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Right ventricular strain in patients with pulmonary embolism and syncope

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Abstract
Patients with acute pulmonary embolism (PE) can present with various clinical manifestations including syncope. The mechanism of syncope in PE is not fully elucidated and data of right ventricular (RV) function in patients has been limited. We retrospectively identified 477 consecutive patients hospitalized with acute PE diagnosed with a computed tomogram (CT) who also had a transthoracic echocardiogram (TTE) 24 h prior to or 48 h after diagnosis. Parameters of RV strain on CT, TTE, electrocardiogram (ECG), and clinical characteristics and adverse outcomes were collected. Patients with all three studies available for assessment were included (n = 369) and those with syncope (n = 34) were compared to patients without syncope (n = 335). Patients with syncope were more likely to demonstrate RV strain on all three modes of assessment compared to those without syncope [17 (50%) vs. 67 (20%); p = 0.001], and those patients were more likely to receive advanced therapies [9 (53%) vs. 15 (22%); p = 0.02]. PE-related mortality was highest among those presenting with high-risk PE and syncope (36%, OR 20.1, 95% CI 5.3–81.1; p < 0.001) and was low in patients with syncope without criteria for high-risk PE (3%, OR 1.2, 95% CI 0.2–10.0; p < 0.001). In conclusion, acute PE patients with syncope are more likely to demonstrate multimodality evidence of RV strain and to receive advanced therapies. Syncope was only associated with increased PE-related mortality in patients presenting with a high-risk PE. Syncope alone without evidence of RV strain is associated with low short-term adverse events and is similar to those without syncope.

Keywords Acute pulmonary embolism · Syncope · Right ventricular dysfunction

Highlights

- Acute PE patients with syncope are more likely to demonstrate multimodality evidence of RV strain and to receive advanced therapies.
- Syncope was only associated with increased PE-related mortality in patients presenting with a clinical presentation of high-risk PE.
- Syncope alone without evidence of RV strain is associated with low short-term adverse events and is similar to those without syncope.
- Further studies are required for optimal utilization of a presentation of syncope in risk stratification of patients with PE.

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Introduction

Acute pulmonary embolism (PE) is a leading cause of cardiovascular death with an increasing incidence [1–4]. Patients can present with various clinical manifestations, including syncope in 5–13% [5–8]. Syncope in PE was first reported in a case series of patients in the 1970s and was associated with increased clot burden, evidence of right ventricular (RV) strain on electrocardiogram (ECG), and hypotension [8]. The pathophysiology of PE is due to abrupt increase in RV afterload due to obstruction by thrombus in the pulmonary arteries, hypoxemia, and release of mediators that cause arterial vasoconstriction and resultant RV dysfunction [9]. Syncope has been considered an ominous prognostic symptom in patients with PE and thought to be due to transient hypotension secondary to RV dysfunction. In one study of patients < 35 years old who had died from a PE, 18% had presented with syncope [10]. There has been wide range of estimates of frequency of PE as cause of syncope from 1.4 out of 100, in more recent trials, to 1 out of 6 [11, 12]. In patients presenting with syncope without clear etiology after initial evaluation, of those with a PE, 25% did not have any signs or symptoms suggestive of PE or deep vein thrombosis. Only 41.7% of the patients diagnosed by computed tomography had a main pulmonary thrombus. No data were reported regarding RV strain in this study [12]. We sought to evaluate the prevalence of RV dysfunction evaluated by various modalities in patients with PE and syncope in order to better understand the factors associated with a presentation of syncope and predicting adverse outcomes in patients with acute PE and syncope.

Methods

We performed a sub-analysis of a previously published study [13]. In brief, we retrospectively identified all consecutive hospitalized patients at Beth Israel Deaconess Medical Center between May 1, 2007 and December 31, 2014 with an International Classification of Diseases (ICD) code for PE, diagnosed with acute PE by CT and had a TTE performed 24 h prior to or 48 h after the diagnostic CT scan. If available, ECGs from the same time period were also reviewed. Patient demographics, clinical characteristics and patient outcomes were extracted from the patient's electronic medical record, including if the patient presented with syncope. Syncope was considered a loss of consciousness without another obvious etiology; those with cardiac arrest were not considered to have syncope. PE severity was defined as high-risk if there was demonstration of hypotension < 90 mmHg for > 15 min, cardiac arrest, respiratory failure necessitating mechanical ventilation, or vasopressors were instituted; intermediate-risk if the above criteria were absent but evidence of RV strain was present on CT or TTE; and low-risk if none of the above characteristics were present. Adverse events included 30-day mortality related to PE, advanced therapy (e.g., systemic fibrinolysis, catheter-directed therapy, or pulmonary embolectomy), or need for vasopressors [14]. Mortality was considered related to PE if classified as death secondary or possibly secondary to PE by two or more of the three physicians who independently adjudicated each case.

