL]	Comorbidities
Patient 1	76	male	80	160	25,001	2.3	36,880	type 2 diabetes, chronic kidney disease
Patient 2	30	male	105	110	2,930	0.8	4,480	ulcerative colitis
Patient 3	79	female	105	130	1,641	1	unknown	rheumatoid arthritis, pneumonia on admission

NT-proBNP – N-terminal pro-brain natriuretic peptide; HR – heart rate; SBP – systolic blood pressure.

Table 3. ROC analysis of NT-proBNP in predicting a complicated clinical course

Parameter	AUC	95% CI	p-value
NT proBNP	0.918	0.831–1.0	<0.013

AUC – area under the ROC curve; 95% CI – 95% confidence interval.

with a history of rheumatoid arthritis and co-existing pneumonia. On the 10th day of the hospital stay, a sudden cardiac arrest occurred, which resulted in death. During CPR, an echocardiographic study was performed, which revealed a widely enlarged right ventricle. It should be noted that each patient with a CE was classified as intermediate-to-high risk after echocardiography.

The Receiver operating characteristic (ROC) analysis showed that the area under the curve (AUC) for NT-proBNP in the prediction of CE was 0.918 (95% CI: 0.831–1.00; $p = 0.013$, Table 3). With reference to Youden’s index, an optimal cutoff was determined to be $\geq 1,641$ pg/mL with 100% sensitivity and 85% specificity (Fig. 2). Therefore, all patients who experienced CEs had NT-proBNP concentrations exceeding this value, and all 292 patients with NT-proBNP concentrations below this level had a favorable clinical course. A comparison between the thresholds of $\geq 1,641$ and ≥ 600 pg/mL (which is recommended in the current ESC guidelines) is presented in Table 4.

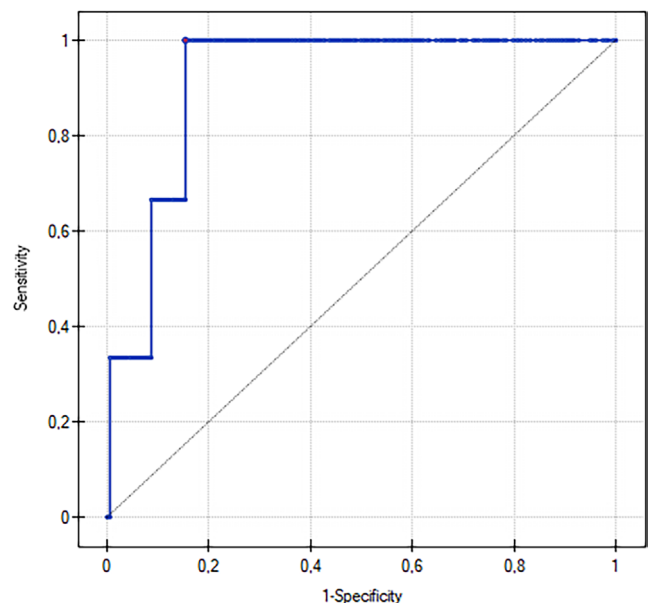


Fig. 2. Receiver operating characteristic (ROC) curve for NT-proBNP in the prediction of a complicated clinical course. The proposed cutoff is marked with a red dot

Discussion

First of all, our study revealed that a risk stratification model based exclusively on clinical findings is not sufficient

Table 4. NT-proBNP cutoff values

Cutoff value [pg/mL]	PPV	NPV	Sensitivity	Specificity
≥600	3.3	100	100%	74%
≥1,641	5.4	100	100%	85%

PPV – positive predictive value; NPV – negative predictive value.

to select candidates for outpatient treatment, as 0.86% of initially sPESI 0-point patients experienced clinical deterioration and required intensive medical care. Moreover, plasma NT-proBNP concentrations $\geq 1,641$ pg/mL seemed to identify those with an elevated risk of severe adverse events and requiring closer attention. Conversely, the remaining patients could be classified as the “very low-risk” group and might be considered for treatment in ambulatory care. These findings may be useful as a part of a quick decision-making algorithm that could be utilized to predict outcomes, especially when the echocardiographic study required to perform the risk stratification model suggested by ESC is not immediately available.

Several scales used to describe the APE patient’s clinical status are available (e.g., PESI, sPESI, Hestia); however, the main advantage of sPESI is its simplicity, which makes it preferable to use in everyday clinical practice. Furthermore, its value in predicting outcomes was confirmed in numerous studies. In a meta-analysis by Elias et al., the overall 30-day mortality rate was 1.5% (0.9–2.5%) in the low-risk group and 10.7% (8.8–12.9%) in the high-risk group for sPESI (11 studies).⁹ In the HOME-PE randomized trial, decision-making regarding ambulatory treatment based on Hestia and sPESI had comparable safety and effectiveness, no deaths or recurrent pulmonary embolism (PE) were observed in patients selected for home treatment with the use of both discussed scales.¹⁰ Nevertheless, final decisions regarding outpatient treatment in each case were made by the physician in charge. Combining clinical findings with a biomarker assessment (such as NT-proBNP or cardiac troponin) would supposedly provide objective criteria for safe early discharge.¹⁰ According to scientific knowledge, the sPESI scale alone is not sufficient to identify candidates for safe home treatment and it should be accompanied by biomarkers and/or RV assessment on imaging studies.³

