DOI: 10.1002/pul2.12367

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

NT-pro-BNP is predictive of morbidity and mortality after pulmonary thromboendarterectomy and is independent of preoperative hemodynamics

Emanuel A. Keiler[1] | **Kim M. Kerr**[1] | **David S. Poch**[1] | **Jenny Z. Yang**[1] | **Demosthenes G. Papamatheakis**[1] | **Mona Alotaibi**[1] | **Angela Bautista**[1] | **Victor G. Pretorius**[2] | **Michael M. Madani**[2] | **Nick H. Kim**[1] | **Timothy M. Fernandes**[1]

[1]Division of Pulmonary, Critical Care and Sleep Medicine, San Diego Health System, University of California, La Jolla, California, USA

[2]Division of Cardiovascular and Thoracic Surgery, San Diego Health System, University of California, La Jolla, California, USA

Correspondence
Timothy M. Fernandes, Division of Pulmonary, Critical Care and Sleep Medicine, San Diego Health System, University of California, 9300 Campus Point Dr, #7381, La Jolla, CA 92037-7381, USA.
Email: tfernandes@health.ucsd.edu

Funding information
None

Abstract

Current predictors of clinical outcomes after pulmonary thromboendarterectomy (PTE) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) are largely limited to preoperative clinical characteristics. N-terminal-pro-brain natriuretic peptide (NT-pro-BNP), a biomarker of right ventricular dysfunction, has not yet been well described as one such predictor. From 2017 to 2021, 816 patients with CTEPH referred to the University of California, San Diego for PTE were reviewed for differences in NT-pro-BNP to predict preoperative characteristics and postoperative outcomes up to 30 days post-PTE. For analysis, NT-pro-BNP was dichotomized to less than/equal to or greater than 1000 pg/mL based on the mean of the study population. Mean NT-pro-BNP was 1095.9 ±1783.4 pg/mL and median was 402.5 pg/mL (interquartile range: 119.5–1410.8). Of the 816 patients included, 250 had NT-pro-BNP > 1000 pg/mL. Those with NT-pro-BNP > 1000 pg/mL were significantly more likely to have worse preoperative functional class (III–IV) and worse preoperative hemodynamics. Patients with NT-pro-BNP > 1000 pg/mL also tended to have more postoperative complications including reperfusion pulmonary edema (22% vs. 5.1%, $p < 0.001$), airway hemorrhage (8.4% vs. 4.9%, $p = 0.075$), residual pulmonary hypertension (11.9% vs. 3.1%, $p < 0.001$), and 30-day mortality (4.8% vs. 1.1%, $p = 0.001$). Even after adjusting for confounders, patients with NT-pro-BNP > 1000 pg/mL had a 2.48 times higher odds (95% confidence interval: 1.45–4.00) of reaching a combined endpoint that included the above complications. Preoperative NT-pro-BNP > 1000 pg/mL is a strong predictor of more severe preoperative hemodynamics and identifies patients at higher risk for postoperative complications.

KEYWORDS
cardiovascular diseases, pulmonary circulation, pulmonary hypertension, risk stratification and biomarkers, thoracic surgery

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by incomplete resolution of pulmonary emboli leading to chronic organized obstruction of pulmonary arteries. This may in turn lead to increased pulmonary vascular resistance (PVR), progressively worsening right ventricular (RV) failure and even death if untreated.[1,2] However, CTEPH is potentially curable with pulmonary thromboendarterectomy (PTE), a surgical procedure that relieves pulmonary hypertension (PH) by mechanical removal of the chronic thromboembolic material, and should be considered for all CTEPH patients. Although a potential cure, PTE surgery is associated with significant morbidity and mortality even in experienced centers. Thirty-day mortality after PTE has been reported as high as 24.4%, with a meta-analysis suggesting mortality closer to 8.4%.[3] Various nonfatal complications are also associated with PTE including residual PH, severe hypoxemia secondary to reperfusion lung injury and/or ventilation/perfusion mismatch, and airway bleeding.[4] As such, careful consideration of the potential risks versus benefits of PTE is warranted when evaluating treatment options for CTEPH. Currently, predictors of surgical outcomes after PTE for CTEPH are limited to clinical characteristics such as functional status, 6-min walking distance, comorbidities, as well as preoperative hemodynamics, such as PVR.[5–7] While these variables are helpful in counseling patients about mortality risks before offering surgery, additional information is necessary to further risk stratify patients for other postoperative complications.

N-terminal-pro-brain natriuretic peptide (NT-pro BNP) is released from cardiac myocytes in response to pressure and volume overload. Natriuretic peptides, such as brain natriuretic peptide (BNP) and NT-pro-BNP, have emerged as potential biomarkers for predicting outcomes after PTE in CTEPH patients. Studies have demonstrated that both NT-pro-BNP and BNP increase in response to RV remodeling and dysfunction, which is commonly observed in CTEPH patients.[8] These biomarkers could provide additional information for risk stratification and potentially improve patient selection for PTE surgery.

