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Original Article

Intermediate-risk pulmonary embolism: Aiming to improve patient stratification

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ABSTRACT

Background: Intermediate-risk pulmonary embolism (PE) patients present a therapeutic dilemma. While some are at risk for developing adverse events, possibly requiring escalation therapy, most will have a benign course. Our aim was to define predictors which will identify those patients who will not deteriorate despite the presence of RV involvement.

Methods: We evaluated 179 consecutive intermediate-risk PE patients (47% males; mean age: 66 ± 16 years), allocating them to those who did and did not need escalation therapy and evaluating the predictors for deterioration. We then formulated a score to distinguish between those who would not require escalation therapy.

Results: Twenty-six patients (15%) required escalation therapy which was associated with significantly more episodes of syncope (42% vs. 15%, p = 0.001), higher D-Dimer levels (10,810 ± 19,147 vs. 3816 ± 6255, p < 0.001), echocardiographic evidence of severe right ventricular (RV) dysfunction (42% vs. 19%, p < 0.01), or a higher RV/left ventricular (LV) diameter ratio on computed tomography (CT) (1.9 ± 0.6 vs. 1.46 ± 0.5, p < 0.001). On multivariate analysis the presence of syncope (HR 2.8 CI 1.1–7.1) and severe RV dysfunction on echocardiography (HR 3.5 CI 1.4–9.3) were found to be independent predictors for escalation therapy. A combined score of 1 was associated with only a 1.9% risk for escalation, while a maximum score of 4 was associated with a 57% risk for escalation therapy (P for trend < 0.001). Conclusions: A small but significant number of intermediate-risk PE patients required escalation therapy. A combined score comprising clinical, imaging, and laboratory parameters might aid in further risk stratification, identifying those intermediate risk PE patients with a more benign clinical course.

1. Introduction

In recent years there has been a substantial rise in pulmonary embolism (PE) hospitalizations [1,2]. Current guidelines differentiate between low, intermediate, and high-risk patients in order to identify those who are least likely (< 1%) to have an uneventful course and those whose clinical situation is more likely (> 15%) to deteriorate. While anticoagulation therapy will suffice in hemodynamic stable patients presenting with no signs of right ventricular (RV) dysfunction or injury (low-risk PE), those patients presenting with overt hemodynamic compromise (high-risk PE) mandate aggressive reperfusion therapy. However, data regarding the prognosis of the subgroup of intermediate-risk PE patients are variable with adverse events and mortality reported between 6 and 15% [3–7]. While in some intermediate-risk PE patients escalation therapy, especially reperfusion therapy, might be beneficial, current guidelines [8,9] recommend continuous monitoring and the possible administration of thrombolysis only in cases where there are signs of clinical or hemodynamic deterioration. Several studies published in recent years have focused on the identification of predictors for clinical deterioration and identification of normotensive PE patients with "higher" risk of adverse events [10–12]. Yet, these included a rather heterogenous patient population of normotensive PE patients and did not selectively evaluated an homogenous group of those meeting the criteria for intermediate risk PE, and especially those with evidence of RV involvement. Contrarily, identification of intermediate-risk PE patients which are less prone to deteriorate and will not be in need of reperfusion, might influence the decision-making process regarding the need for enhanced monitoring and the individual tailoring of appropriate therapy. The aim of the current study was to evaluate a relatively large and homogeneous cohort of intermediate-risk PE

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patients with evidence of RV involvement, to identify those patients who will less likely deteriorate despite the presence of RV involvement.