Assessment of RV strain on ECG, CT, and TTE was performed by three physicians, who were blinded to clinical outcomes and the analysis of the other modalities. ECG evidence of RV strain was defined as (1) an S wave in lead I, Q wave in lead III, and T wave inversion in lead III; (2) right bundle branch block (RBBB); (3) T wave inversions in the early precordial leads (if present in leads V1–V2, V1–V3, or V1–V4) (Table 1) [15–17].

One fellowship trained cardiothoracic radiologist initially blinded to the presence of RV strain on other modalities assessed the transverse CT images for RV strain by measuring the maximum distance from the interventricular septum to the endocardial border, perpendicular to the long axis of the respective ventricle. The RV/LV diameter ratio was then calculated, with an abnormal ratio defined by current literature: (1) ≥ 0.9 and (2) ≥ 1.0 [18].

Each TTE was over-read by a board-certified echocardiographer blinded to the other imaging modalities and to patient outcomes. The RV/LV ratio was calculated by measurement of the basal RV end-diastolic dimension on the apical four-chamber view [19] and the basal LV end-diastolic dimension on the parasternal long axis view. RV/LV ratio was considered to be abnormal by using the thresholds: (1) ≥ 0.9 and (2) ≥ 1.0 [20]. Tricuspid annular plane systolic excursion (TAPSE) was assessed in the M-mode presentation by placing the cursor at the level of the lateral aspect of the tricuspid annulus and measuring the maximum displacement with systole. A TAPSE of < 16 mm was considered abnormal [19, 21].

The study was conducted in accordance with the amended Declaration of Helsinki and was approved by our institutional review board (Committee on Clinical Investigations, IRB# 2015P000425) which waived informed consent.

Statistical analysis

All analyses were performed with STATA (v14.2, StataCorp LP, College Station, TX). Continuous variables are expressed as mean ± standard deviation (SD), or as median [interquartile range] as appropriate. Categorical variables are

Table 1 Patient demographics and clinical characteristics of presentation with PE

Characteristic (N = 477 unless otherwise specified)	Total cohort (N = 477 unless otherwise specified)	Syncope (N = 41)	No syncope (N = 436)	P-value
Age (years)	63.0 ± 16.2	58.4 ± 19.4	63.5 ± 15.8	0.052
Gender (male)	226 (47)	20 (49)	206 (47)	0.87
Comorbidities				
Hypertension	291 (61)	23 (56)	268 (61)	0.51
Hyperlipidemia	181 (38)	18 (44)	163 (37)	0.41
Diabetes	83 (17)	9 (22)	74 (17)	0.40
Coronary artery disease	62 (13)	6 (15)	56 (13)	0.81
Atrial fibrillation	44 (9)	1 (2)	43 (10)	0.16
Prior cerebrovascular accident	34 (7)	2 (5)	32 (7)	0.76
Chronic obstructive pulmonary disease	37 (8)	1 (2)	36 (8)	0.35
Chronic kidney disease	22 (5)	0 (0)	22 (5)	0.24
Never smoker	251 (53)	19 (48)	232 (53)	0.61
Prior venous thromboembolism	133 (28)	14 (34)	119 (27)	0.36
Family history of VTE	41 (9)	4 (10)	37 (5)	0.77
Thrombophilia	8 (2)	1 (2)	7 (2)	0.52
Surgery within 90 days	81 (17)	8 (20)	73 (17)	0.66
Hospitalized within 90 days	129 (27)	10 (24)	119 (27)	0.85
Active malignancy	163 (34)	10 (24)	153 (35)	0.23
Other presenting symptoms				
Lightheadedness without syncope	22 (5)	0 (0)	22 (5)	0.24
Dyspnea	301 (63)	17 (41)	284 (65)	0.004
Chest pain	140 (29)	6 (15)	134 (31)	0.03
Back pain	13 (3)	0 (0)	13 (3)	0.62
Hemoptysis/cough	23 (5)	0 (0)	23 (5)	0.25
Leg swelling/pain	60 (13)	2 (4)	58 (13)	0.14
Asymptomatic	32 (7)	0 (0)	32 (7)	0.10
Known concomitant DVT	165 (36)	12 (33)	153 (36)	0.68
PE clinical severity				<0.001
Low-risk	58 (12)	1 (3)	58 (13)	
Intermediate-risk	377 (78)	29 (71)	351 (81)	
High-risk	38 (10)	11 (33)	27 (6)	
PE clot location				
Saddle PE	52 (11)	10 (24)	42 (10)	0.008
Left main PA PE	74 (16)	7 (17)	67 (15)	1.0
Right main PA PE	111 (23)	12 (29)	99 (23)	0.34
RV strain on CT (473)				
RV/LV ratio ≥ 0.9	326 (69)	38 (93)	288 (67)	<0.001
RV/LV ratio ≥ 1.0	244 (52)	30 (73)	214 (50)	0.005
RV strain on TTE				
TAPSE < 16 mm (429)	115 (27)	15 (42)	100 (25)	0.048
RV/LV ratio ≥ 0.9 (431)	246 (57)	28 (76)	218 (55)	0.02
RV/LV ratio ≥ 1.0 (431)	187 (43)	23 (62)	164 (42)	0.02
RV hypokinesis (455)	186 (41)	25 (63)	161 (39)	0.004
Moderate to severe RV hypokinesis (455)	94 (21)	15 (38)	79 (19)	0.01
TR Gradient (in mmHg) (347)	35.1 ± 13.4	36.1 ± 13.6	35.0 ± 10.3	0.60
McConnell's sign (450)	63 (14)	9 (23)	54 (13)	0.094
Septal bowing present (448)	108 (24)	19 (49)	89 (22)	<0.001
Any RV strain on ECG (415)	166 (40)	24 (63)	142 (38)	0.003

