Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism

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ABSTRACT The optimal N-terminal pro-brain natriuretic peptide (NT-proBNP) cut-off value for risk stratification of pulmonary embolism remains controversial.

In this study we validated and compared different proposed NT-proBNP cut-off values in 688 normotensive patients with pulmonary embolism.

During the first 30 days, 28 (4.1%) patients reached the primary outcome (pulmonary embolism-related death or complications) and 29 (4.2%) patients died. Receiver operating characteristic analysis yielded an area under the curve of 0.70 (0.60–0.80) for NT-proBNP. A cut-off value of 600 pg·mL^{-1} was associated with the best prognostic performance (sensitivity 86% and specificity 50%) and the highest odds ratio (6.04 (95% CI 2.07–17.59), p=0.001) compared to the cut-off values of 1000, 500 or 300 pg·mL^{-1}. Using multivariable logistic regression analysis, NT-proBNP $\geqslant$600 pg·mL^{-1} had a prognostic impact on top of that of the simplified Pulmonary Embolism Severity Index and right ventricular dysfunction on echocardiography (OR 4.27 (95% CI 1.22–15.01); p=0.024, c-index 0.741). The use of a stepwise approach based on the simplified Pulmonary Embolism Severity Index, NT-proBNP $\geqslant$600 pg·mL^{-1} and echocardiography helped optimise risk assessment.

Our findings confirm the prognostic value of NT-proBNP and suggest that a cut-off value of 600 pg·mL^{-1} is most appropriate for risk stratification of normotensive patients with pulmonary embolism. NT-proBNP should be used in combination with a clinical score and an imaging procedure for detecting right ventricular dysfunction.

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Stepwise approach based on sPESI, NT-proBNP and echocardiography for pulmonary embolism risk stratification http://ow.ly/tsMud

Introduction

Current guidelines emphasise the importance of early risk stratification of the prognostic heterogeneous group of normotensive patients with acute pulmonary embolism [1, 2]. Numerous studies investigated the performance of various biomarkers, imaging procedures detecting right ventricular (RV) dysfunction, combination models and clinical prediction rules for optimising risk stratification of patients with acute pulmonary embolism [3]. The Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) [4] are the most extensively validated clinical scores to date. Its major strength lies in the identification of low-risk patients who might be candidates for home treatment [5, 6]. N-terminal pro-brain natriuretic peptide (NT-proBNP) is a frequently cited biomarker for risk stratification of acute normotensive pulmonary embolism. However, the optimal cut-off values and, thus the contribution of NT-proBNP to clinical decision making, remain controversial. Four different NT-proBNP cut-off values have been proposed to distinguish between patients with low and elevated risk of short-term clinical adverse outcome: $\geqslant 300$ pg·mL^{-1} [7], $\geqslant 500$ pg·mL^{-1} [8–10], $\geqslant 600$ pg·mL^{-1} [11–13], and $\geqslant 1000$ pg·mL^{-1} [14–16]. Additionally, some authors investigated combination models based on NT-proBNP plus evidence of RV dysfunction on echocardiography [14, 15, 17], RV enlargement (right/left ventricle ratio $\geqslant 1.0$) on computed tomography [11], or cardiac troponin T elevation [13, 18].

In the present study we prospectively validated and compared different cut-off values for NT-proBNP regarding their prognostic value in a large European, multicentre cohort of normotensive patients with acute symptomatic pulmonary embolism. Furthermore, we tested whether integration of NT-proBNP in a stepwise approach, based on the sPESI, might help optimise risk assessment.

Material and methods

Patient population and study design

We prospectively included consecutive patients who were diagnosed with acute symptomatic pulmonary embolism at 12 cooperating European centres in three countries. The participating sites are listed in the Acknowledgements section. All sites followed the same study protocol as previously reported [19]. Patients were excluded from the study if they met at least one of the following criteria: 1) haemodynamic instability at presentation [19]; 2) pulmonary embolism being an accidental finding during diagnostic workup for another suspected disease; and 3) denial of consent or withdrawal of previously given consent for participation in the study. The study protocol strongly recommended a transthoracic echocardiogram (TTE) within 48 h of pulmonary embolism diagnosis. RV dysfunction was defined as dilatation of the right ventricle (end-diastolic diameter >30 mm from the parasternal view, or a right/left ventricle diameter ratio $\geqslant 1.0$ from the subcostal or apical view) combined with the absence of inspiratory collapse of the inferior vena cava, or an elevated systolic gradient through the tricuspid valve (>30 mmHg) in the absence of left ventricular or mitral valve disease [19, 20]. The sPESI was calculated as suggested by JIMÉNEZ et al. [4] and patients were classified into either a "low-risk" (0 points) or "high-risk" ($\geqslant 1$ point(s)) group.