In this study, we investigated the use of NT-pro-BNP levels as a preoperative biomarker to improve the predictive power of post-PTE outcomes in patients with operable CTEPH. We retrospectively analyzed our database of patients who underwent PTE at the University of California, San Diego and evaluated whether elevated NT-pro-BNP was predictive of surgical outcomes, including the risk for clinical endpoints such as reperfusion pulmonary edema, airway hemorrhage, residual PH, and death. Additionally, we determined whether the predictive ability of NT-pro-BNP was independent of other clinical variables known to predict morbidity and mortality after PTE.

METHODS

Patients/study subjects

This study utilized data obtained from an Institutional Review Board-approved database of patients who had previously received a diagnosis of CTEPH or chronic thromboembolic disease and underwent PTE at the University of California, San Diego between January 2017 and April 2021. A multidisciplinary team comprising radiologists, pulmonary vascular medicine specialists, and cardiothoracic surgeons assessed surgical eligibility based on the presence of surgically accessible disease via imaging, significant symptoms, and hemodynamic dysfunction attributed to CTEPH. Hemodynamic data was collected via right heart catheterization both preoperatively (approximately 1 week before PTE) and postoperatively (within the first 48–72 h after PTE). Postoperative complications, including reperfusion pulmonary edema (defined as new infiltrates in end-endarterectomized territories with PaO_2:$FiO_2 < 150$), airway hemorrhage (defined as any airway bleeding requiring change in management, including holding anticoagulation, use of bronchial blockers, or requiring extracorporeal membrane oxygenation support), residual PH (defined as PVR > 400 dynes s/cm^5), and mortality within 30-days post-PTE, were assessed in all patients. Although these complications are rare in experienced PTE referral centers like the University of California, San Diego, they are among the most common associated with PTE. The development of one or more perioperative outcome was considered a "combined endpoint."

NT-pro-BNP

Before PTE, peripheral blood samples were collected for serum NT-pro-BNP during routine clinical evaluations. A

