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Clinical factors associated with massive pulmonary embolism and PE-related adverse clinical events

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ABSTRACT

Background: Clinicians evaluating acute PE patients often have to identify risks for massive PE, a measure of hemodynamic instability and its consequence, massive PE related adverse clinical events (PEACE). We investigated the association of these risk factors with massive PE and PEACE in a consecutive PE cohort ($n = 364$).
Methods: Massive PE was defined as an acute central clot (proximal to the lobar artery) in a patient with right heart strain and systolic blood pressure ≤ 90 mg. PEACE was defined as any massive PE who died or required one or more of the following: ACLS, assisted ventilation, vasopressor use, thrombolytic therapy, or invasive thrombectomy, within seven days of PE diagnosis. Univariate and multivariate analysis assessing associations between the risk factors (age, gender, comorbidities, PE provoking risks, and whether the PE was felt to be idiopathic) and massive PE or PEACE were performed. Significance was determined at $p < 0.05$.
Results: Thirteen percent ($n = 48$) of patients presented with massive PE, and 9% ($n = 32$) had PEACE. In the final multivariate model, recent invasive procedure (RR = 7.4, $p = 0.007$), recent hospitalization (RR = 7.3, $p = 0.002$), and idiopathic PE (RR = 6.5, $p = 0.003$) were associated with massive PE. Only idiopathic PE (RR = 5.7, $p = 0.005$) was significantly associated with PEACE. No comorbidities or other PE provoking risks were associated with massive PE or PEACE.
Conclusions: As a take-home message, recent invasive procedure, recent hospitalization, and idiopathic PE were associated with massive PE, and only idiopathic PE was associated with PEACE. Simultaneously, comorbidities like age or chronic cardiopulmonary disease seem not to be associated with massive PE or PEACE.

1. Introduction

Acute pulmonary embolism (PE) presentation varies from no symptoms and little hemodynamic consequence to massive PE with evidence of hemodynamic collapse with an estimated mortality of 20%. [1–3] The annual incidence of PE has been increasing globally, and it has also been identified as an important clinical complication in SARS-COV2 (severe acute respiratory syndrome coronavirus 2) [4,5]. Clinicians evaluating patients with suspicion of acute PE often have to identify risks for massive PE, a measure of hemodynamic instability and its consequence, massive PE related adverse clinical events (PEACE). [6,7] Understanding those risks can help clinicians institute goal-directed therapy to decrease PEACE.

Conventional venous thromboembolism (VTE) risks such as recent trauma or immobilization, active cancer, and comorbidities such as advanced age, coronary or peripheral artery disease, chronic kidney disease, cirrhosis, history of stroke have been proposed to lead a state of hemostatic imbalance associated with PE. However, it is unclear if these factors also increase the risk of hemodynamic collapse due to PE, i.e., massive PE or PEACE. [6,8–18] Patients with massive PE or PEACE often present with proximal pulmonary artery thrombus, right heart strain (RHS), shock index ≥ 1 (heart-rate/blood pressure), and troponin elevation. [11,19,20] Many PE prognostic models include age, chronic cardiopulmonary disease, or cancer; however, other VTE risks could be associated with PEACE. [21–24] Identifying such risks may have diagnostic and prognostic implications for clinicians involved in the evaluation of acute PE and may aid in prognostic modeling. [25] We sought to determine the association of VTE risks and comorbidities with massive PE and PEACE.

2. Methods

We prospectively enrolled patients treated by the Pulmonary Embolism Response Team at Massachusetts General Hospital (MGH-PERT)

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[1] The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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referred between 10/2012–10/2015. [26] Patients are referred to the MGH-PERT by the primary treatment team, and when appropriate, a multidisciplinary virtual meeting is organized to provide a diagnostic and therapeutic plan. The human research committee of Partners Healthcare approved this study (protocol number 2016P000179).