30-day clinical follow-up data were obtained from all patients included in the study. The primary outcome of the study was adverse 30-day outcome, defined as pulmonary embolism-related death or at least one of the following major complications [19]: 1) need for intravenous catecholamine administration; 2) endotracheal intubation; and 3) cardiopulmonary resuscitation. The secondary outcome was all-cause mortality within 30 days. The cause of death was determined by three of the authors (M. Lankeit, D. Jiménez and M. Kostrubiec) who reviewed the patients' medical records and the results of the autopsy, if performed. The authors were unaware of the results of biomarker measurements, echocardiographic examination or the calculated sPESI. Death was determined to be related to pulmonary embolism if it was confirmed by autopsy, or if it followed a clinically severe pulmonary embolism episode, either immediately or shortly after an objectively confirmed recurrent event, and in the absence of an alternative diagnosis.

The study protocol was approved by the Ethics Committees of the participating sites and all patients gave informed consent for their participation in the study. Treatment decisions were made by the physicians caring for the patient and were not dictated by the study protocol. Biomarker levels were not communicated to the clinicians and, thus, were not used to guide the patients' management or monitor the effects of treatment during the hospital stay or at any time during the follow-up period.

Laboratory parameters and biomarker testing

Venous plasma samples were collected on admission and immediately stored at -80°C. Samples were later shipped to the core laboratory of the University of Göttingen (Göttingen, Germany) and analysed in batches after a single thaw. Samples from Spanish patients were provided by the Hospital Universitario Ramón y Cajal-IRYCIS Biobank (Madrid, Spain) integrated in the Spanish Hospital Biobanks Network (RetBioH; www.redbiobancos.es) and were processed following standard operation procedures with appropriate approval of the Ethical and Scientific Committees. Concentrations of NT-proBNP were measured centrally in the laboratory of the Dept of Clinical Chemistry of the University of Göttingen, using a quantitative electrochemiluminescence assay (Elecsys 2010 analyser; Roche Diagnostics, Mannheim, Germany) as previously described [14]. Elevated NT-proBNP levels were defined as concentrations $\geqslant$300 pg·mL^{-1} [7], $\geqslant$500 pg·mL^{-1} [8–10], $\geqslant$600 pg·mL^{-1} [11–13] and $\geqslant$1000 pg·mL^{-1} [14–16]. Routine laboratory parameter measurements were performed at the Dept of Clinical Chemistry of the University of Göttingen, the Central Laboratory of Infant Jesus Teaching Hospital (Warsaw, Poland) and the Biochemistry Dept at Ramón y Cajal Hospital. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease study equation; renal insufficiency was defined as GFR <60 mL·min^{-1} per 1.73 m^2 body surface area.

Statistical analysis

Continuous variables were found to not follow a normal distribution, as tested with the modified Kolmogorov–Smirnov test (Lilliefors test). Results are expressed as median (25th to 75th percentiles) and compared using the unpaired Mann–Whitney U-test. Categorical variables were compared using Fisher's exact test or Chi-squared test, as appropriate.

Receiver operating characteristic (ROC) analysis was used to determine the area under the curve (AUC) of NT-proBNP with regard to the study outcomes. Sensitivity, specificity, positive and negative predictive values, and the positive and negative likelihood ratio for different NT-proBNP cut-off values and dichotomous/dichotomised variables were calculated and presented with 95% CI. The optimal cut-off value for NT-proBNP was defined using ROC analysis as the concentration with maximum sensitivity and specificity. The prognostic value of different NT-proBNP cut-off values and other baseline parameters (table 1) with regard to study outcomes, was estimated using logistic regression analysis. Furthermore, to estimate the prognostic relevance of these parameters with regard to an adverse 30-day outcome, a multivariable logistic regression model with forward stepwise selection was used (inclusion criterion: p-value of the score test $\leqslant$5%; exclusion criterion: p-value of the likelihood-ratio test $\geqslant$10%). Of note, to assure model stability, the sPESI was used instead of its separate variables. To assess the additive prognostic relevance of different NT-proBNP cut-off values they were entered separately into the multivariable logistic regression model in a second step and c-indices were calculated. The results are presented as OR (95% CI). For the secondary outcome no multivariable model was performed since all variables found to be associated with all-cause 30-day mortality are included in the sPESI.

All tests were two-sided and used a significance level of 0.05. All analyses were performed using R (version 2.15.1; R Project, University of Vienna, Vienna, Austria) and the SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA).