Table 1 (continued)

Characteristic (N = 477 unless otherwise specified)	Total cohort (N = 477 unless otherwise specified)	Syncope (N = 41)	No syncope (N = 436)	P-value
S1Q3T3	72 (17)	13 (34)	59 (16)	0.01
T wave inversions	120 (29)	19 (50)	101 (27)	0.004
RBBB	35 (8)	6 (16)	29 (8)	0.12
Sinus tachycardia	201 (45)	19 (49)	182 (45)	0.62
Other tachycardia	47 (10)	3 (8)	44 (11)	0.78
Non-sinus, normal heart rate	13 (3)	1 (3)	12 (3)	1.0
Troponin > 0.10 mg/mL (291)	76 (21)	15 (43)	61 (18)	0.002

Numbers in parenthesis indicate percentages

DVT deep vein thrombosis, *VTE* venous thromboembolism, *ECG* electrocardiogram, *PA* pulmonary artery, *PE* pulmonary embolism, *RV* right ventricular, *CT* computed tomography, *LV* left ventricular, *OR* odds ratio, *RBBB* right bundle branch block, *RV* right ventricular, *RVS* right ventricular strain, *S1Q3T3* S wave in Lead I, Q wave in lead III, T wave inversion in lead III, *TWI* T wave inversions in V1–V2, V1–V3, or V1–V4, *TAPSE* tricuspid annular plane systolic excursion, *TTE* transthoracic echocardiogram

expressed as number (percentage). Patients with and without syncope were compared with respect to demographic variables, risk factors for VTE, presenting symptoms, PE clot location, RV strain on various modalities, treatment, and 30-day mortality. Logistic regression was performed to evaluate risk of PE-related mortality by presentation. A two-sided p value of < 0.05 was used to indicate statistical significance.

Results

The study population included 477 patients (47% men; 63 ± 16.2 years) of whom 41 had syncope (49% male; 58.4 ± 19.4) (Table 1). There was a trend toward younger age in those with syncope ($p = 0.052$). The presence of sinus tachycardia on ECG was similar between the two groups. High-risk PE was more common in those with syncope ($p = < 0.001$). Saddle PE was more common in patients with syncope ($p = 0.008$). The syncope group had a high prevalence of RV strain on CT (Table 2) [LV diameter ratio ≥ 0.9 ($p < 0.02$) and RV/LV diameter ratio ≥ 1.0 ($p < 0.02$)]. The syncope group had a higher prevalence of septal bowing present on TTE as compared to the non-syncope group ($p = 0.001$) and RV hypokinesis [25 (63%) vs. 161 (39%); $p = 0.004$]. Any evidence of RV strain on ECG was present on 24 (63%) of syncope patients. Of the 369 patients whom had TAPSE, RV/LV diameter on CT, and ECG available for review, those with syncope were more likely to demonstrate RV strain on all three modalities (abnormal TAPSE and/or RV/LV diameter ratio ≥ 1.0), and abnormal CT (RV/LV diameter ratio ≥ 1.0) compared to patients without syncope [17 (50%) vs. 67 (20%); $p = 0.001$].