Although a number of studies revealed the usefulness of NT-proBNP as an indicator of RV dysfunction, data on the prognostic significance of NT-proBNP in low-risk APE patients comes mainly from recent years.^{4,7,11} In 2019, Barco et al. published a meta-analysis including 22 cohort studies with 3,295 low-risk APE patients according to PESI or sPESI. Early all-cause or APE-related mortality rates were significantly higher in study participants with RV dysfunction on imaging studies or elevated plasma troponin or natriuretic peptide levels.¹² Becattini et al. published a meta-analysis, incorporating data from 5,010 low-risk APE patients from 18 studies, which

revealed similar results.¹³ Both meta-analyses identified NT-proBNP as an independent predictor of severe adverse events in low-risk APE patients. However, the cutoff value for NT-proBNP for each incorporated study was different, ranging from 90 pg/mL to 1,136 pg/mL. Our study revealed that using a combination of sPESI and a NT-proBNP assessment with a cutoff value of 600 pg/mL identified patients with a favorable outcome. Furthermore, it appears to be safe to raise the threshold to 1,641 pg/mL, which increases the positive predictive value of the test. Applying our findings in clinical practice would allow early discharge of 292 out of the 348 (84%) patients in the studied population. Thus, it is worth considering a higher cutoff value for NT-proBNP than suggested in the current guidelines for predicting adverse events in low-risk APE patients. Nevertheless, due to a very low number of endpoints in our study, those findings require further validation.

Another biomarker used in outcome prediction in APE is cardiac troponin.³ Its clinical value was confirmed in multiple studies, including those incorporating sPESI 0-point patients. A meta-analysis by Barco et al. identified troponin as an independent predictor of all-cause mortality in low-risk APE patients.¹² Similarly, in a meta-analysis by Becattini et al., elevated plasma troponin levels were linked to greater short-term mortality and death within 3 months.¹³ We previously analyzed data from 409 sPESI 0-point APE patients. The study participants with troponin levels not exceeding 1.7 times the upper limit of normal could be classified to the group of “very low-risk” with an excellent prognosis.⁶ Taking available scientific data into consideration, we recommend assessing plasma cardiac troponin levels as well as NT-proBNP in all sPESI 0-point patients before making a decision regarding outpatient treatment. This procedure is likely to increase patient safety and may be easily performed in most medical facilities.

Apart from biomarkers, imaging studies are another way of detecting RV dysfunction secondary to an APE. The role of echocardiography in the risk stratification process is well established.^{3,12–15} Nevertheless, performing this study requires an experienced physician, who is not always immediately reachable, whereas biochemical tests (such as NT-proBNP level assessment) are usually easily accessible and enable quick and efficient decision-making. The use of CTPA for RV dysfunction detection is an interesting idea as this study is usually necessary to confirm the diagnosis of APE; however, results from available scientific studies are equivocal. A study by Singanayagam et al. identified RV dilatation as an independent predictor of 30-day mortality in APE.¹⁶ Similarly, a meta-analysis by Trujillo-Santos et al. revealed a connection between APE-related adverse events and right ventricular dysfunction (RVD) on CT.¹⁷ Conversely, a study by Cote et al. showed no association between RV dilatation on CT, defined as a RV/LV ≥ 0.9

or ≥ 1.0 , and a complicated course of the disease. However, a link was observed after increasing the cutoff value to ≥ 1.1 .¹⁸ In the PROTECT study, RVD on CT did not affect the prognosis in the cohort of normotensive patients with a cutoff value (RV/LV) ≥ 0.9 .¹⁹ Recently, O'Hare et al. analyzed data of 817 APE patients of which 331 (40.5%) were low-risk using the PESI score. Low-risk patients had similar short-term outcomes regardless of CT scan results.²⁰ Although available scientific data gives the impression that CT might play a significant role in the risk stratification process, optimal criteria for RV overload recognition have yet to be determined.

Limitations

It is commonly known that the risk of APE-related severe adverse events in sPESI 0-point patients is below 1%; therefore, only a few patients from the studied population reached the CE. Furthermore, CEs were limited to in-hospital severe adverse events and data regarding possible complications that study participants might have experienced after discharge were not available. In addition, this was a single-center study. Taking those facts into consideration, our results, especially the cutoff value of 1,641 pg/mL for NT-proBNP assessment, should be interpreted with caution and require external validation.

Conclusions

Risk assessment in APE based exclusively on clinical examination is insufficient and each patient with 0 points on the sPESI requires further risk stratification, in which the assessment of NT-proBNP levels might play an important role. Study participants with a concentration of this biomarker exceeding 1,641 pg/mL belong to the group with an elevated risk of clinical deterioration and might require close attention, while those who do not meet this criterion could be considered as candidates for outpatient treatment. Nevertheless, taking into consideration the limitations of this study, these findings, with special emphasis on the cutoff point of 1,641 pg/mL, require further analyses in a large, prospective group of patients to be introduced in clinical practice.








Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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