Results
Baseline clinical and laboratory findings

Overall, 688 normotensive patients with acute pulmonary embolism were included in the study. Of these, 526 (76.5%) patients had been included in our previous study investigating the prognostic value of troponin T measured with a highly sensitive assay in normotensive patients with acute pulmonary embolism [19]. Diagnosis of pulmonary embolism was confirmed by contrast-enhanced multidetector computed tomography in 648 (94.2%) cases, by ventilation/perfusion lung scan in 36 (5.2%) cases, and by pulmonary angiography in nine (1.3%) cases. Of note, 11 (1.6%) patients had two imaging procedures. In six (0.9%) patients, the diagnosis of pulmonary embolism was established by TTE showing mobile thrombi in the right atrium or ventricle, or in the proximal portions of the pulmonary artery. Overall, a TTE was performed in 615 (89.4%) patients, of which 231 (37.6%) were diagnosed with RV dysfunction (as defined in the Methods section). The baseline clinical characteristics of the study patients are summarised in table 1.

Overall, 64 (9.3%) patients received early recanalisation treatment (thrombolysis, inclusion in the PEITHO (Pulmonary Embolism Thrombolysis) study [21], or surgical embolectomy). More specifically, 35 patients received early (within 24 h of diagnosis) thrombolysis, 23 patients were included in the PEITHO study and randomised in a double-blind fashion to placebo *versus* single-bolus tenecteplase, and eight patients underwent surgical embolectomy (of those, two patients after failure of initial thrombolysis). A total of four (0.6%) patients received an inferior vena cava filter.

TABLE 1 Baseline characteristics, comorbidities and clinical symptoms on admission of normotensive patients with acute pulmonary embolism (PE)

Parameter	All study patients	NT-proBNP <600 pg·mL⁻¹	NT-proBNP ⩾600 pg·mL⁻¹	p-value
Subjects n[#]	688	335	353	
Sex				
Male	326 (47.4)	188 (56.1)	138 (39.1)	
Female	362 (52.6)	147 (43.9)	215 (60.9)	<0.001
Age years	70 (54–78)	65 (46–74)	73 (64–81)	<0.001
Comorbidities and risk factors for VTE				
History of DVT and/or PE	153 (22.3) (n=687)	75 (22.5) (n=334)	78 (22.1)	0.927
Immobilisation[¶]	198 (28.8) (n=687)	77 (23.1) (n=334)	122 (34.3)	0.001
Trauma or major surgery[¶]	117 (17.0) (n=687)	64 (19.1)	59 (15.1) (n=352)	0.187
Cancer	113 (16.4)	57 (17.0)	56 (15.9)	0.682
Chronic heart failure	68 (9.9) (n=687)	15 (4.5) (n=335)	53 (15.0)	<0.001
Chronic pulmonary disease	87 (12.6)	31 (9.3)	56 (15.9)	<0.011
Renal insufficiency	222 (30.8)	69 (20.6)	143 (40.5)	<0.001
Symptoms and clinical status				
Dyspnoea	562 (81.7)	257 (76.7)	305 (86.4)	0.001
Chest pain	314 (45.6)	173 (51.6)	141 (39.9)	0.004
Signs of DVT	227 (33.0)	122 (36.4)	105 (29.7)	0.057
Syncope	122 (17.7)	51 (14.9)	72 (20.4)	0.110
Systolic blood pressure mmHg	130 (115–147) (n=685)	130 (118–146) (n=333)	130 (113–147) (n=352)	0.163
Hypotension[+]	29 (4.2) (n=685)	9 (2.7) (n=333)	20 (5.7) (n=352)	0.059
Heart rate beats·min⁻¹	90 (80–108) (n=686)	87 (77–100) (n=334)	97 (84–111) (n=352)	<0.001
Tachycardia[§]	161 (23.4)	54 (16.1)	107 (30.3)	<0.001
Oxyhaemoglobin saturation <90%	128 (22.0) (n=610)	36 (12.0) (n=299)	92 (29.6) (n=311)	<0.001

Data are presented as n (%) or median (25th to 75th percentile), unless otherwise stated. Patients were stratified according to the N-terminal pro-brain natriuretic peptide (NT-proBNP) cut-off value of 600 pg·mL⁻¹. VTE: venous thromboembolism; DVT: deep vein thrombosis. [#]: numbers of patients with available data is shown where appropriate; [¶]: within the past 4 weeks; [+]: defined as a systolic blood pressure between 90 and 100 mmHg; [§]: heart rate ⩾110 beats·min⁻¹.

NT-proBNP concentrations measured on admission ranged from 5 pg·mL⁻¹ to 33 739 pg·mL⁻¹ with a median value of 683 (25th to 75th percentile 160–2591 pg·mL⁻¹). Overall, 424 (61.6%) patients had NT-proBNP levels ⩾300 pg·mL⁻¹, 374 (54.4%) patients ⩾500 pg·mL⁻¹, 353 (51.3%) patients ⩾600 pg·mL⁻¹, and 301 (43.8%) patients ⩾1000 pg·mL⁻¹.