2. Methods

We evaluated 179 consecutive patients hospitalized with a diagnosis of intermediate-risk PE to our intensive cardiac care unit (ICCU) between the years 2008–2014. All patients underwent computed tomography (CT) for diagnosis of PE. Intermediate risk was defined as hemodynamically-stable patients at presentation who exhibited at least one of the following: 1. Evidence of RV involvement on either CT or two-dimensional echocardiography. 2. Elevated cardiac troponin, suggestive of myocardial damage secondary to the PE. RV involvement on CT was defined as one of the following: a) a RV/left ventricular (LV) ratio of ≥0.9; b) a shift of the interventricular septum towards the LV; or c) backflow of contrast to the inferior vena cava on CT. RV involvement on echocardiography was defined as one of the following: a) an increased RV/LV ratio; b) an enlarged RV diameter of > 35 mm at the mid-ventricular level or > 41 mm at the base of the RV; or c) RV contractile dysfunction. The severity of RV dysfunction was estimated quantitively based on 2-dimensional echocardiography and categorized as either normal, mild, moderate, or severe RV dysfunction.

Data were collected for: prior medical history, presenting signs and symptoms, in-hospital findings, treatment provided, clinical course (including clinical deterioration), and mortality (both in-hospital and at 30 days). All patients underwent rigorous monitoring including continuous (either invasive or non-invasive) blood pressure monitoring and daily echocardiographic evaluation.

Clinical deterioration or the need for escalation therapy was defined as any one of the following: 1. A drop in systolic blood pressure to < 90 mmHg for at least 15 min, or a drop of blood pressure of > 30 mmHg from baseline, accompanied by signs of end-organ hypoperfusion; 2. The need for vasopressor support to maintain adequate organ perfusion or blood pressure of > 90 mmHg; 3.The need for cardiopulmonary resuscitation; 4. The need for mechanical ventilation; 5. The need for reperfusion (either by thrombolysis or surgical embolectomy) and 6. Mortality during hospitalization. As the decision of treatment upgrading can be influenced by the severity of RV dysfunction, we included an additional sub analysis without the need for reperfusion in the combined outcome looking only at clinical deterioration. The study was approved by the Sheba Medical Center institutional review board, project number 2258-15-SMC.

2.1. Statistical analysis

We used either the Chi-square or Fisher exact test for comparing categorical variables, cited as a percentage. In addition, we applied the Kolmogorov-Smirnov test for continuous variables. For variables that did not follow the normal distribution pattern, Mann-Whitney *U* test was applied, and the *t*-test was used for those variables that followed normal distribution. Continuous variables were cited as mean ± SD. Multivariate analysis was used for predicting the occurrence of clinical deterioration and\or the need for escalation therapy. Variables included: age, gender, syncope at presentation, troponin, D-dimer, RV dysfunction severity by echocardiography, and RV/LV diameter ratio on CT.

We formulated a combined scoring system in order to predict a hospitalization course. The score was comprised from high-risk elements shown to be associated with clinical deterioration or the need for escalation therapy. A score of 1 point was given for the presence of each of the following: syncope, the presence of moderate or severe RV dysfunction on echocardiography, elevated troponin in the upper tertile (> 0.7 μg/l), and the presence of an RV/LV ratio above the median (> 1.425) on CT. The presence of a normal ECG was given a negative point in those with an overall score of > 0. Thus, the overall maximum score was 4 and the minimum was 0. All tests were two-sided and the significant statistical level was < 0.05. All calculations were done with the SPSS ver. 23 (SPSS Inc., Chicago, IL, USA).

Table 1a
Patient characteristics and presenting symptoms

Baseline characteristics	No. of patients = 179 (%)
Age (years ± SD)	66 ± 16
Males (%)	84 (47%)
Prior VTE event (%)	28 (15%)
Family history of VTE event (%)	11 (6.1%)
Smoking (%)	30 (18%)
HTN (%)	95 (53%)
Diabetes (%)	47 (26%)
CAD (%)	18 (10%)
Hyperlipidemia (%)	72 (40%)
Malignancy (%)	33 (18%)
Immobilization	74 (41%)

CAD: Coronary artery disease; HTN: hypertension; VTE: venous thromboembolism.

3. Results

A total of 179 consecutive, intermediate-risk PE patients were included in the current analysis all with evidence of RV involvement either by imaging or with elevated troponin. Baseline clinical characteristics and presenting symptoms are detailed in Table 1a. Mean patient age was 66 ± 16 years and 47% were male. The sPESI score of was 0 in 41% of the patients and 48% were in PESI I-II. Malignancy, either active or inactive, was present in 18%, and immobilization was evident in 41%, with 15% having had a prior venous thromboembolism event. The most common complaint at presentation was dyspnea (81%).