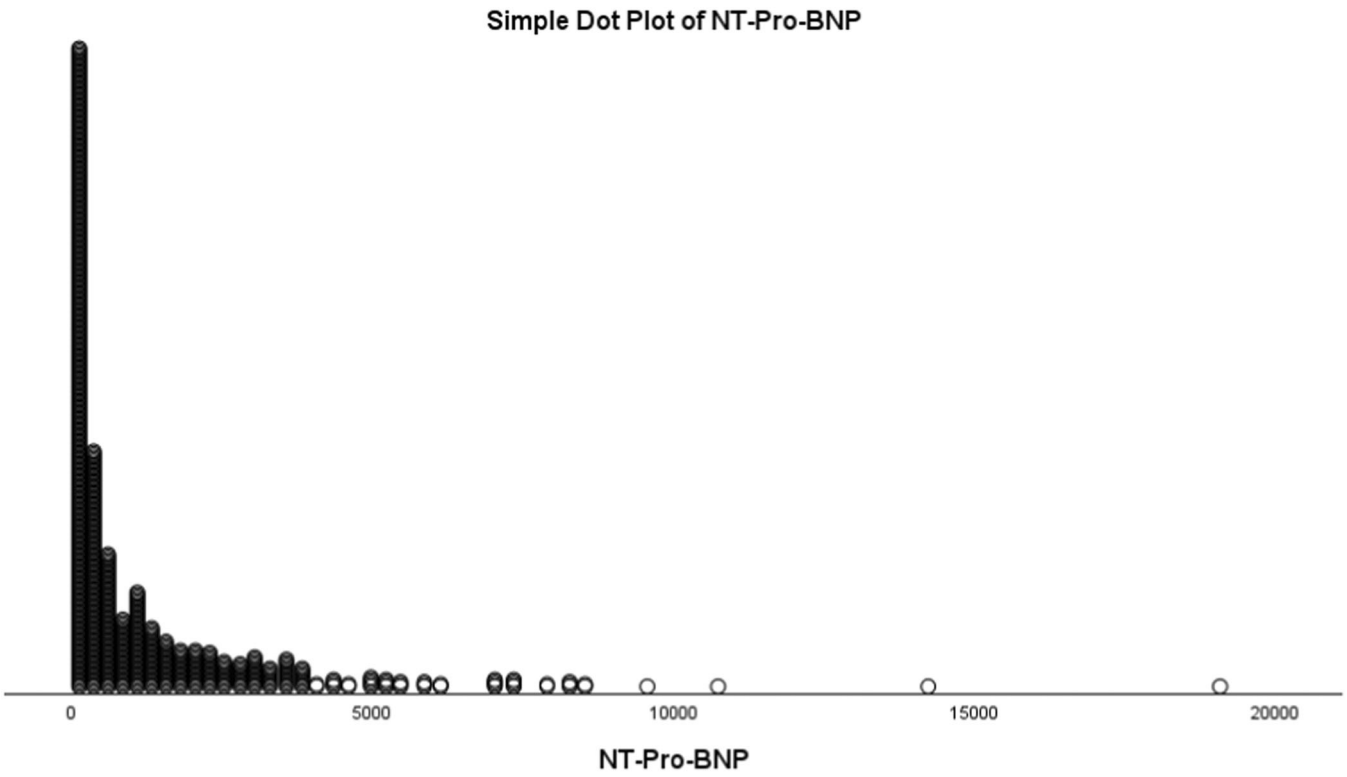

FIGURE 1 Simple dot plot of preoperative NT-pro-BNP. Each circle represents one patient. Given the right-skew, the NT-pro-BNP was normalized by taking the log NT-pro-BNP. For the assessment of outcomes, an NT-pro-BNP of 1000 pg/mL was chosen as the cut point because it was near the population mean (1095 pg/mL) and the center of the normalized curve of log NT-pro-BNP. NT-pro-BNP, N-terminal-pro-brain natriuretic peptide.

standard assay with a cut-off value of 50 pg/mL was used for analysis. Serum creatinine levels were also measured at the same time as serum NT-pro-BNP and served as a surrogate for renal function. To compare outcomes, the distribution of NT-pro-BNP was analyzed and then dichotomized into values less than/equal to or greater than 1000 pg/mL. As the data was rightward skewed, we normalized the distribution of NT-pro-BNP by using a logarithmic transformation with a base of 10 (Figure 1). The cut-off value of 1000 pg/mL was chosen for analysis as it was the round number closest to the mean value of NT-pro-BNP for the study population.

Statistical analysis

Statistical analysis was performed using SPSS version 28 by IBM. Differences in normally distributed, continuous variables were assessed using *t* tests, while Fisher exact tests were used to compare categorical variables. A Pearson correlation was used to determine the relationship between preoperative PVR and baseline NT-pro-BNP. To determine the odds ratio for postoperative complications, logistic regression was employed after establishing the incidence of each component of the combined endpoint. Given the right skew of the data, the log NT-pro-BNP was analyzed first as a continuous variable then was dichotomized to either less than/equal to or greater than 1000 pg/mL. The forward likelihood method was used to identify variables that may be associated with the combined endpoint (e.g., hemodynamics, use of PAH medications, sex, age, and body mass index [BMI]) or could increase NT-pro-BNP (e.g., serum creatinine as a proxy for renal function), which were included in the final models to allow for adjustment.

RESULTS

During the study period, 816 patients underwent PTE. Of these, 35 patients were excluded due to incomplete data for preoperative serum NT-pro-BNP levels. Baseline demographics and preoperative characteristics of the remaining patients are shown in Table 1. The mean age of the study population was 54 years. The majority of patients were New York Heart Association functional class III. Over 50% of the patients were on pulmonary arterial hypertension-targeted

TABLE 1 Population characteristics ($n = 816$).

Age (years)	54 ± 16
Sex (M:F)	394:421
Percent female	51.60%
BMI (kg/m^2)	30.4 ± 7.5
Preop NYHA functional class	
I	0.7% ($n = 6$)
II	19.6% ($n = 160$)
III	71.0% ($n = 579$)
IV	8.3% ($n = 68$)
History of DVT	346 (42.4%)
History of splenectomy	33 (4.0%)
Known coagulopathy	194 (23.8%)
IV device	45 (5.5%)
History of malignancy	95 (11.6%)
Preop PH medications	421 (51.6%)
Preop RA (mmHg)	9.5 ± 5.7
Preop mean PA (mmHg)	38.3 ± 13.7
Preop CI (L/min/m^2)	2.4 ± 0.6
Preop PVR (dyn s/cm^5)	522.3 ± 328.8
Preop TAPSE (cm)	1.9 ± 0.6
Preop NT-pro-BNP (pg/mL)	1095.9 ± 1783.4

Abbreviations: BMI, body mass index; CI, cardiac index; DVT, deep vein thrombosis; F, female; IV, intravenous; M, male; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PH, pulmonary hypertension; Preop, preoperative; PVR, pulmonary vascular resistance; RA, right atrial; TAPSE, tricuspid annular plane systolic excursion.

medical therapies before surgery. The patients had a wide range of PH with mean preoperative PVR of 522.3 ± 328.8 dyn s/cm^5, right atrial pressure (RAP) of 9.5 ± 5.7 mmHg, and mean pulmonary artery pressure (mPAP) of 38.3 ± 13.7 mmHg. There was no significant difference in pulmonary artery wedge pressure (PAWP) between the two groups ($p = 0.264$). The mean preoperative NT-pro-BNP level was 1095.9 ± 1783.4 pg/mL (Figure 1); the median NT-pro-BNP level was 402.5 pg/mL (interquartile range: 119.5–1410.8). Baseline NT-pro-BNP had a strong positive correlation with preoperative PVR ($r^2 = 0.478$) (Supporting Information S1: Table 1). Adjusting for potential confounding variables, including age, sex, BMI, preoperative PAH medication use, preoperative PVR, and baseline creatinine, the log(NT-pro-BNP) was associated with an odds ratio of 2.63 (95% confidence interval [CI]: 1.73–3.98, $p < 0.001$) for developing any of the components of the combined endpoint.