Prognostic performance of different NT-proBNP cut-off values

During the first 30 days, 28 (4.1%) patients reached the primary outcome (as defined in the Methods section) and 29 (4.2%) patients died. Of these, 18 (2.6%) deaths were directly related to the pulmonary embolism. As expected, patients who reached the primary outcome or died during the first 30 days had significantly higher levels of NT-proBNP on admission compared to patients with a favourable clinical course (primary outcome median 1979 (25th to 75th percentile 748–9358) pg·mL⁻¹ versus 591 (149–2504) pg·mL⁻¹, p<0.001, respectively; and secondary outcome 2158 (948–10 473) pg·mL⁻¹ versus 585 (149–2496) pg·mL⁻¹, p<0.001; respectively). The AUCs for NT-proBNP measured on admission with regard to the primary and secondary outcome are shown in figure 1. Using ROC analysis, concentrations of 637 pg·mL⁻¹ and 697 pg·mL⁻¹ were identified as the optimal cut-off values for predicting an adverse 30-day outcome and all-cause 30-day mortality, respectively. An NT-proBNP cut-off value of 600 pg·mL⁻¹ was associated with an overall better prognostic performance compared to those of 1000, 500 or 300 pg·mL⁻¹ (table 2).

Out of 353 (51.3%) patients with NT-proBNP values ⩾600 pg·mL⁻¹ on admission, 24 (6.8%) patients reached the primary outcome compared to four (1.2%) patients with NT-proBNP values <600 pg·mL⁻¹ (n=335 on admission; p<0.001). 25 (7.1%) patients with NT-proBNP values ⩾600 pg·mL⁻¹ reached the secondary outcome compared to four (1.2%) patients with NT-proBNP values <600 pg·mL⁻¹ (p<0.001). As shown in table 1, patients with NT-proBNP levels ⩾600 pg·mL⁻¹ were older, were more often female and had been diagnosed with chronic heart failure or chronic pulmonary disease more frequently. They were also more likely to present with tachycardia and dyspnoea. Moreover, patients with elevated NT-proBNP plasma concentrations were more frequently diagnosed with RV dysfunction on echocardiography; 172 (53.6%) out of 322 patients with NT-proBNP ⩾600 pg·mL⁻¹ who underwent echocardiographic examination
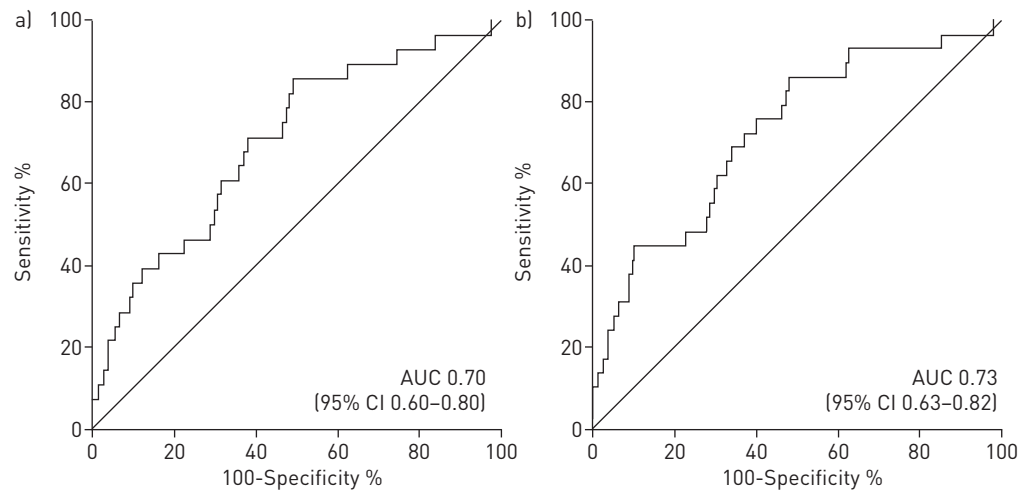
FIGURE 1 Receiver operating characteristics curves for N-terminal pro-brain natriuretic peptide values measured on admission with regard to a) adverse 30-day outcome (primary outcome) and b) all-cause 30-day mortality (secondary outcome). AUC: area under the curve.

had signs of RV dysfunction compared to 59 (20.1%) out of 294 patients with NT-proBNP <600 pg·mL^{-1} (p<0.001). Using logistic regression analysis, a NT-proBNP cut-off value of 600 pg·mL^{-1} was associated with the highest odds ratio for predicting both an adverse 30-day outcome (OR 6.04 (95% CI 2.07–17.59), p=0.001) and all-cause 30-day mortality (OR 6.31 (95% CI 2.17–18.32), p=0.001) (table 3). Other variables univariably associated with the primary and/or secondary outcome are shown in table 3.