All-cause 30-day mortality was higher in syncope patients [8 (20%) vs. 35 (8%); $p = 0.02$]. More patients in the syncope group received advanced therapy [8 (20%) vs. 21 (5%); $p = 0.002$] (Table 2). Patients with syncope and RV strain on all three modalities were more likely to receive advanced therapies in comparison to patients without syncope and without RV strain on all three modalities [9 (53%) vs. 15 (22%); $p = 0.02$] (Fig. 1). The overall rate of PE-related mortality was 4% and was highest in those presenting with a high-risk PE and syncope (36%, < 0.001) (Table 2).

Subgroup analysis was performed with exclusion of patients with high-risk PE. The rate of adverse outcome in this subgroup with syncope was similar between the two groups (9% with syncope and 8% without syncope; $p = 0.70$). Patients with low or intermediate-risk PE who had syncope had a higher incidence of RV strain on all three modalities–CT, TTE, or ECG– in comparison to patients with low or intermediate-risk PE without syncope ($p = 0.02$) (Fig. 2). In patients with low or intermediate-risk PE with syncope, an adverse outcome only occurred when RV strain was present on all three modalities of assessment (Fig. 3).

Discussion

In this large, retrospective study of consecutive patients presenting with acute PE we performed comprehensive evaluation of RV strain and found significantly higher rates of RV strain by multiple parameters on CT, TTE, and ECG in patients presenting with syncope in the setting of acute PE. Patients presenting with syncope were also more likely to have RV strain on ECG, CT, and TTE and were more likely to receive advanced therapy. Patients with syncope were also more likely to have an adverse outcome; however, rates of adverse outcome were similar between groups in non-high-risk PE. PE-related mortality was significantly higher in

Table 2 Management, outcomes, and pulmonary embolism-related mortality

	Total cohort (N = 477 unless otherwise specified)	Syncope (N = 41)	No syncope (N = 436)	P-value
CT to TTE timing (hours)				0.57
Mean	16.3 ± 14.9			
− 24 to < 0 h	68 (14)	8 (20)	60 (14)	
0 to ≤ 24 h	289 (61)	23 (56)	266 (61)	
> 24 to 48 h	120 (25)	10 (24)	110 (25)	
CT To ECG timing (hours) (N = 415)				1.0
Mean	− 1.1 ± 8.2			
− 24 h to < 0	294 (71)	27 (71)	267 (71)	
0 to ≤ 24 h	117 (28)	11 (29)	106 (28)	
> 24 to 48 h	4 (1)	0 (0)	4 (1)	
Intubation	47 (10)	8 (20)	39 (9)	0.05
Vasopressors administered	32 (7)	8 (20)	24 (6)	0.003
Treatment				
Anticoagulation	457 (96)	38 (93)	419 (96)	0.24
Advanced therapy	29 (6)	8 (20)	21 (5)	0.002
Intravenous fibrinolysis	22 (5)	6 (15)	16 (4)	0.007
Catheter-directed therapy	6 (1)	2 (5)	4 (1)	0.09
Surgical embolectomy	1 (1)	0 (0)	1 (1)	1.0
IVC filter	80 (17)	12 (29)	68 (16)	0.05
Adverse outcome	108 (22)	24 (58)	84 (19)	<0.01
30-day mortality	43 (9)	8 (20)	35 (8)	0.02
PE-attributable mortality (overall)	19 (4)	7 (17)	12 (3)	<0.01

Clinical presentation	PE-related mortality rate (n = 477)	Odds ratio (95% CI)	p-value
Non-high-risk PE without syncope	11/409 (3)	–	–
Non-high-risk PE with syncope	1/30 (3)	1.2 (0.2–10.0)	0.84
High-risk PE without syncope	3/27 (11)	4.5 (1.2–17.3)	0.03
High-risk PE with syncope	4/11 (36)	20.7 (5.3–81.1)	<0.001

Values are mean ± SD or n (%)