After dichotomizing the patients into those with NT-pro-BNP levels less than/equal to or greater than 1000 pg/mL, significant differences were observed in baseline characteristics. Patients with preoperative NT-pro-BNP levels > 1000 pg/mL had a lower BMI, higher creatinine, and worse functional class preoperatively (Table 2). However, there were no differences in risk factors for the development of CTEPH. Patients with preoperative NT-pro-BNP levels > 1000 pg/mL also had worse preoperative hemodynamics, including lower cardiac index, higher mPAP, higher PVR, higher RAP, higher total pulmonary resistance, lower tricuspid annular plane systolic excursion, larger RV size, worse RV function, and were more likely to have pericardial effusion (Table 2).

Postoperatively, the patients with preoperative NT-pro-BNP > 1000 pg/mL had significantly worse hemodynamics compared to the low NT-pro-BNP group. Though the mean PVR in patients with NT-pro-BNP > 1000 pg/mL improved from 799.6 dynes s/cm^5 preoperatively to 269.0 dynes s/cm^5 postoperatively, this was significantly higher compared to patients with NT-pro-BNP ≤ 1000 pg/mL (Tables 2 and 3). Elevated preoperative NT-pro-BNP levels > 1000 pg/mL were also associated with a higher incidence of postoperative complications, including reperfusion pulmonary edema (22.0% vs. 5.1%, $p < 0.001$), residual PH (11.9% vs. 3.1%, $p < 0.001$) and 30-day mortality (4.8% vs. 1.1%, $p = 0.001$) compared to the ≤1000 pg/mL group (Table 4). Although not statistically significant, there was a trend for patients to have an increased risk of airway hemorrhage (8.4% vs. 4.9%, $p = 0.075$).

Using multivariate logistic regression analysis, we calculated the odds ratio for the occurrence of a combined endpoint that included reperfusion pulmonary edema, airway hemorrhage, residual PH, and 30-day mortality. We compared patients with preoperative NT-pro-BNP levels > 1000 pg/mL to those with levels 1000 pg/mL. Adjusting for potential confounding variables, including age, sex, BMI, preoperative PAH medication use, preoperative PVR, and baseline creatinine, patients with preoperative NT-pro-BNP levels > 1000 pg/mL had 2.48 times higher odds of meeting a combined endpoint compared to those with levels ≤1000 pg/mL (95% CI: 1.48–4.14, $p < 0.001$) (Table 5).

DISCUSSION

The present study highlights the utility of preoperative NT-pro-BNP levels as a tool for risk stratification in patients with CTEPH undergoing PTE surgery. The results suggest that patients with NT-pro-BNP levels >

TABLE 2 Preoperative characteristics of CTEPH patients undergoing PTE stratified by degree of NT-pro-BNP elevation ($n = 781$).

Preoperative characteristic	NT-pro-BNP ≤ 1000 pg/mL	NT-pro-BNP > 1000 pg/mL	*p* Value
Age, years ($n = 781$)	53.5 ± 15.7	55.4 ± 16.6	0.116
Sex, % female	50.1% ($n = 266$)	56.6% ($n = 141$)	0.081
BMI, kg/m^2 ($n = 726$)	31.1 ± 7.5	28.9 ± 7.0	<0.001
Creatinine, mg/dL ($n = 781$)	1.0 ± 0.3	1.2 ± 1.0	0.001
Preop NHYA functional class			<0.001
I	1.1% ($n = 6$)	0.0% ($n = 0$)	
II	24.9% ($n = 132$)	8.8% ($n = 22$)	
III	70.4% ($n = 374$)	75.6% ($n = 189$)	
IV	3.6% ($n = 19$)	15.6% ($n = 39$)	
History of PE	96.0% ($n = 510$)	96.0% ($n = 240$)	0.976
History of thrombolysis	15.2% ($n = 25$)	10.9% ($n = 7$)	0.400
History of thrombectomy	11.1% ($n = 4$)	10.5% ($n = 2$)	0.947
History of DVT	57.3% ($n = 304$)	58.4% ($n = 146$)	0.762
History of upper extremity DVT	4.5% ($n = 24$)	4.8% ($n = 12$)	0.862
History of IV device	5.3% ($n = 28$)	6.4% ($n = 16$)	0.524
History of splenectomy	4.9% ($n = 26$)	2.4% ($n = 6$)	0.101
History of known coagulopathy[a]	23.7% ($n = 126$)	22.4% ($n = 56$)	0.682
Preop pulmonary hypertension meds	55.0% ($n = 292$)	50.4% ($n = 126$)	0.230
Preop hemodynamics			
Preop RA, mmHg	8.2 ± 4.6	12.6 ± 6.8	<0.001
Preop mean PA, mmHg	35.5 ± 11.5	45.1 ± 14.4	<0.001
Preop PAWP, mmHg	12.2 ± 4.4	11.8 ± 5.4	0.264
Preop CO, L/min	5.3 ± 1.3	4.0 ± 1.3	<0.00
Preop CI, L/min/m^2	2.6 ± 0.6	2.0 ± 0.5	<0.001
Preop PVR, dyn s/cm^5	394.9 ± 225.1	799.6 ± 346.1	<0.001
Preop TPR, dyn s/cm^5	588.4 ± 249.5	1051.0 ± 392.0	<0.001
Preop S′, cm/s	0.135 ± 0.179	0.114 ± 0.139	0.115
Preop TAPSE, cm	2.08 ± 0.56	1.61 ± 0.63	<0.01
Preop LVEF, %	64.7% ± 7.8%	64.3% ± 9.3%	0.505
Preop LA volume index, mL/m^2	24.5 ± 7.8	23.0 ± 9.6	0.057
Preop RV size			<0.001
Normal	20.2% ($n = 98$)	0.8% ($n = 2$)	
Mild	36.8% ($n = 179$)	6.0% ($n = 15$)	
Moderate	26.1% ($n = 127$)	18.4% ($n = 46$)	
Severe	16.0% ($n = 78$)	74.4% ($n = 186$)	
Preop RV function			<0.001
Normal	56.4% ($n = 274$)	7.6% ($n = 19$)	
Reduced	42.6% ($n = 207$)	91.6% ($n = 229$)	