Optimising risk assessment using a three-step approach

The sPESI assigned 430 (62.5%) patients to the "high-risk" category (⩾1 point(s)). These patients presented more often with elevated NT-proBNP levels ⩾600 pg·mL^{-1} (267 (62.1%) out of 430) compared to "low-risk" patients (86 (33.3%) out of 258, p<0.001). Patients who reached the primary or secondary outcome have been stratified more frequently as being at high risk using sPESI. Of the 28 patients who had an adverse 30-day outcome, 26 (92.9%) patients had a sPESI ⩾1 point(s) (compared to 61.2% of patients with a favourable clinical course, p<0.001) and all the patients who died had a sPESI ⩾1 point(s) (compared to 60.8% of patients who survived the acute phase, p<0.001) (table 2). Using logistic regression analysis, a sPESI ⩾1 point(s) was associated with an increased risk for an adverse 30-day outcome (OR 8.24 (95% CI 1.94–35.00), p=0.004). In multivariable logistic regression analysis using stepwise forward selection (as described in the Methods section), both the sPESI and evidence of RV dysfunction on echocardiography had an impact on primary outcome (table 4). Attaching NT-proBNP to this model provided significant additional impact, with the highest C-index (0.741) for the cut-off value of ⩾600 pg·mL^{-1}.

Based on these results, we tested whether the addition of NT-proBNP measurements to the sPESI could provide additive prognostic information. In 430 patients classified as "high-risk" by the sPESI, only elevation of NT-proBNP ⩾600 pg·mL^{-1} emerged as a predictor both for the primary (OR 3.57 (95% CI 1.22–10.55), p=0.022) and secondary outcome (OR 4.11 (95% CI 1.40–12.02), p=0.010). Additionally, evidence of RV dysfunction on echocardiography was associated with an increased risk for an adverse 30-day outcome (OR 3.15 (95% CI 1.28–7.78), p=0.013) and renal insufficiency with an increased risk for all-cause 30-day mortality (OR 2.17 (95% CI 1.02–4.65), p=0.045). By further stratifying patients with an sPESI ⩾1 point(s) using NT-proBNP ⩾600 pg·mL^{-1} as a second step, the number of patients at risk could be reduced from 430 to 267 (38.8% of the total study population and 62.1% of the patients with sPESI ⩾1 point(s)) (fig. 2). Of the latter patients, 22 (8.2%) reached the primary outcome (sensitivity 85 (66–94)%, specificity 39 (35–44)%, positive predictive value 8 (6–12)%, negative predictive value 98 (94–99)%, positive likelihood ratio 1.40 (1.16–1.67), negative likelihood ratio 0.39 (0.16–0.97)).

When patients were further stratified using TTE as a third step (fig. 2), patients with NT-proBNP ⩾600 pg·mL^{-1} plus RV dysfunction on echocardiography had a 10.8% incidence of an adverse early outcome, while patients with NT-proBNP <600 pg·mL^{-1} plus absence of RV dysfunction on echocardiography reached the primary outcome to a similar proportion (0.9%) as patients with sPESI of 0 points (0.8%). In this regard, only two patients with sPESI of 0 points had an adverse 30-day outcome, and both had NT-proBNP ⩾600 pg·mL^{-1}. Patients with either NT-proBNP ⩾600 pg·mL^{-1} or RV

TABLE 2 Prognostic performance of biomarkers with regard to primary and secondary outcomes