As shown in Table 1b, the most common ECG findings were sinus tachycardia and T-wave inversion in $V_{1–4}$ in 56% and 37% of the patients respectively. The ECG was normal in 30% of the patients. Laboratory findings revealed a positive cardiac troponin in 75% of the patients. CT revealed signs suggestive of RV involvement in 80% of cases which included: an enlarged RV in 60%, leftward deviation of the interventricular septum in 73%, and/or backflow of contrast to the

Table 1b
Diagnostic tests and findings

Diagnostic tests	No. of Patients = 179 (%)
E.C.G.	
Normal E.C.G.	53 (30%)
Sinus tachycardia (%)	100 (56%)
Inverted T-Wave ($V_{1–4}$) (%)	66 (37%)
Laboratory	
Positive D-Dimer (N, %)	165 (92)
D-Dimer value (ng/ml)	4887 ± 9696
Troponin-I + (N, %)	133 (75)
Troponin value (mcg/l)	0.97 ± 1.82
CTA findings	
IVS shift (%)	132 (75%)
Enlarged RV (%)	105 (60%)
Backflow of contrast to IVC (%)	88 (50%)
Echocardiographic findings	
LVEF (%)	59 ± 8
RV dysfunction (%):	117 (66%)
Mild (%)	37 (21%)
Moderate (%)	40 (22%)
Severe (%)	39 (22%)
SPAP (mmHg)	50 ± 14
Elevated SPAP (%)	78

CTA: Computed tomography angiography; IVC: inferior vena cava; IVS: interventricular septum; LVEF: left ventricular ejection fraction; RV: right ventricular; SPAP: systolic pulmonary arterial pressure.

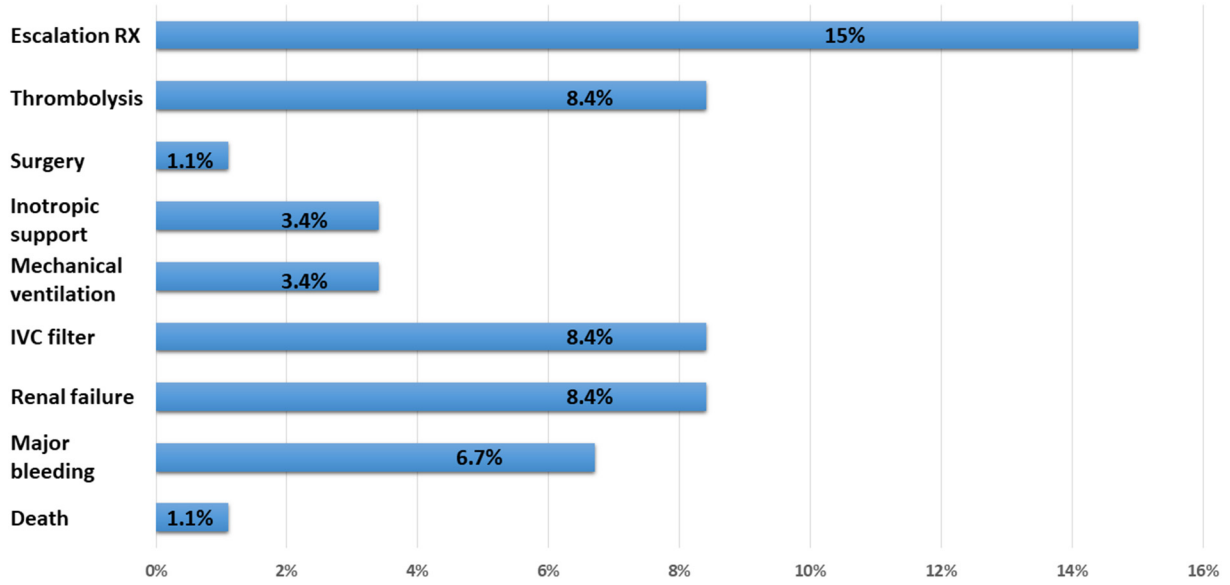

Fig. 1. In-hospital adverse outcomes. Need for escalation therapy and adverse outcomes during hospitalization.
IVC = inferior vena cava.

inferior vena cava in 50% of the patients.