(Continues)

TABLE 2 (Continued)

Preoperative characteristic	NT-pro-BNP ≤ 1000 pg/mL	NT-pro-BNP > 1000 pg/mL	*p* Value
Preop pericardial effusion			<0.001
None	89.1% ($n = 433$)	61.6% ($n = 154$)	
Trivial	8.6% ($n = 42$)	26% ($n = 65$)	
Small	1.4% ($n = 7$)	10.4% ($n = 26$)	
Moderate	0.2% ($n = 1$)	0.8% ($n = 2$)	
Large	0.0% ($n = 0$)	0.8% ($n = 2$)	

Note: All categorical variables compared using a χ^2 test. *t* test used for continuous variables.

Abbreviations: BMI, body mass index; CI, cardiac index; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; IV, intravenous; LA, left atrial; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PE, pulmonary embolism; Preop, preoperative; PTE, pulmonary thromboendarterectomy; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricle; S′, tissue doppler velocity; TAPSE, tricuspid annular plane systolic excursion; TPR, total pulmonary resistance.

[a]Factor V Leiden, antithrombin III, protein S or protein C deficiency, lupus anticoagulant, or anticardiolipin antibodies.

TABLE 3 Postoperative hemodynamics of CTEPH following PTE stratified by degree of NT-pro-BNP elevation ($n = 781$).

Postoperative hemodynamics	NT-pro-BNP ≤ 1000 pg/mL	NT-pro-BNP > 1000 pg/mL	*p* Value
RA, mmHg	8.0 ± 3.2	8.3 ± 3.8	0.401
mean PA, mmHg	21.5 ± 6.1	25.8 ± 8.4	<0.001
CO, L/min	5.7 ± 1.3	5.4 ± 1.2	<0.002
CI, L/min/m^2	2.8 ± 0.5	2.8 ± 0.5	0.316
PVR, dyn s/cm^5	199.6 ± 98.5	269.0 ± 131.9	<0.001
TPR, dyn s/cm^5	317.8 ± 119.0	399.4 ± 167.6	<0.001
ΔPVR, dyn s/cm^5	203.8 ± 198.2	528.2 ± 337.3	<0.001
ΔTPR, dyn s/cm^5	276.8 ± 230.3	648.4 ± 390.5	<0.001

Note: Comparison using *t* test.

Abbreviations: CI, cardiac index; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; PA, pulmonary artery; PTE, pulmonary thromboendarterectomy; PVR, pulmonary vascular resistance; RA, right atrial; TPR, total pulmonary resistance.

TABLE 4 Primary outcomes of patients stratified by degree of NT-pro-BNP elevation ($n = 781$).

	NT-pro-BNP ≤ 1000 pg/mL	NT-pro-BNP > 1000 pg/mL	*p* Value
Reperfusion pulmonary edema	5.1% ($n = 27$)	22% ($n = 55$)	<0.001
Airway hemorrhage	4.9% ($n = 26$)	8.4% ($n = 21$)	0.075
Residual pulmonary hypertension	3.1% ($n = 15$)	11.9% ($n = 27$)	<0.001
30-day mortality	1.1% ($n = 6$)	4.8% ($n = 12$)	0.001

Note: Comparison using χ^2 test.

Abbreviation: NT-pro-BNP, N-terminal-pro-brain natriuretic peptide.