	Sensitivity %	Specificity %	PPV %	NPV %	Positive LR	Negative LR
Primary outcome						
NT-proBNP						
$\geqslant$1000 pg·mL^{-1}	71 (53–85)	57 (54–61)	7 (4–10)	98 (96–99)	1.68 (1.31–2.16)	0.50 (0.28–0.90)
$\geqslant$600 pg·mL^{-1}	86 (69–94)	50 (46–54)	7 (5–10)	99 (97–100)	1.72 (1.45–2.04)	0.29 (0.11–0.71)
$\geqslant$500 pg·mL^{-1}	86 (69–94)	47 (43–51)	6 (4–9)	99 (97–100)	1.62(1.37–1.91)	0.30 (0.12–0.76)
$\geqslant$300 pg·mL^{-1}	85 (69–94)	40 (36–43)	6 (4–8)	99 (96–99)	1.42 (1.22–1.67)	0.36 (0.14–0.90)
Echocardiography						
RV dysfunction	69 (50–83)	64 (60–68)	8 (5–12)	96 (94–98)	1.91 (1.45–2.53)	0.48 (0.27–0.86)
sPESI $\geqslant$1 point(s)	93 (77–98)	39 (35–43)	6 (4–9)	99 (97–100)	1.52 (1.34–1.71)	0.18 (0.04–0.70)
Secondary outcome						
NT-proBNP						
$\geqslant$1000 pg·mL^{-1}	76 (58–88)	58 (54–61)	7 (5–11)	98 (96–99)	1.79 (1.43–2.24)	0.42 (0.22–0.80)
$\geqslant$600 pg·mL^{-1}	86 (69–95)	50 (46–54)	7 (5–10)	99 (97–100)	1.73 (1.47–2.04)	0.27 (0.11–0.68)
$\geqslant$500 pg·mL^{-1}	86 (69–95)	47 (43–51)	7 (5–10)	99 (97–100)	1.63 (1.35–1.91)	0.29 (0.12–0.73)
$\geqslant$300 pg·mL^{-1}	86 (69–95)	40 (36–44)	6 (4–9)	99 (96–99)	1.43 (1.22–1.68)	0.35 (0.14–0.87)
Echocardiography						
RV dysfunction	50 (32–68)	63 (59–67)	6 (3–98)	97 (94–98)	1.35 (0.90–2.01)	0.79 (0.54–1.17)
sPESI $\geqslant$1 point(s)	100 (88–100)	39 (35–43)	7 (5–10)	100 (99–100)	1.64 (1.55–1.75)	

Data are presented as % or absolute number (95% CI). PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio; NT-proBNP: N-terminal pro-brain natriuretic peptide; RV: right ventricular; sPESI: simplified Pulmonary Embolism Severity Index.

dysfunction on echocardiography (but not both) had a similar, intermediate incidence of an adverse 30-day outcome (5.6% and 5.8%, respectively) (fig. 2).

Discussion

This large European multicentre prospective cohort study confirms the prognostic value of elevated NT-proBNP plasma levels on admission in normotensive patients with acute pulmonary embolism. This finding is in accordance with the position statement of the Study Group on Biomarkers in Cardiology of the European Society of Cardiology (ESC) Working Group on Acute Cardiac Care recommending the use of natriuretic peptides as prognostic markers in acute pulmonary embolism [22] and the ESC guidelines on the diagnosis and management of acute pulmonary embolism [1] recommending further risk stratification in normotensive pulmonary embolism patients. To date, five meta-analyses have investigated the prognostic value of natriuretic peptides in patients with acute pulmonary embolism [23–27], concluding that elevated natriuretic peptides are associated with an adverse short-term outcome. However, only three analyses focused on haemodynamically stable patients [24, 26, 27]. To our best knowledge, a total of six studies have

TABLE 3 Predictors of study outcomes by univariable logistic regression analysis

	Primary outcome		Secondary outcome	
	OR (95% CI)	p-value	OR (95% CI)	p-value
NT-proBNP				
$\geqslant$1000 pg·mL^{-1}	3.37 (1.46–7.77)	0.004	4.28 (1.80–10.16)	0.001
$\geqslant$600 pg·mL^{-1}	6.04 (2.07–17.59)	0.001	6.31 (2.17–18.32)	0.001
$\geqslant$500 pg·mL^{-1}	5.31 (1.82–15.49)	0.002	5.55 (1.91–16.13)	0.002
$\geqslant$300 pg·mL^{-1}	3.95 (1.36–11.51)	0.012	4.13 (1.42–11.99)	0.009
Age years	1.04 (1.01–1.07)	0.017	1.07 (1.04–1.11)	<0.001
Chronic heart failure	4.82 (2.09–11.13)	<0.001	5.45 (2.42–12.26)	<0.001
Chronic pulmonary disease	2.94 (1.25–6.89)	0.013	3.98 (1.78–8.87)	0.001
Renal insufficiency	2.33 (1.09–4.99)	0.003	2.91 (1.37–6.16)	0.005
Tachycardia[#]	4.06 (1.89–8.73)	<0.001	1.26 (0.55–2.90)	0.587
Arterial oxyhaemoglobin saturation <90%	3.46 (1.56–7.68)	0.002	3.01 (1.39–6.54)	0.005
RV dysfunction on echocardiography	3.97 (1.70–9.29)	0.001	1.70 (0.78–3.74)	0.185

NT-proBNP: N-terminal pro-brain natriuretic peptide; RV: right ventricular. [#]: heart rate $\geqslant$110 beats·min^{-1}.