We limited our analysis to patients with radiographically proven PE on computed tomography pulmonary angiogram (CTPA) (Fig. 1). Tumor embolus, PE diagnosed with Ventilation-Perfusion (V/Q) scan, and PE diagnosed 72 h before or after PERT consult were excluded. We included information about the date, activation site of PERT, demographics, comorbidities, VTE risk factors, and outcomes. Study staff obtained all information from electronic medical records or interviewed medical providers at the time of the PERT consult and during the following follow up periods: < 24 h, 2–3 days, 4–7 days, 8–30 days, 31–90 days, 91–180 days and 181–365 days. Data were recorded using a HIPAA compliant web-based application (www.project-redcap.org). Case reports were reviewed for consistency and integrity after initial data abstraction, and discrepancies in measurements were reconciled through consensus of the data abstractors and study PI. We utilized STROBE (Strengthening the reporting of observational studies in epidemiology) guidelines to report our study.

Table 1 and supplemental Table 1 lists the risk variables related to demographics, comorbidities, PE provoking factors, PE presentation characteristics, and PEACE recorded for this study. [19,27–34] We defined active cancer as patients receiving chemotherapy, radiation, or surgery for cancer in the three months preceding PE diagnosis or yet to be initiated on treatment after a new diagnosis of cancer. [35]

In an earlier study to identify markers of clinical deterioration after PE, [11] we reported an independent association of central clot location and CTPA Severity Score (measured as the sum of the sizes (in mm) of the most proximal clot in the right and left pulmonary arteries, measured in the transverse axis) with PEACE in the presence of hemodynamic instability. [19] Therefore, in this analysis, we quantified clot location, a priori, based on the thrombus' location in the pulmonary vasculature and issued an incremental score from 1 point through 9 points based on the site of most proximal thrombus in the final CTPA reports (Table 1). Clot Burden Scores ≥ 5 points were considered to be central clots.

We defined RHS based on echocardiography, CTPA, and troponin-T (Roche Diagnostics) results. Echocardiography was performed at the discretion of the treating physician. We considered a patient to have RHS, if an echocardiogram performed within three days of PE diagnosis showed right ventricular (RV) wall motion abnormalities, or RV dilation, or abnormal interventricular septum movement consistent with right ventricle overload. A subject with no RHS signs on echocardiogram was considered to have no RHS for this analysis. When an echocardiogram was not performed, we considered a patient to have RHS if the reporting radiologist read the 4-chamber cardiac view on CTPA as showing right ventricular dilatation or if the troponin-T was positive at ≥ 0.1 ng/ml.

To define massive PE, we used vital signs recorded at the time of diagnosis of PE by CTPA and before PERT activation. [19] We considered that hemodynamic collapse in a patient with isolated peripheral (segmental or smaller) clots was unlikely to be related to PE. This consideration is consistent with the American Heart Association and European Respiratory Society guideline definitions for massive PE, where other causes of hemodynamic collapse in PE have to be excluded. [3] Therefore, we defined massive PE based on a composite of clot location, RHS, and vital signs as defined below:

1) Massive PE: Acute central clots with RHS and presenting with systolic blood pressure ≤ 90 mg.
2) Non-massive PE: Acute PE not meeting the definition of massive PE.

We defined PEACE as any massive PE in a patient who died or required one or more of the following: Advanced Cardiac Life Support, assisted ventilation, vasopressor use, thrombolytic therapy, or invasive thrombectomy, within seven days after PERT consultation. [11]

2.1. Statistical methods

We used SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.2 for analysis. We analyzed baseline characteristics with simple means and proportions. We tested for differences in risk variables between massive PE and non-massive PE patients and PEACE using a Chi-squared test (for categorical variables) and Wilcoxon Rank-Sum