1000 pg/mL are more likely to have worse hemodynamics pre- and postoperatively, and are at an increased risk for postoperative complications, including reperfusion pulmonary edema, residual PH, and mortality within 30 days post-PTE. These findings remained significant even after adjusting for confounding variables such as preoperative hemodynamics, use of PAH medications, sex, age, BMI, and renal function. Therefore, NT-pro-BNP may be a valuable tool in identifying high-risk patients who may require closer postoperative monitoring or alternative management strategies to allow for preoperative optimization.

TABLE 5 Odds of CTEPH patient meeting combined endpoint within 30 days post-PTE ($n = 781$).

Exposure	Odds ratio (95% CI)	*p* Value
NT-pro-BNP ≥ 1000 pg/mL	2.48 (1.48–4.14)	<0.001**
Age (per year)	1.02 (1.00–1.03)	0.014*
Sex	2.10 (1.33–3.29)	0.001**
BMI (per kg/m^2)	1.01 (0.98–1.04)	0.435
Preop use of PAH medications	1.54 (0.99–2.40)	0.053
Preop PVR (per 1 dyn s/cm^5)	1.00 (1.00–1.00)	<0.001**
Creatinine (per 1 mg/dL)	0.84 (0.51–1.41)	0.516

Abbreviations: BMI, body mass index; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; Preop, preoperative; PVR, pulmonary vascular resistance; PTE, pulmonary thromboendarterectomy; TPR, total pulmonary resistance.
*$p < 0.05$ comparison between patients not meeting combined endpoint and meeting combined endpoint.; **$p < 0.01$ comparison between patients not meeting combined endpoint and meeting combined endpoint.

The ability to prognosticate postoperative complications is currently limited to clinical variables. There is extensive literature suggesting preoperative hemodynamics are a crucial factor driving postoperative complications, especially perioperative mortality and postoperative residual PH.[5,6,9] Reperfusion pulmonary edema (also referred to as reperfusion lung injury) is associated with longer, more complicated intensive care unit stays and higher mortality.[10,11] The incidence may be decreasing in more recent series but still affects about 10% of patients.[12] Preoperative hemodynamics, especially RAP and PVR, appear to increase the risk for reperfusion pulmonary edema[13] and for postoperative airway hemorrhage.[14] Airway hemorrhage is also increased in those with preoperative hemoptysis. Finally, comorbid medical condition, age, and sex may also influence postoperative morbidity and mortality.[5,15,16]

Aside from the preoperative hemodynamics, we have little else that can be used for prognostication. NT-pro-BNP is a marker of atrial and myocardial stress that correlates with volume overload of the right and left ventricles (LV); it is widely established as a biomarker that increases in response to ventricular remodeling/dysfunction and increased ventricular filling pressures. Others have evaluated left atrial pressures in CTEPH and saw higher NT-pro-BNP levels in the group with LV filling pressures > 15 mmHg.[17] However, in the current analysis, while there were differences in PVR and mean PA pressure between the groups with NT-pro-BNP less than/equal to or greater than 1000 pg/mL, there were no differences in the PAWP. This suggests the elevated NT-pro-BNP levels are due to RV dysfunction. In the European Society of Cardiology/European Respiratory Society guidelines for PH, NT-pro-BNP is used as part of a three-strata risk assessment tool to estimate initial prognosis in pulmonary arterial hypertension. Specifically, patients with NT-pro-BNP of 300−1000 and >1100 ng/L (pg/mL) are associated with intermediate and high-risks strata, suggesting estimated 1-year mortality risks of 5%–20% and >20%, respectively. Risk strata for CTEPH are not yet defined, but our findings suggest a potential use of preoperative NT-pro-BNP to develop similar risk assessment tools.[18] While NT-pro-BNP correlated with preoperative PVR in this study, it explained less than half of its variation. Patients may frequently present with discordance between the PVR and NT-pro-BNP. Some of this discordance may be due to co-morbidities such as renal failure which has been shown to increase NT-pro-BNP.[19] Furthermore, PVR may be lowered by the use of PAH-targeted medical therapies. In the CHEST study of patients with inoperable or recurrent CTEPH after PTE, treatment with riociguat was associated with a 291 pg/mL reduction in NT-pro-BNP after 16 weeks,[20] highlighting the effects of medical therapy on NT-pro-BNP in CTEPH.

To account for the multiple conditions that could affect NT-pro-BNP levels in the present study, we adjusted for known potential confounders including age,[21] sex,[22] BMI,[23] renal function,[19] preoperative PAH medication use,[20] and preoperative PVR.[8] Despite these adjustments, we still observed a statistically significant association between preoperative NT-pro-BNP levels > 1000 pg/mL and the combined endpoint of reperfusion pulmonary edema, airway hemorrhage, residual PH, and 30-day mortality.

The present study represents the largest investigation to date exploring the utility of NT-pro-BNP in predicting post-PTE surgical outcomes including both morbidity and mortality in patients with CTEPH. However, our study had several limitations including its retrospective nature and the lack of long-term follow-up beyond 30 days post-PTE. Additionally, the study was conducted at a single center with expertise in CTEPH with a postoperative mortality rate much lower than other published registries. We have developed an expertise in selecting appropriate patients for surgery, including those at higher risk, operating on technically difficult cases, and managing various complications; thus, these results may not be generalizable to other centers with differing experience levels. In a recent meta-analysis, postoperative morbidity and mortality were noted to decrease as the volume of PTE cases at a center increased.[3] Future studies may seek to validate our findings at a multicenter level, with varying surgical volumes and experience.