TABLE 4 Predictors of an adverse 30-day outcome by multivariable logistic regression analysis

	OR (95% CI)	p-value	C-index
sPESI ⩾1 point(s)	5.88 (1.36–25.44)	0.018	0.677
RV dysfunction on echocardiography	3.15 (1.33–7.44)	0.009	
Additional impact of NT-proBNP			
⩾1000 pg·mL^{-1}	2.51 (0.95–6.63)	0.063	0.719
⩾600 pg·mL^{-1}	4.27 (1.22–15.01)	0.024	0.741
⩾500 pg·mL^{-1}	3.73 (1.06–13.07)	0.040	0.731
⩾300 pg·mL^{-1}	2.53 (0.71–8.96)	0.152	0.706

sPESI: simplified Pulmonary Embolism Severity Index; RV: right ventricular; NT-proBNP: N-terminal pro-brain natriuretic peptide.

investigated the prognostic value of NT-proBNP concentrations on admission with regard to short-term clinical outcome in normotensive patients with acute pulmonary embolism [8, 11, 13, 15, 16, 18]. These studies are summarised in table S1. Although all studies demonstrated an association of elevated NT-proBNP concentrations with adverse short-term outcome, different cut-off values were used. In the present study, we showed that an NT-proBNP cut-off value of 600 pg·mL^{-1} was associated with the best prognostic performance compared to the cut-off values of 1000, 500 and 300 pg·mL^{-1}. This cut-off value was very close to the calculated optimal cut-off value (637 pg·mL^{-1}) in our patient population and the median NT-proBNP concentration (683 pg·mL^{-1}).

To further optimise risk assessment strategies for identification of normotensive patients with an elevated risk of an unfavourable early clinical course, we tested an approach based on the sPESI, followed by NT-proBNP using a cut-off value of 600 pg·mL^{-1} and, finally, TTE. Using this three-step approach, we were able to identify 37.5% of all patients as being at low-risk on the basis of the sPESI (primary outcome, 0.8%) without the need for additional laboratory or echocardiographic testing. Using NT-proBNP with a cut-off value of 600 pg·mL^{-1} as the next step, patients with a sPESI of ⩾1 point(s) could be further classified
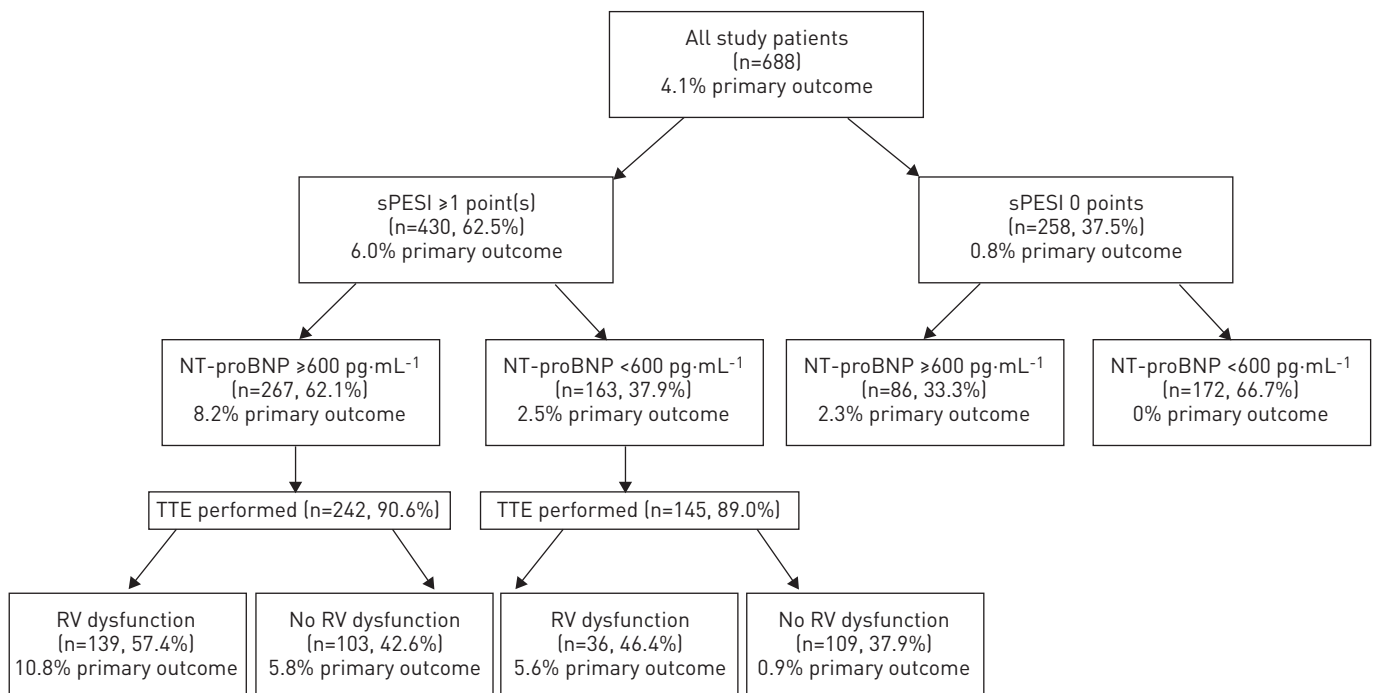