CT computed tomography, *PE* pulmonary embolism, *RV* right ventricle, *TTE* transthoracic echocardiogram

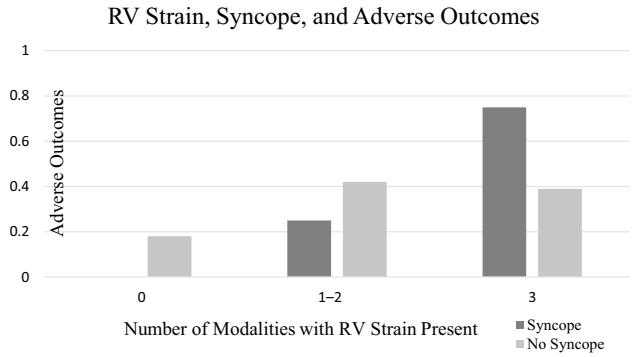

Fig. 1 Percentage of patients with adverse outcomes with and without syncope segregated by the number of modalities (CT, TTE, or ECG) with signs of RV strain (p = 0.002)

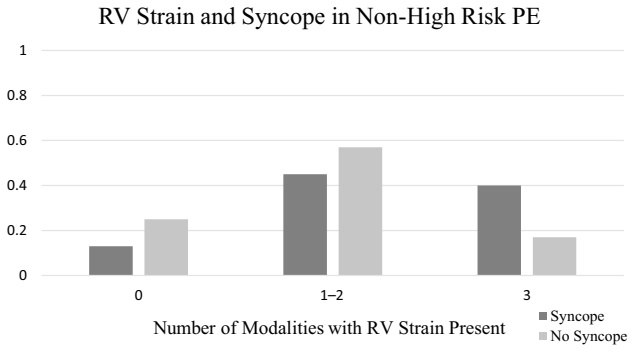

Fig. 2 Percentage of patients with non-high risk PE with and without syncope segregated by the number of modalities (CT, TTE, or ECG) with signs of RV strain (p = 0.028)

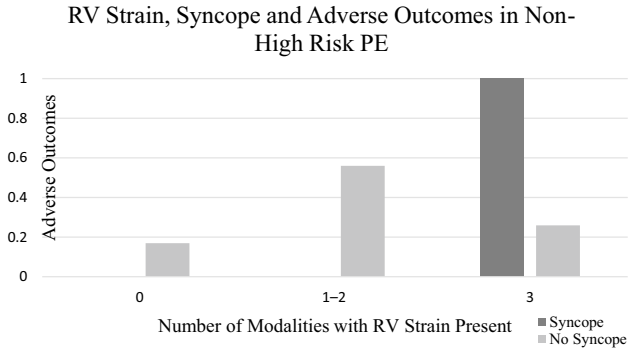

Fig. 3 Percentage of patients with non-high-risk PE with adverse outcomes in those with and without syncope segregated by the number of modalities (CT, TTE, or ECG) with signs of RV strain ($p = 0.02$)

those with syncope and high-risk PE, but was not elevated in those with syncope and a non-high-risk PE.

Syncope has been previously reported to occur in approximately 10% of patients presenting with PE, a similar frequency in our cohort [6, 22]. It has been traditionally believed that syncope is a concerning feature of patients presenting with acute PE though the underlying mechanism of syncope is not fully understood. Similar to prior reports, we found a higher rate of massive PE among patients presenting with syncope, suggesting patients with syncope have a greater degree of RV strain. We confirm this suspicion demonstrating over 90% have an RV-to-LV diameter ratio of ≥ 0.9 on CT, while such a finding was present on less than 2/3 of patients without syncope. These rates are similar to findings of RV strain in patients with acute PE by echocardiography by Jenab et al. [6]. Half of patients with syncope had RV strain on ECG, CT, and TTE, more than twice the rate seen in those without syncope. In our prior analysis, we demonstrated that RV strain on CT, TTE, and ECG was associated with increased risk of an adverse outcome, but no association was present when RV strain on only 1 or 2 modes of assessment [13]. Interestingly, 75% of those with syncope and an adverse outcome (use of vasopressors or thrombolytic therapy), demonstrated RV strain on all three modalities, compared to only 39% in those without syncope and an adverse outcome suggesting clinicians may be more aggressive in treating patients with syncope despite similar degrees of RV strain.