CONCLUSIONS

In summary, our study showed that preoperative NT-pro-BNP levels greater than 1000 pg/mL were associated with poor baseline hemodynamics, worse postoperative hemodynamics, and high risk for postoperative morbidity and mortality in patients with CTEPH who underwent PTE. Our results suggest that NT-pro-BNP can be a useful tool in assessing the risk of adverse outcomes and predicting hemodynamic improvements in CTEPH patients undergoing PTE. Altogether, NT-pro-BNP is a widely accessible and cost-effective tool that can be obtained preoperatively to improve prognostication of postoperative risks and predict improvements in hemodynamics in CTEPH patients being considered for PTE.

AUTHOR CONTRIBUTIONS

Emanuel A. Keiler: Conceptualization; data curation; investigation; formal analysis; writing—original draft. **Kim M. Kerr**: Investigation; writing—review and editing. **David S. Poch**: Investigation; writing—review and editing. **Jenny Z. Yang**: Investigation; writing—review and editing. **Demosthenes G. Papamatheakis**: Investigation; writing—review and editing. **Mona Alotaibi**: Investigation; writing—review and editing. **Angela Bautista**: Investigation; data curation; writing—review and editing. **Victor G. Pretorius**: Investigation; writing—review and editing. **Michael M. Madani**: Investigation; writing—review and editing; **Nick H. Kim**: Investigation; writing—review and editing. **Timothy M. Fernandes**: Conceptualization; methodology; investigation; formal analysis; writing—original draft, supervision.

ACKNOWLEDGMENTS

The authors have no funding to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

All patient information was obtained from a deidentified quality improvement database for the University of California, San Diego (UCSD) Pulmonary Thromboendarterectomy Program. Informed consent was waived and data collected in accordance with the standards set by UCSD's Institutional Review Board.

ORCID

Emanuel A. Keiler http://orcid.org/0000-0001-6753-5868
David S. Poch http://orcid.org/0000-0002-7669-3662
Jenny Z. Yang https://orcid.org/0000-0002-4844-8715
Victor G. Pretorius http://orcid.org/0000-0001-6360-4002

REFERENCES

1. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, Ogo T, Tapson VF, Ghofrani HA, Jenkins DP. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53(1):1801915. https://doi.org/10.1183/13993003.01915-2018
2. Papamatheakis DG, Poch DS, Fernandes TM, Kerr KM, Kim NH, Fedullo PF. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol. 2020;76(18):2155–69. https://doi.org/10.1016/j.jacc.2020.08.074
3. Brookes JDL, Li C, Chung STW, Brookes EM, Williams ML, McNamara N, Martin-Suarez S, Loforte A. Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension: a systematic review. Ann Cardiothorac Surg. 2022;11(2):68–81. https://doi.org/10.21037/acs-2021-pte-25
4. Fedullo P, Kerr KM, Kim NH, Auger WR. Chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2011;183(12):1605–13. https://doi.org/10.1164/rccm.201011-1854CI
5. Tscholl D. Pulmonary thromboendarterectomy - risk factors for early survival and hemodynamic improvement. Eur J Cardiothorac Surg. 2001;19(19):771–6.
6. Perrot M, McRae K, Donahoe L, Abdelnour-Berchtold E, Thenganatt J, Granton J. Pulmonary endarterectomy in severe chronic thromboembolic pulmonary hypertension: the Toronto experience. Ann Cardiothorac Surg. 2022;11(2):133–42. https://doi.org/10.21037/acs-2021-pte-14
7. Suntharalingam J, Goldsmith K, Toshner M, Doughty N, Sheares KK, Hughes R, Jenkins D, Pepke-Zaba J. Role of NT-proBNP and 6MWD in chronic thromboembolic pulmonary hypertension. Respir Med. 2007;101(11):2254–62. https://doi.org/10.1016/j.rmed.2007.06.027
8. Reesink HJ, Tulevski II, Marcus JT, Boomsma F, Kloek JJ, Vonk Noordegraaf A, Bresser P. Brain natriuretic peptide as noninvasive marker of the severity of right ventricular dysfunction in chronic thromboembolic pulmonary hypertension. Ann Thorac Surg. 2007;84(2):537–43. https://doi.org/10.1016/j.athoracsur.2007.04.006
9. Saouti N, Morshuis WJ, Heijmen RH, Snijder RJ. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a single institution experience. Eur J Cardiothorac Surg. 2009;35(6):947–52. https://doi.org/10.1016/j.ejcts.2009.01.023
10. Thistlethwaite PA, Madani M, Jamieson SW. Outcomes of pulmonary endarterectomy surgery. Semin Thorac Cardiovasc Surg. 2006;18(3):257–64. https://doi.org/10.1053/j.semtcvs.2006.09.008
11. Kerr KM, Auger WR, Marsh JJ, Devendra G, Spragg RG, Kim NH, Channick RN, Jamieson SW, Madani MM, Manecke GR, Roth DM, Shragg GP, Fedullo PF. Efficacy of methylprednisolone in preventing lung injury following pulmonary thromboendarterectomy. Chest. 2012;141(1):27–35. https://doi.org/10.1378/chest.10-2639

