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Right Ventricular Dysfunction is Superior and Sufficient for Risk Stratification by a Pulmonary Embolism Response Team

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Abstract

Introduction: Several risk stratification tools are available to predict short-term mortality in patients with acute pulmonary embolism (PE). The presence of ventricular (RV) dysfunction is an independent predictor of mortality and may be a more efficient way to stratify risk for patients assessed by a Pulmonary Embolism Response Team (PERT).

Methods: We evaluated 571 patients presenting with acute PE, then stratified them by the Pulmonary Embolism Severity Index (PESI), by the BOVA score, or categorically as low risk (no RV dysfunction by imaging), intermediate risk (RV dysfunction by imaging), or high risk PE (RV dysfunction with sustained hypotension). Using imaging data to firstly define the presence of RV strain, and plasma cardiac biomarkers as additional evidence for myocardial dysfunction, we evaluated whether PESI, BOVA, or RV strain were more appropriate for determining patient risk by a PERT where rapid decision making is important.

Results: Cardiac biomarkers poorly distinguished between PESI classes and BOVA stages in patients with acute PE. Cardiac TnT and NT-proBNP easily distinguished low risk from submassive PE with an area under the curve (AUC) of 0.84 (95% C.I. 0.73 – 0.95, $p < 0.0001$), and 0.88 (95% C.I. 0.79–0.97, $p < 0.0001$), respectively. Cardiac TnT and NT-proBNP easily distinguished low risk from massive PE with an area under the curve (AUC) of 0.89 (95% C.I. 0.78 – 1.00, $p < 0.0001$), and 0.89 (95% C.I. 0.82–0.95, $p < 0.0001$), respectively. In patients with RV dysfunction, the predicted short-term mortality by PESI score or BOVA stage was lower than the observed mortality by a two-fold order of magnitude.

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Conclusions: The presence of RV dysfunction alone in the context of acute PE is sufficient for the purposes of risk stratification. More complicated risk stratification tools which require the consideration of multiple clinical variables may under-estimate short-term mortality risk.

Keywords

Pulmonary Embolism (PE); Right Ventricle (RV); Biomarker; Pulmonary Embolism Response Team (PERT); Pulmonary Embolism Severity Index (PESI); BOVA Score

Introduction

Pulmonary embolism (PE) is a life-threatening thrombotic emergency. As the third leading cause of cardiovascular mortality following myocardial infarction and stroke, PE is responsible for approximately 200,000 deaths yearly [1, 2]. Various risk stratification algorithms may be utilized to determine short-term mortality following PE. The Pulmonary Embolism Severity Index (PESI) is one such algorithm used widely for predicting 30-day mortality in patients diagnosed with relatively low risk acute PE [3–6]. The PESI score is based on vital signs as well as multiple clinical and hemodynamic variables [3, 7]. The BOVA score is also useful for predicting 30-day mortality and incorporates some higher risk features of acute PE including the presence of RV dysfunction [8].

The presence of RV dysfunction appears to be an independent variable predicting increased mortality in acute PE by approximately two-fold [9]–[10, 11]. RV dysfunction can be determined qualitatively or quantitatively by various imaging modalities or indirectly inferred by an elevated concentration of plasma cardiac biomarkers. The American College of Chest physicians (ACCP) does not endorse routine assessment of plasma cardiac biomarkers in patients diagnosed with acute PE. The European Society of Cardiology (ESC) guidelines, conversely, include the PESI score as well as elevated cardiac biomarkers and imaging information to determine RV dysfunction to further risk stratify a patient with acute PE [12–14]. Recent studies suggest that elevated plasma cardiac troponin in patients with PE is associated with an increase in all-cause mortality [12].

The use of Pulmonary Embolism Response Teams (PERTs) to rapidly assess patient risk and to institute a treatment algorithm for patients with submassive and massive PE has gained popularity around the world, and may improve the efficiency of treatment in acute care environments such as the emergency department [15–18]. Prognostic information obtained during expedited patient evaluation may influence the choice of advanced treatment options which recently was reported as an independent variable predicting mortality [19].

A much simpler way to categorize acute PE for the purposes of a PERT evaluation may be the presence of RV dysfunction: 1. Low risk PE (normotensive, no RV dysfunction), 2. Intermediate risk or “submassive” PE (normotensive with RV dysfunction), 3. High risk or “massive” PE (SBP < 90 mmHg for at least 15 minutes attributable to RV dysfunction) [20]. To illustrate this point, Sanchez et al. reported that RV dysfunction by either echocardiography or CTA, or by elevated plasma cardiac biomarkers predict increased mortality — even in normotensive patients [21].