Echocardiography demonstrated RV dysfunction in 70% of the patients, with severe RV dysfunction present in 22%. LV ejection fraction was 58 ± 9%. Systolic pulmonary artery pressure was elevated (> 35 mmHg) in 78% of the patients, and mean systolic pulmonary artery pressure was 50 ± 14 mmHg.

Anticoagulation therapy was initiated for all patients with the majority (98%) receiving heparin, either unfractionated (90%) or low molecular weight (8.9%). Average ICCU hospitalization stay was 4.7 ± 3 days. As shown in Fig. 1, a total of 26 patients (15%) had clinical deterioration and/or required escalation therapy which consisted of: reperfusion therapy in 17 (9.5%), mechanical ventilation in 6 (3.4%), inotropic support in 6 patients (3.4%), and in-hospital mortality in 2 patients (1.1%) with both cases being due to hemodynamic deterioration and considered PE related.

Bleeding events occurred in 21 patients (12%): In 12 of them (6.7%) bleeding was considered as major bleeding. A trend for higher events of major bleeding was noted in the escalation therapy group (15.4% vs. 5.3%, p = 0.06). Non-major bleeding was seen in 19.2% of patient in the escalation group as compared to 2.6% in those that did not require escalation therapy (p < 0.001). Acute renal failure developed in 15 patients (8.4%). The 30-day mortality was low (N = 3, 1.7%).

Upon univariate analysis patients requiring escalation therapy compared with those who did not (Table 2) were more likely to present with syncope (42% vs. 15%, p = 0.001), sinus tachycardia (88% vs. 51%, p = 0.001), inverted T waves in V_{1-4} on the ECG (60% vs. 34%, p = 0.01), new onset atrial fibrillation (14% vs. 2.9%, p = 0.02), higher D-Dimer levels (10,810 ± 19,147 vs. 3816 ± 6255, p < 0.001), echocardiographic evidence of severe RV dysfunction (42% vs. 19%, p < 0.01), and a higher RV/LV diameter ratio on CT angiography (1.9 ± 0.6 vs. 1.46 ± 0.5, p < 0.001).

Multivariate analysis revealed syncope at presentation (HR 2.8 CI 1.1–7.1), and the presence of severe RV dysfunction on echocardiography (HR 3.5, CI 1.4–9.3, p = 0.03), to be significant independent predictors for the need for escalation therapy.

After calculating a score (0–4) which was comprised of high-risk elements (Fig. 2), An increase in the score from 0 to 4 was associated with a gradual and significant increase in the risk for clinical deterioration and the need for escalation therapy (p < 0.001). Patients with a score of 4 had a 57% chance for requiring escalation therapy, while those with a score of 0 had a 1.9% (p < 0.001) chance for requiring escalation therapy. A total of 31% of the patients in the current cohort had a score of 0. Even among those who were classified as intermediate-high risk PE patients < 5% of those with a score of 0 required escalation therapy.

A sub analysis looking into predictors for clinical deterioration (without the need for reperfusion therapy, Supplementary Table S1) demonstrated that these patients were older (74 ± 8.3 vs.

Table 2
Escalation vs. no escalation therapy.