12. Fernandes TM, Kim NH, Kerr KM, Auger WR, Fedullo PF, Poch DS, Yang J, Papamatheakis DG, Alotaibi M, Bautista MA, Pretorius VG, Madani MM. Distal vessel pulmonary thromboendarterectomy: results from a single institution. J Heart Lung Transplant. 2023;42:1112–9. https://doi.org/10.1016/j.healun.2023.02.1500
13. Fernandes TM, Poch DS, Papamatheakis DG, Fedullo PF, Kim NH, Auger WR, Kerr KM. Pre-operative determinants of reperfusion lung injury after pulmonary thromboendarterectomy. J Heart Lung Transplant. 2016;35(4):S175–6. https://doi.org/10.1016/j.healun.2016.01.487
14. Kabadi AA, Fernandes TM, Papamatheakis DG, Poch DS, Kim NH, Yang JZ, Bautista A, Pretorius VG, Madani MM, Kerr KM. Airway hemorrhage complicating pulmonary thromboendarterectomy: risk factors and outcomes. Ann Thorac Surg. 2023;116(22):121–8. https://doi.org/10.1016/j.athoracsur.2022.11.003
15. Fernandes TM, Auger WR, Fedullo PF, Kim NH, Poch DS, Madani MM, Pretorius VG, Jamieson SW, Kerr KM. Baseline body mass index does not significantly affect outcomes after pulmonary thromboendarterectomy. Ann Thorac Surg. 2014;98(5):1776–81. https://doi.org/10.1016/j.athoracsur.2014.06.045
16. Ogino H, Ando M, Matsuda H, Minatoya K, Sasaki H, Nakanishi N, Kyotani S, Imanaka H, Kitamura S. Japanese single-center experience of surgery for chronic thromboembolic pulmonary hypertension. Ann Thorac Surg. 2006;82(2):630–6. https://doi.org/10.1016/j.athoracsur.2006.03.121
17. Gerges C, Pistritto AM, Gerges M, Friewald R, Hartig V, Hofbauer TM, Reil B, Engel L, Dannenberg V, Kastl SP, Skoro-Sajer N, Moser B, Taghavi S, Klepetko W, Lang IM. Left ventricular filling pressure in chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol. 2023;81(7):653–64. https://doi.org/10.1016/j.jacc.2022.11.049
18. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, ESC Scientific Document G. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67–119. https://doi.org/10.1093/eurheartj/ehv317
19. Takase H, Dohi Y. Kidney function crucially affects B-type natriuretic peptide (BNP), N-terminal proBNP and their relationship. Eur J Clin Invest. 2014;44(3):303–8. https://doi.org/10.1111/eci.12234
20. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 2013;369(4):319–29. https://doi.org/10.1056/NEJMoa1209657
21. Park HJ, Baek SH, Jang SW, Kim DB, Shin DI, Shin WS, Kim PJ, Jung HB, Jung HO, Seung KB, Choi KB. Direct comparison of B-type natriuretic peptide and N-terminal pro-BNP for assessment of cardiac function in a large population of symptomatic patients. Int J Cardiol. 2010;140(3):336–43. https://doi.org/10.1016/j.ijcard.2008.11.107
22. Franke J, Lindmark A, Hochadel M, Zugck C, Koerner E, Keppler J, Ehlermann P, Winkler R, Zahn R, Katus HA, Senges J, Frankenstein L. Gender aspects in clinical presentation and prognostication of chronic heart failure according to NT-proBNP and the Heart Failure Survival Score. Clin Res Cardiol. 2015;104(4):334–41. https://doi.org/10.1007/s00392-014-0786-z
23. Krauser DG, Lloyd-Jones DM, Chae CU, Cameron R, Anwaruddin S, Baggish AL, Chen A, Tung R, Januzzi JL. Effect of body mass index on natriuretic peptide levels in patients with acute congestive heart failure: a ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) substudy. Am Heart J. 2005;149(4):744–50. https://doi.org/10.1016/j.ahj.2004.07.010

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Keiler EA, Kerr KM, Poch DS, Yang JZ, Papamatheakis DG, Alotaibi M, Bautista A, Pretorius VG, Madani MM, Kim NH, Fernandes TM. NT-pro-BNP is predictive of morbidity and mortality after pulmonary thromboendarterectomy and is independent of preoperative hemodynamics. Pulm Circ. 2024;14:e12367. https://doi.org/10.1002/pul2.12367