The present investigation examined individuals presenting to a single center with a diagnosis of acute PE. We used cardiac imaging data and blood pressure to stratify PE into low risk, submassive, or massive categories. We then assessed cardiac biomarkers as indirect surrogates of RV dysfunction. The goal was to ascertain whether cardiac biomarkers, often obtained immediately on patient arrival, are useful in distinguishing between PESI classes, BOVA stages, and PE stratified categorically as low risk, submassive, and massive. We also assessed whether short-term mortality predicted by the PESI score and BOVA stages provide additional useful information when used employed for a PERT.

Methods

Study Design

This is a single center retrospective analysis of adult patients during a twenty-month period (May 2014 to December 2015) with a diagnosis of “pulmonary embolism” or “venous thromboembolism” based on International Classification of Diseases, 9th Clinical Modification (ICD-9-CM) codes. The study protocol, data collection and storage were approved by University of Rochester Institutional Review Board All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments for comparable ethical standards

Patient Population

Adult patient presenting to the ED with acute PE were assessed by a PERT. Clinical variables were used to stratify short term patient mortality using the PESI score which does not account for the presence of RV dysfunction (Supplemental Figure 1) and the BOVA score which considers the presence of RV dysfunction for the purposes of risk stratification (Supplemental Figure 2). Lastly, patients were stratified in a simple manner by category where low risk acute PE includes those patients without imaging data suggestive of RV dysfunction, submassive PE which includes patients with acute PE and imaging data suggestive of RV dysfunction (Supplemental Figure 2), and massive PE which includes patients with acute PE with RV dysfunction as well as sustained hypotension (Supplemental Figure 3). Excluded patients included those with low-risk PE (not meeting massive or submassive criteria), chronic VTE, and patient transfers from an outside facility where the diagnosis of PE was made previously.

Data Collection and Outcomes:

Patients were categorized into low risk PE, submassive PE, or massive PE groups and their respective PESI classes and BOVA based on score. PESI scores were calculated then grouped as follows: PESI I (< 65 points), PESI II/III (66–105 points) and PESI IV/V (>106 points) [22]. BOVA scores were documented as BOVA stage I (0–2 points), BOVA stage II (3–4 points, BOVA stage III (> 4 points) [8]. We defined the diagnosis of low risk PE as normotensive and the absence of documented RV dysfunction by imaging. Submassive PE was defined as RV dysfunction by computed tomography angiography (CTA) or echocardiography. Massive PE was defined as hypotension with a systolic blood pressure <

90 mm Hg for at least 15 minutes or cardiopulmonary arrest or cardiogenic shock by clinical exam.

Statistical Analysis:

Data collected included the initial set of plasma cardiac biomarkers (NT-proBNP, cardiac troponin), objective documentation of RV function by imaging, and mortality at 1 month, 3 months, and 6 months. Cardiac biomarker data was used to distinguish between low risk PE, submassive PE, and massive PE as well as between PESI classes and BOVA stages using indicated by Receiver Operator Characteristic (ROC) curve analysis. ROC curve data were reported as the area under the curve (AUC), along with sensitivity and specificity and biomarker concentration cut-points. It is important to note that the ROC curves used for categorically assigned classes of PE were based on RV dysfunction determined from imaging. This allowed for the fair assessment of the prognostic ability of cardiac biomarkers in acute PE. Dichotomous variables are presented as frequencies and continuous variables as mean with standard error of mean (SEM) unless otherwise stated. The distribution of data was interrogated for normality using the Shapiro–Wilk test before comparison between groups. For data that were not Gaussian-distributed, the Mann-Whitney U test was used when comparing two groups, and the Kruskal–Wallis test followed by Dunn post-test was used for three or more group comparisons. For Gaussian-distributed data, the student's t-test was used to compare two groups and, for three or more group comparisons, 1-way ANOVA then the Bonferroni multiple comparisons test was used. Significance was determined if the P value was < 0.05 . All data were analyzed with GraphPad Prism 7 (GraphPad Software, Inc, La Jolla, CA).

Results

571 patient charts were reviewed, 286 of which were determined to be clinical presentations of acute PE. Patients were excluded following chart review if a primary diagnosis other than PE was determined, if the diagnosis was made at another institution, or if the patient had only a history of VTE/PE (Supplemental Figure 4). The demographic variables and observed short-term outcomes for the evaluated patient population are shown in Table 1.

We used imaging data to determine the presence of RV dysfunction. We then examined categorical assignment of PE severity, observing a stepwise increase in plasma cTnT and NT-proBNP from low risk PE to massive PE. Conversely, using the PESI scoring system, a similar upward trend in plasma cardiac biomarker concentration was not clearly observed with ascending PESI class (Figure 1).