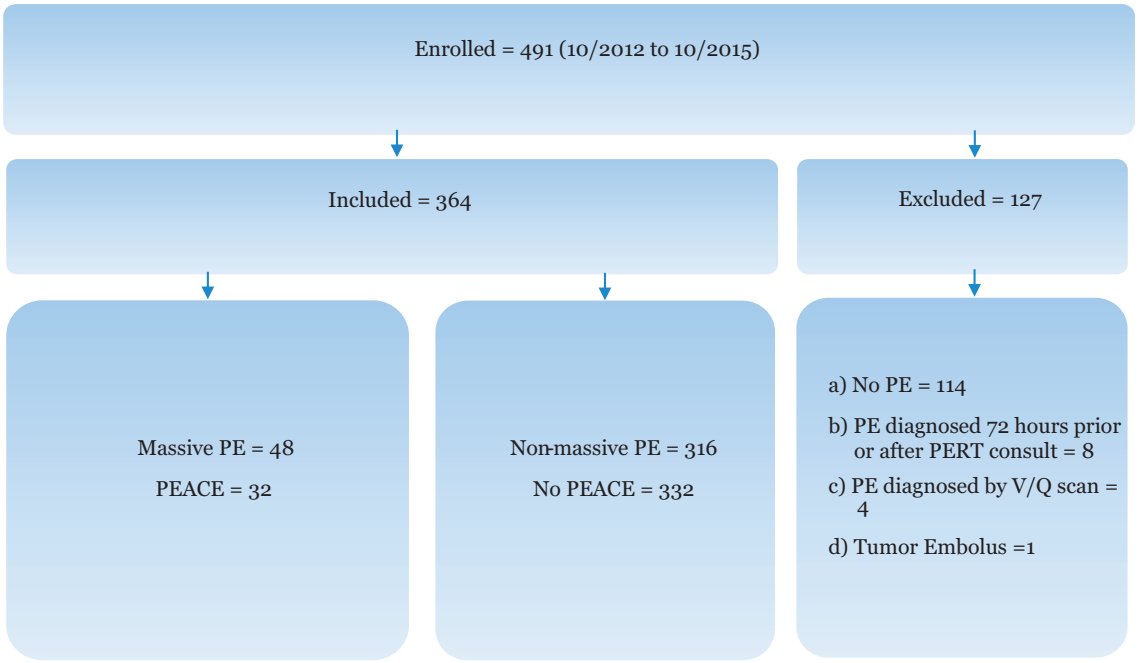

Fig. 1. Flowchart of enrollment. Key for Fig. 1: PEACE: Massive PE related adverse clinical events V/Q: Ventilation-perfusion PERT: Pulmonary Embolism Response Team PE: Pulmonary Embolism

Table 1
Baseline characteristics of included patients ($n = 364$).

Baseline characteristics	n (%, or SD)
Mean age (±SD) (Years)	61 (±16)
Men	190 (52%)
Comorbid illness	
Congestive heart failure	26 (7%)
Chronic lung disease[a]	71 (20%)
Pulmonary hypertension	6 (2%)
Body Mass Index > 30 kg/m[b]	148 (42%)
Coronary or peripheral artery disease (CPAD)	62 (17%)
Cerebrovascular disease (CVD)	25 (7%)
Diabetes	71 (20%)
Chronic kidney disease	31 (9%)
Chronic liver disease	9 (2%)
Smoking	118 (32%)
Cancer associated thrombosis risk factors	
Active cancer[b]	103 (28%)
Active cancer treatment[c]	75 (21%)
VTE risk factors	
Past history of hereditary or acquired thrombophilia[d]	20 (5%)
Recent trauma (<4 weeks)	25 (7%)
Recent hospitalization (<4 weeks)	132 (36%)
Reduced mobility[e]	121 (33%)
Recent invasive procedures[f]	98 (27%)
Taking any contraceptive hormones	26 (7%)
Idiopathic[g]	117 (32%)
Hypothyroidism ($n = 263$)[h]	51 (22%)
PE presenting characteristics	
Central clot with Clot Burden Score[i] ≥ 5 points	316 (87%)
Non-central clot with Clot Burden Score <5 points	49 (14%)
Right Heart Strain[j]	227 (62%)

Key for Table 1:
SD: Standard Deviation.
VTE: Venous Thromboembolism.
PE: Pulmonary Embolism.
CBS: Clot Burden Score.
RHS: Right Heart Strain.

[a] Chronic lung disease was defined as patients having asthma or chronic obstructive pulmonary disease or another chronic lung disease.

[b] Active cancer was defined as a patient receiving chemotherapy or radiation or surgery for cancer in the past 3 months of PE diagnosis or receiving treatment for ongoing cancer or patients with new diagnosis of cancer and yet to be initiated on treatment.

[c] Active cancer treatment was defined as patients receiving any treatment for cancer including chemotherapy, radiation or surgery.