The exceptionally high rate of RV strain supports RV dysfunction as a driving force for the development of syncope in acute PE. Though the incidence of RV strain was higher in those with syncope, the positive predictive value is still relatively low and lack of RV strain is insufficient to exclude PE in those presenting with syncope given the wide spectrum of RV strain in those with PE and syncope. Additionally, there are likely alternative mechanisms contributing to the syncope as well given 50% of patients with syncope did not have RV strain on all three modalities and less than half of patients with syncope had moderate to severe RV hypokinesis or interventricular septal bowing on TTE. Alternative potential mechanisms include a vasovagal reflex with abrupt obstruction during the initial PE that can lead to neurogenic syncope. A tachyarrhythmia after PE is also a potential mechanism. Though we cannot exclude transient tachyarrhythmias at the onset of a PE, the rate of non-sinus rhythm at the time of presentation was low in the overall cohort and similar between those with and without syncope.

The overwhelming majority of adverse outcomes in patients with syncope occurred in those meeting criteria for high-risk PE. The rate of adverse outcome was $< 10\%$ in those with low or intermediate risk PE regardless of the presence of syncope or not. Both patients with low or intermediate-risk PE and syncope who had an adverse outcome had RV strain on all three modalities, while present in only 26% in those without syncope and an adverse outcome. Given the increased risk for patients with syncope and PE with RV strain on all three modalities, we perform a TTE in all patients with such a presentation.

Patients with high-risk PE warrant consideration for advanced therapy, regardless of presenting symptoms; however, only intermediate-risk PE with very concerning features warrant advanced therapy. Traditionally, syncope has been felt to be one of those concerning features, but we find a low PE-related mortality and adverse event rate in those with syncope that do not meet criteria for high-risk PE. These rates were similar to those with low or intermediate-risk PE without syncope. Our data suggests that syncope in itself should not warrant aggressive management, rather only with incorporation of comprehensive assessment of RV strain and clinical stability, given good short-term outcomes in those without significant RV strain and hemodynamic stability even with syncope as a presenting symptom. Supporting this assertion, two prior studies did not demonstrate increased mortality in patients with syncope and PE; however, the rate of hypotension was very low in both studies [22, 23]. The study by Seyyedi et al. evaluated patients with acute PE divided into those with and without syncope. The effect of syncope on 30-day adverse events and mortality was non-significant after adjustment for confounding factors [22]. Alternatively, Iqbal et al. did find a correlation with syncope and mortality; however, 25% of the syncope group had hypotension [24]. Similarly, a recent evaluation of syncope and pre-syncope in a large registry demonstrated that there was an association with 30-day mortality in those with both syncope or pre-syncope. The prevalence of hemodynamic instability was 16.8% in those with syncope or pre-syncope versus 6.0% in those without syncope or pre-syncope. Interestingly, syncope was not an independent predictor of mortality in those with hemodynamic instability. This supports our findings that syncope alone is unlikely to be the driver of poor outcomes, rather it is the hemodynamic instability that can

often accompany patients with acute PE and syncope that is most worrisome.

Limitations

Though large and consecutive, our study is retrospective. Thus, analysis was limited to data available in the medical record and not all patients had an available ECG, troponin or adequate CT and TTE images. Selection bias of particular patients with acute PE is likely present in our cohort, as it represented only a subset of patients hospitalized with PE. The cohort may not be representative of all patients presenting with acute PE and syncope given the imaging inclusion criteria. Very low-risk patients may have been less likely to have a TTE performed and very high-risk patients (e.g. patients in active cardiac arrest), may not have survived long enough for a TTE to be acquired. Though clinical patient features and vital signs are important in assessment of patients with PE, we did not have sufficient data to incorporate comprehensive clinical risk scores or vital signs outside of differentiation of high-risk, intermediate-risk, and low-risk clinical severity and presence of sinus tachycardia on ECG.

Conclusions

Acute PE patients with syncope are more likely to demonstrate RV strain on ECG, CT, and TTE. Adverse outcomes are higher in those with syncope; however, the rate is similar in those with low and intermediate-risk PE. PE-related mortality is not elevated in those with syncope and low or intermediate-risk PE. Syncope was not associated with adverse outcomes, including mortality, among those with low and intermediate-risk PE. These findings suggest that the increased mortality associated with syncope is driven by the presence of RV dysfunction and clinical instability. Syncope alone without any other high-risk features in PE is associated with a low short-term adverse event.

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Compliance with ethical standards

Conflict of interest All authors have no conflicts of interests to disclose.

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