Based on the ROC analysis of cardiac biomarkers in patients with RV dysfunction determined by imaging alone, cTnT easily distinguished between low risk PE and submassive PE with AUC 0.84 (95% C.I. 0.73 – 0.95). Similarly, TnT distinguished between low risk PE and massive PE with AUC 0.89 (95% C.I. 0.78 – 1.00). For NT-proBNP, low risk PE was distinguished from submassive PE with an AUC of 0.88 (95% C.I. 0.79 – 0.97), and low risk PE was distinguished from massive PE with an AUC of 0.89 (95% C.I. 0.78 – 1.0) (Figure 2A).

In striking contrast, cTnT distinguished poorly between all PESI classes: PESI I vs. PESI II/III with an AUC of only 0.52 (95% C.I. 0.28 – 0.73), and PESI I vs. IV/V with an AUC of only 0.55 (95% C.I. 0.31 – 0.76). NT-proBNP was similarly less precise in distinguishing among the severity of PESI classes, with an AUC of 0.68 (95% C.I. 0.57 – 0.79) for PESI I vs. II/III, and an AUC of 0.77 (95% C.I. 0.69 – 0.85) for PESI I vs. IV/V (Figure 2B).

Using the categorical classification of low risk, submassive, or massive PE, the mean calculated PESI scores trended in an ascending manner. However, when attempting to determine a PESI score cut-point by ROC curve analysis, the value obtained to distinguish low risk from submassive PE was 93 (30 day predicted mortality of 4.8%, Figure. 3) which was 1.8-fold lower than the observed mortality (Table 1). Similarly, the predicted PESI score cut point to distinguish low risk PE from massive PE by ROC curve analysis was 108 (30 day predicted mortality of 4.8%) which was 7.2-fold lower than the observed mortality for massive PE (Table 1).

The BOVA score was validated as a short-term predictor of mortality in patients with normotensive (low risk and submassive) acute PE [8]. Components of BOVA (Supplemental Figure 2) do include higher-risk features such as RV dysfunction and elevation of a plasma biomarker for myocardial necrosis. Each calculated BOVA stage, however, showed markedly lower plasma cTnT concentration compared to patients who were stratified as submassive PE based only on radiographic evidence of RV dysfunction (Figure 4). Furthermore, assessing the BOVA score for each patient with low risk PE compared to submassive PE, ROC curve analysis revealed a BOVA stage cut-point predicting a 30-day mortality of 3.1%, which was 2.7-fold lower than the observed mortality in our patients with submassive PE (Table 1).

Together, these data imply that elevated cardiac biomarkers and the presence of RV dysfunction determined radiographically provide simple and possibly more accurate information regarding patient mortality not accounted for by PESI or BOVA.

Discussion

According to published registries, the average 3-month mortality for a patient with submassive PE is 20–25% and 50–60% for a patient for massive PE [20]. Therefore, the presence of RV dysfunction or sustained hypotension are simple and relevant clinical variables to rapidly determine patient risk irrespective of whether a hospital utilizes the PERT concept to assist in risk stratification. As proof of concept, we calculated the PESI score and BOVA score for patients shown to have low risk, submassive, or massive PE. Our data suggest both PESI and BOVA may underestimate short-term mortality for patients with acute PE in the setting of RV dysfunction. We further substantiated this observation by showing cardiac biomarkers suggestive of myocardial necrosis (cTnT) and strain (NT-proBNP) track more reliably with categorical assignment of a patient as low risk, submassive, or massive PE.

Cardiac troponin can be released from necrotic myocytes in the setting of ischemia as well as both acute and chronic myocardial loading conditions. BNP and its inactive N-terminal

fragment NT-proBNP, unlike atrial natriuretic peptide (ANP) or cTnT, are not present in healthy cardiac myocytes in large quantities, and require chronic myocyte stretch to be synthesized and stored as myocyte granules ready for secretion [12, 23–28]. We postulate the time needed to synthesize and release granules containing BNP accounts for the more impressive increase in plasma NT-proBNP concentration observed in patients with submassive PE—many of whom experience a subacute or chronic increase in myocardial load. When cardiac biomarkers were evaluated by PESI classes or BOVA stage, we found no reliable association between plasma cTnT concentration and calculated scores. Prior reports document that plasma cardiac troponin and natriuretic peptides predict adverse patient events in the setting of acute PE [29–31]. These variables are not incorporated into the PESI score or BOVA stage.

Our investigation has several limitations. Consistent with previous studies of patients with acute PE in whom RV dysfunction was documented, there is a subjective component to this interpretation, particularly when echocardiography is the imaging modality utilized. In addition, while a measured RV/LV ratio > 0.9 in the apical 4 chamber view on either CTA or echocardiography suggests RV dilation, volume status, and chronic medical conditions such as obesity, pulmonary hypertension, and right-sided valvular insufficiency all augment RV loading conditions may be interpreted as evidence of “RV dysfunction” [20, 32–34]. These factors require external validation.