[d] Past history of hereditary or acquired thrombophilia was defined as presence of one of the following: Factor V leiden, Prothrombin gene mutation 20210A, Protein C or S or antithrombin III or plasminogen deficiency, Dysfibrinogenemia, Anti-phospholipid antibody syndrome, Paroxysmal nocturnal hemoglobinuria, Heparin induced thrombocytopenia, Disseminated intravascular coagulation, Nephrotic syndrome.

[e] Reduced mobility was defined as presence of one of the following: Chronic bed bound, bed rest for more than 3 days but not chronically, limb immobility (cast or splint), paralyzed limb or recent flight for > 6 h.

[f] Recent invasive procedure was defined as surgery or minor invasive procedure i.e. catheterization or endoscopy/biopsy within past 4 weeks.

[g] Idiopathic PE was defined as PE with none of the following transient or persistent VTE specific risk: no recent trauma, recent invasive procedure, recent hospitalization, oral contraceptive hormone therapy, indwelling catheter, active malignancy, pregnancy, active acquired thrombophilia.

[h] Hypothyroidism was defined patients with documented history of hypothyroidism prior to PE or levothyroxine therapy, or biomarker evidence of primary hypothyroidism (low Free T4 and high Thyroid Stimulating Hormone -TSH > 5 MU/L) or central hypothyroidism (low TSH < 0.5 MU/L).

[i] CBS (Clot Burden Score) was obtained from the most proximal clot location: Single subsegmental PE = 1 point, Multiple subsegmental PE = 2 points. Single segmental PE = 3 points, Multiple segmental PE = 4 points. Single lobar PE (includes lingular) = 5 points, Multiple lobar PE (includes lingular) = 6 points. Single main pulmonary artery PE = 7 points, Multiple main pulmonary artery PE = 8 points. Saddle PE = 9 points.

[j] We defined Right Heart Strain (RHS) based on echocardiography, CTPA, and troponin-T (Roche Diagnostics) results. We considered a patient to have RHS, if an echocardiogram performed within three days of PE diagnosis showed right ventricular (RV) wall motion abnormalities, or RV dilation, or abnormal interventricular septum movement consistent with right ventricle overload. Echocardiography was performed at the discretion of the treating physician. We considered no RHS when echocardiogram did not demonstrate RV function abnormalities. When echocardiogram was not performed, we considered a patient to have RHS if the reporting radiologist read the 4-chamber cardiac view on CTPA as showing right ventricular dilatation or if the troponin-T was positive at ≥ 0.1 ng/ml.

Test (for continuous variables). Risk variables with frequencies >5 in subgroups and demonstrating $p \leq 0.1$ in univariate analysis for either outcome were selected for multivariate logistic regression analysis. We utilized stepwise backward selection and identified predictor variables for the final regression models. We performed interaction tests among predictor variables used in the final regression models by adding two or more predictors (recent hospitalization, recent invasive procedures, active cancer treatment) as an interaction term. We excluded idiopathic PE, which, by definition, does not interact with other predictor variables. We compared the areas under the curve of the models with and without interaction terms. We considered statistical significance for multivariate models at $p < 0.05$.

3. Results

We identified 491 consecutive PERT patients from October 2012 to 2015 and excluded 127 patients without radiographic evidence of PE (i.e., with PERT activations due to suspected PE without confirmatory imaging) or meeting other exclusion criteria (Fig. 1). Table 1 describes the baseline characteristics of enrolled patients. The majority of PERT activations were from the emergency department ($n = 223$, 61%) followed by medical floors ($n = 58$, 16%) and the medical intensive care unit ($n = 36$, 10%). Twenty-eight percent ($n = 103$) of patients had active cancer, and solid tumors ($n = 95$, 92%) accounted for most cancers. Many patients had multiple potential risk factors, with substantial overlap in patients who had a recent hospitalization and a recent invasive procedure, followed by patients who had a recent hospitalization and reduced mobility, and patients who had a recent invasive procedure and reduced mobility (Fig. 2). Eighty-seven percent ($n = 316$) of included patients had a central clot, and RHS was prevalent in 62% ($n = 227$) patients. We observed that 35% ($n = 17$) of patients with non-central clots had RHS.