FIGURE 2 Proposed stepwise approach for risk assessment based on the simplified Pulmonary Embolism Severity Index (sPESI), N-terminal pro-brain natriuretic peptide (NT-proBNP) and echocardiography. The flow chart shows the proportion of patients who reached the primary outcome stratified by the sPESI (cut-off ⩾1 point(s); first step), NT-proBNP (cut-off ⩾600 pg·mL^{-1}; second step), and echocardiography (evidence of right ventricular (RV) dysfunction; third step). TTE: transthoracic echocardiogram.

into a group with "intermediate" (primary outcome 8.2%) and a group with "lower" risk (primary outcome 2.5%) of an adverse 30-day outcome. Finally, using TTE as the last step we were able to stratify sPESI-positive patients in a group with "higher" intermediate risk (NT-proBNP $\geqslant$600 pg·mL^{-1} plus RV dysfunction) and "lower" intermediate risk (NT-proBNP $\geqslant$600 pg·mL^{-1} or RV dysfunction) of an adverse 30-day outcome, and into a low-risk group (NT-proBNP <600 pg·mL^{-1} plus no RV dysfunction) with a comparable rate of an adverse 30-day outcome as the sPESI-negative group.

Our stepwise approach might help identify patients with an elevated risk who might benefit from thrombolytic therapy. Recent findings from a large randomised trial [21] support the notion that early thrombolytic therapy may prevent clinical deterioration in normotensive patients with evidence of RV dysfunction and myocardial injury [28]. The present prospective cohort study, which included 688 patients at 12 European centres and, thus, more patients than all meta-analysis on this subject [23–27], suggests that these results might also be extrapolated to normotensive patients with evidence of RV dysfunction and NT-proBNP level elevation. Recently, 938 pulmonary embolism patients with elevation of NT-proBNP $\geqslant$500 pg·mL^{-1}, who were included in the HOKUSAI-VTE study [29], less frequently reached the primary outcome of recurrent venous thromboembolism (VTE) if treated with edoxaban compared to warfarin (3.3% *versus* 6.2%). These data suggest that treatment with a novel oral anticoagulant might be favoured in patients with NT-proBNP elevation.

At the other end of the risk spectrum, although all tested cut-off values for NT-proBNP had a high negative predictive value (98–99%), as many as 1.5% of the patients with an NT-proBNP <300 pg·mL^{-1} had an adverse 30-day outcome. Thus, and in contrast to the findings of a management study [10] and previous reports [9, 13, 18], low NT-proBNP concentrations on admission alone might not be sufficient to identify a low-risk patient subgroup that might be suitable for home treatment. However, patients with NT-proBNP <600 pg·mL^{-1} and a sPESI of 0 points or absence of RV dysfunction on echocardiography had a favourable prognosis.

Current guidelines [1] and position statements [22] do not provide clear recommendations on whether brain natriuretic peptide (BNP) should be favoured over NT-proBNP or *vice versa* for risk stratification of patients with acute pulmonary embolism. Following pressure or volume ventricular overload, cardiomyocytes process the 108 amino acid proBNP which is cleaved into BNP 1–32 and NT-proBNP 1–76. While BNP promotes natriuresis, diuresis and vasodilation, and antagonise the effects of the renin-angiotensin-aldosterone and sympathetic nervous system, NT-proBNP has no biological activity [30]. Although there are no differences in the diagnostic use of BNP and NT-proBNP [22], the *in vitro* stability of BNP is assay-dependent and limited in samples after 4 h at room temperature and even if frozen at -80°C. Since NT-proBNP is still more stable than BNP [31], the use of this biomarker might be favoured.

A potential limitation of our study is that the exact time interval between diagnosis of pulmonary embolism and echocardiographic examination was not documented. However, as recommended by the study protocol, all echocardiograms were performed within 48 h of pulmonary embolism diagnosis. Furthermore, the design of this cohort study does not provide a direct extrapolation of our findings into clinical practice.

In conclusion, we identified an NT-proBNP cut-off level of 600 pg·mL^{-1} as the optimal concentration to distinguish between normotensive patients with acute pulmonary embolism with low and intermediate risk of: 1) an adverse 30-day outcome; and 2) all-cause 30-day mortality. A stepwise approach based on the sPESI, NT-proBNP $\geqslant$600 pg·mL^{-1} and TTE makes it possible to optimise risk assessment strategies and the identification of intermediate-risk patients with higher and lower risk.

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