Conclusions

For the purposes of risk stratification by a PERT where rapid decision making is often required with limited clinical information, using elevated cardiac biomarkers as a surrogate to determine RV dysfunction or using imaging to directly determine the presence of RV dysfunction are simple and sufficient. Collecting multiple clinical variables—which may take time—to utilize a scoring system such as PESI or BOVA does not add additional information in the setting of acute PE once the presence of RV dysfunction has been established.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Patients with submassive and massive pulmonary embolism have RV dysfunction which carries a significant short-term mortality.
- Pulmonary Embolism Response Teams are increasingly being relied upon to rapidly assess the patient's mortality risk and facilitate an expedited treatment plan.
- We demonstrated that complicated risk stratification scoring systems such as PESI and BOVA, while useful in some clinical contexts, are time-intensive and can under-estimate the true mortality risk once the presence of RV dysfunction is determined.
- The presence of RV dysfunction in any patient with acute PE automatically carries a high short-term mortality risk and is sufficient for rapid risk stratification.

Fig. 1:

Plasma cardiac biomarker concentration of PE by the Pulmonary Embolism Severity Index (PESI) score I through V or by categorical assignment as low risk PE, intermediate risk (submassive) PE, or high risk (massive) PE. Where available, the first plasma biomarker concentration was reported for plasma cardiac troponin and NT-proBNP as mean $\pm$ SEM. TnT=cardiac troponin T. NT-proBNP=N-terminal pro-brain natriuretic peptide.

Fig. 2:

A. Plasma cardiac biomarker prediction of PE by categorical assignment as low risk PE, intermediate risk (submassive) PE by RV dysfunction on imaging, or high risk (massive) PE. The performance of each biomarker in predicting submassive and massive PE was evaluated by Receiver Operator Characteristic (ROC) Curve analysis for specificity, sensitivity, area under curve (AUC), and cut-off shown. The dashed line is the line of identity. **B.** Plasma cardiac biomarker prediction of PE by PESI Scores class I through V. The performance of each biomarker in predicting low risk, intermediate risk (submassive) and high risk (massive) PE was evaluated by Receiver Operator Characteristic (ROC) Curve analysis for specificity, sensitivity, area under curve (AUC), with cut-off shown. The dashed line is the line of identity. C.I.=confidence interval. * $p < 0.0001$ between groups. PESI=Pulmonary Embolism Severity Index. TnT=cardiac troponin T. NT-proBNP=N-terminal pro-brain natriuretic peptide.

Fig. 3:

A PESI Score cut-point was calculated to distinguish between patients with low risk PE and intermediate risk (submassive) PE or high risk (massive) PE by Receiver Operator Characteristic (ROC) Curve analysis for specificity, sensitivity, area under curve (AUC), with cut-off shown. The dashed line is the line of identity. C.I.=confidence interval. * $p < 0.05$ between groups. PESI=Pulmonary Embolism Severity Index.

Fig. 4:

A. Plasma cardiac troponin concentration was assessed in patients determined to have low risk PE or intermediate risk (submassive) PE according to BOVA stages I through III. **B.** A BOVA Score cut-point was calculated to distinguish between patients with low risk PE and intermediate risk (submassive) PE by Receiver Operator Characteristic (ROC) Curve analysis for specificity, sensitivity, area under curve (AUC), with cut-off shown. The dashed line is the line of identity. C.I.=confidence interval.

Table I:

Demographics and baseline data for each population

PE Classification	Low risk	Submassive	Massive
N (%)	149 (52.1)	108 (37.8)	29 (10.1)
Sex, n (M/F)	83/66	60/48	14/15
Race (C/O**)(%)	105/44 (70.5)	76/32 (70.4)	14/15 (48.3)
Age (years $\pm$ SEM)	54.0 $\pm$ 1.4	62.9 $\pm$ 2.9	62.0 $\pm$ 2.6
Smoker (Y/N) (%)	79/70 (53.0)	59/49 (54.6)	14/15 (48.3)
Provoked PE (%)	105/149 (70.5)	72/108 (66.7)	21/29 (72.4)
Cancer (%)	48/105 (45.7)	31/72 (43.1)	8/21(38.1)
Chronic Lung Disease (%)	19/149 (12.7%)	28/108(25.9%)	3/29 (10.3)
Mortality, n (%)			
30d	6 (4.0)	9 (8.3)	9 (31)
3 month	16 (10.7)	21 (19.41)	11 (37.9)
6 month	23 (15.4)	25 (23.1)	12 (41.4)