Variables	Escalation therapy required no. of patients = 26	No escalation therapy required no. of patients = 153	P value
Age (years ± SD)	70.35 ± 10.51	65.13 ± 16.74	P = 0.313
Gender (males)	16 (61.5%)	68 (44.7%)	P = 0.113
Syncope (%)	11 (42%)	23 (15%)	P = 0.001
ECG: Normal	1 (3.8%)	50 (35%)	P < 0.001
Leg swelling (%)	2 (7.7%)	55 (36%)	P = 0.004
CTA: IVC Backflow (%)	17 (65%)	71 (47%)	P = 0.089
CTA: RV/LV diameter ratio	1.91 ± 0.56	1.46 ± 0.48	P < 0.001
Echo: Severe RV dysfunction (%)	11 (42%)	28 (19%)	P = 0.007
Echo: Presence of elevated SPAP (%)	26 (100%)	104/140 (75%)	P = 0.004
Echo: Average SPAP (mmHg)	59.1 ± 12.6	48.8 ± 13.6	P = 0.001
Positive Troponin	91%	73%	P = 0.014
Troponin (mcg/l)	1.49 ± 2.06	0.89 ± 1.78	P = 0.129
D-Dimer	10,810 ± 19,147	3861 ± 6255	P = 0.001

CTA: Computed tomography angiography; IVC: inferior vena cava; LV: left ventricular; RV: right ventricular; SPAP: systolic pulmonary arterial pressure.

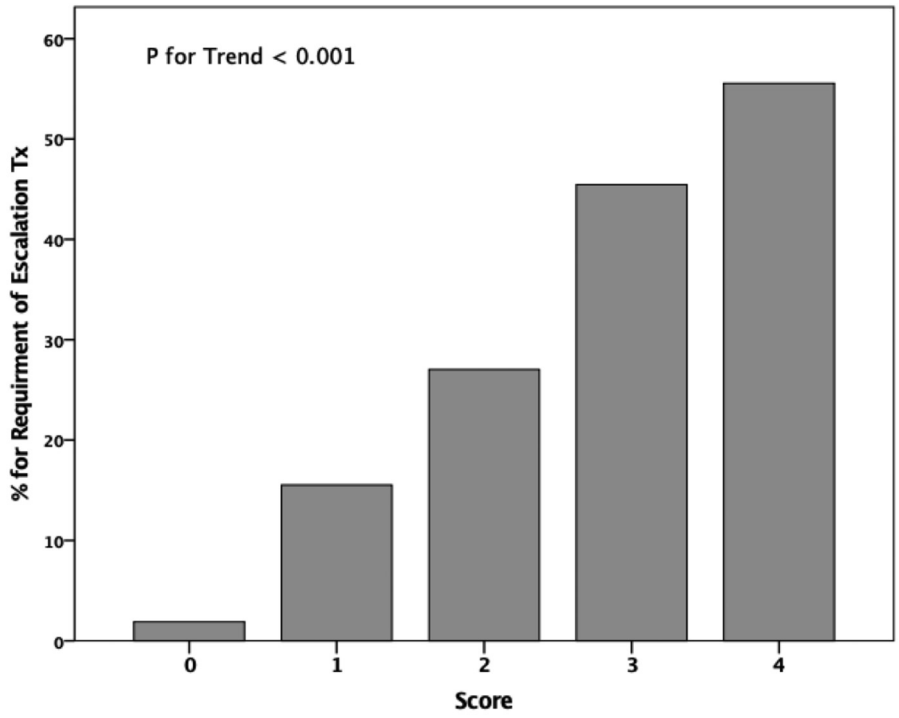

Fig. 2. Score for prediction of a favorable course during hospitalization. A score of 1 point was given for the presence of each of the following: syncope, moderate or severe RV dysfunction upon echocardiography, elevated troponin in the upper tertile (> 0.7 μg/l), and the presence of an RV/LV ratio above the median (> 1.425) upon computed tomography. The presence of a normal ECG was given a negative point.
LV = left ventricular; RV = right ventricular.

Score:	0	1	2	3	4
Escalation	1	5	7	9	4
No-Escalation	52	49	26	16	3
Total	53	54	33	25	7

65 ± 16.4 years, p = 0.04), more likely to present with syncope (63% vs. 15%, p < 0.001), higher D-Dimer levels (14,475 ± 23,485 vs. 3966 ± 6533, p < 0.001), and a higher RV/LV diameter ratio on CT angiography (2.11 ± 0.61 vs. 1.46 ± 0.47, p < 0.001), and elevated troponin levels (1.96 ± 2.43 vs. 0.87 ± 1.74, p = 0.024), none of those with clinical deterioration had a normal ECG. When applying the score comprised to predict clinical deterioration (without the need for reperfusion) there was still a gradual increase between those with a score of 0 (no cases of clinical deterioration) whereas patients with a score of ≥3 had a 32% chance for clinical deterioration (p for trend < 0.001).

4. Discussion

In our study a consecutive cohort of intermediate-risk PE patients with evidence of RV involvement, a small but significant number of patients (N = 26, 15%) required escalation therapy. The most powerful predictors for needing escalation therapy were: the presence of syncope at presentation, as well as severe RV dysfunction on echocardiography. Using a scoring system consisting of clinical, electrocardiographic, imaging, and laboratory parameters, we were able to identify those intermediate-risk PE patients which had evidence of RV involvement and who were unlikely to require escalation therapy and have a rather benign hospitalization course. Even when further stratifying patients to intermediate-high risk, a score of 0 was still associated with a < 5% chance of escalation.

Patients with intermediate-risk PE often present a therapeutic challenge for the clinician, in contrast to those patients with low or high-risk PE, where the treatment algorithm is straightforward, mandating either anticoagulation or primary reperfusion, respectively. While most intermediate-risk PE patients will do well on anticoagulation therapy, the condition of a significant number (15% in the current cohort) will deteriorate necessitating escalation therapy during hospitalization, with the majority of them (9.5%) requiring reperfusion therapy. The main limitation and reason for caution when administering thrombolytic therapy is its resultant excessive bleeding, especially intra-cerebral bleeding [13,14]. Due to this limitation, the recommended treatment approach for intermediate-risk PE patients, as endorsed by current guidelines [8], is close monitoring for signs of hemodynamic deterioration which could mandate reperfusion therapy such as thrombolysis. While it is preferable to undertake such close monitoring in an intensive care setting, it could be cumbersome and place a heavy burden on the medical system thus better risk assessment within this specific population of PE patients is warranted.

Several studies have tried to provide further prognostic indications in order to determine which normotensive PE patients are at higher risk for adverse events [10–12]. From these, several scores such as the BOVA [10], (modified) FAST [11], and SHIeLD [12] have emerged. Only 1 sub-study (from the PEITHO trial) has specifically addressed this issue in a cohort of over 1000 intermediate-risk PE patients with RV involvement [7] in order to find appropriate candidates who would benefit more from thrombolytic therapy. They suggested risk factors that are associated with more adverse events, such as: systolic blood pressure < 110 mm/Hg, a respiratory rate of > 20 per minute, or congestive heart failure. However, even in the sub analysis from the PEITHO trial, the authors state that their data were insufficient to establish definitive clinical criteria to identify appropriate patients for thrombolysis.

The current study focused on a rather selective PE population consisting of intermediate risk patients, with evidence of RV involvement. We implemented a reverse approach aiming to determine within this patient population which patients are not prone to clinical deterioration. Using a combined score which took into account several key factors: 1. Clinical - the presence of syncope; 2. ECG - the presence of an

abnormal ECG (excluding even sinus tachycardia); 3. Imaging - the presence of either moderate or severe RV dysfunction per echocardiogram, or extreme RV enlargement within the upper tertile of our cohort on CT; and 4. Laboratory - elevated troponin in the upper tertile of our cohort we were able to identify those intermediate-risk PE patients who were least likely to deteriorate clinically during their hospitalization (only 1.9%, a score of 0), as opposed to those with a score of 4 who had a 57% chance of requiring escalation therapy. Thus, our score might play a useful role in identifying those patients who are initially classified as being at intermediate risk, based on the presence of either elevated cardiac biomarkers, and/or a positive imaging study demonstrating RV involvement, but who nevertheless demonstrate a low risk for clinical deterioration, and thus might not need a comprehensive monitoring protocol.

The reported mortality among intermediate-risk PE patients is estimated at about 6–15% [3–7]. In our study, we have shown a significantly lower than reported in-hospital as well as 30-day mortality of 1.1% in this population. This lower mortality rate might be attributed to the comprehensive monitoring process outlined above, which includes hospitalization in an ICCU along with continuous invasive blood pressure monitoring, as well as daily echocardiographic evaluation for those patients with RV dysfunction who do not show improvement. On the one hand, these criteria would prompt secondary reperfusion whenever there were initial signs of hemodynamic instability and/or ongoing severe RV failure, while on the other hand it would avoid unnecessary bleeding complication which might arise from a more routine reperfusion therapy. Our approach of watchful waiting is in-line with current guidelines [8] which recommend close monitoring of intermediate-risk PE patients, especially those who fall within the intermediate-high risk subgroup.

The main limitations of our study are that it is both retrospective and based on a single-center registry, as we focused on a rather homogenous group of patients our study consists of a rather low number of subjects. As a result, our findings might reflect only local applicability and are hypothesis-generating. The score proposed in the current study needs to be further validated before it can be incorporated into routine practice. Moreover, the decision of treatment upgrading can be influenced by several parameters, mainly the severity of RV dysfunction which is also part of the score comprised and which was based on 2-dimentional evaluation of the RV without incorporation of additional qualitative measurements such as TAPSE. Larger prospective registries, as well as randomized trials evaluating different therapeutic approaches (e.g. percutaneous reperfusion) for intermediate-risk patients are needed in order to evaluate optimal management and care of this complex group of patients.

In conclusion, intermediate-risk PE patients present a challenging group of patients requiring close monitoring. Clinical, laboratory, and imaging findings might provide additional data for better risk stratification in this patient cohort. While escalation is required in some of these patients, overall mortality at 30 days is low and thus reassuring. A score consisting of five readily available clinical, imaging, and laboratory parameters might further aid in the risk stratification of these patients.

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References

[1] Minges KE, Bikdeli B, Wang Y, et al. National trends in pulmonary embolism hospitalization rates and outcomes for adults aged ≥65 years in the United States (1999 to 2010). Am J Cardiol 2015;116(9):1436–42.
[2] Jiménez D, de Miguel-Díez J, Guijarro R, et al. Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE registry. J Am Coll Cardiol 2016;67(2):162–70.
[3] Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000;101(24):2817–22.
[4] Hamel E, Pacouret G, Vincentelli D, et al. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. Chest 2001;120(1):120–5.
[5] Sanchez O, Trinquart L, Colombet I, et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. Eur Heart J 2008;29(12):1569–77.
[6] Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European society of cardiology risk stratification model. Eur Respir J 2016;48(3):780–6.
[7] Barco S, Vicaut E, Klok FA, et al. Improved identification of thrombolysis candidates amongst intermediate-risk pulmonary embolism patients: implications for future trials. Eur Respir J 2018;51(1).
[8] Konstantinides SV, Torbicki A, Agnelli G, et al. ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35(43):3033–69. 2014. [3069a-3069k].
[9] Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: chest guideline and expert panel report. Chest 2016;149(2):315–52.
[10] Bova C, Sanchez O, Prandoni P, et al. Identification of intermediate-risk patients with acute symptomatic pulmonary embolism. Eur Respir J 2014;44(3):694–703.
[11] Hobohm L, Hellenkamp K, Hasenfuß G, Münzel T, Konstantinides S, Lankeit M. Comparison of risk assessment strategies for not-high-risk pulmonary embolism. Eur Respir J 2016;47(4):1170–8.
[12] Freitas P, Santos AR, Ferreira AM, et al. Derivation and external validation of the SHIeLD score for predicting outcome in normotensive pulmonary embolism. Int J Cardiol 2019 Apr 15;281:119–24.
[13] Kanter DS, Mikkola KM, Patel SR, Parker JA, Goldhaber SZ. Thrombolytic therapy for pulmonary embolism. Frequency of intracranial hemorrhage and associated risk factors. Chest 1997;111(5):1241–5.
[14] Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370(15):1402–11.