Forty-eight (13%) patients presented with massive PE, 32 (9%) suffered PEACE, and 69% of ($n = 22$) patients met more than one criterion of PEACE. The most common were vasopressor therapy use (n = 22, 69%), assisted non-invasive/invasive ventilation ($n = 20$, 63%) or thrombolytic use ($n = 17$, 53%). Among all PERT patients requiring

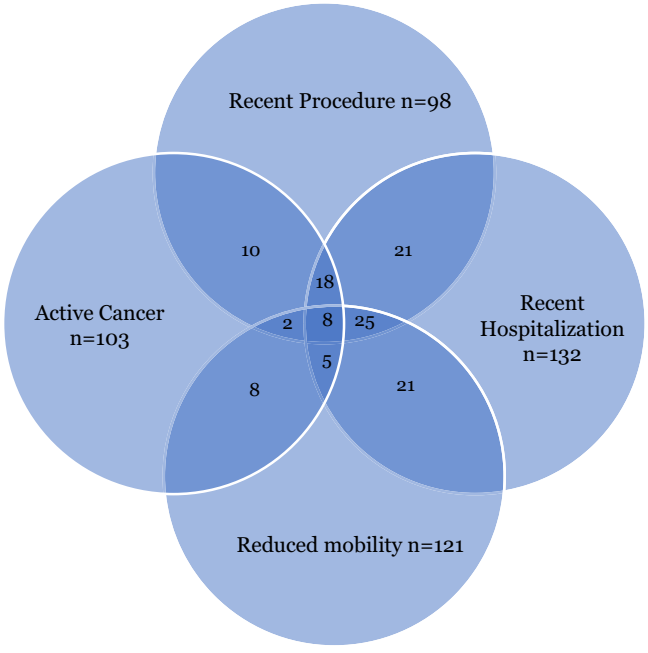

Fig. 2. Venn Diagram of overlapping risks in PE patients.

thrombolytic therapy ($n = 58$), 57 (99%) had central clots. Univariate associations are described in supplemental Table 1.

We performed a multivariable regression analysis of the following predictors with massive PE and PEACE: recent invasive procedures, recent hospitalization, idiopathic PE, and active cancer treatment. We observed an independent association of, recent hospitalization (RR = 7.7, 95% CI: 2.2 to 34.4, $p = 0.003$), recent invasive procedure (RR = 7.4, 95% CI: 1.7 to 33.7, $p = 0.007$), and idiopathic PE (RR = 6.5, 95% CI: 2.1 to 25.1, p = 0.003) with massive PE after accounting for interaction. When we tested for interaction within predictors (Table 2), only the interaction of recent hospitalization and recent invasive procedure was significantly associated with massive PE ($p = 0.037$), but it was not associated with PEACE ($p = 0.18$). When we added the interaction term (recent hospitalization and recent invasive procedure) to the massive PE model, the area under the curve did not change (0.66 vs. 0.68, $p = 0.48$).

Only idiopathic PE (RR = 5.7, 95% CI: 1.8 to 21.1, $p = 0.005$) was significantly associated with PEACE after adjusting for other predictors in the multivariable analysis (Table 3).

4. Discussion

Identifying patients at risk for a hemodynamic collapse in PE is critical for physicians evaluating acute PE. We found idiopathic PE, recent invasive procedure, and recent hospitalization were associated with massive PE. We also found that idiopathic PE was significantly associated with PEACE.

While multiple prior studies have reported associations between individual risk variables with massive PE or PEACE, the studies were mostly limited to subgroups such as cancer patients, emergency department patients, or hemodynamically stable patients. [34,36–41] Our multivariate analysis did not demonstrate a significant association between age or comorbidities and massive PE or PEACE. Our observation contrasts with other PE prognostic models that have demonstrated associations between age and chronic cardiopulmonary diseases with adverse events. [6,22] Our results are, however, consistent with Exter et al., who found no association between age, gender, COPD, and CHF, comparing subsegmental PE to proximal PE (segmental, lobar, and central) [40]. The study by Exter et al. was a sub-analysis of patients suspected of PE enrolled across 12 centers in the Netherlands between 2002 and 2004. Besides, in a retrospective analysis of confirmed PE patients presenting to the emergency department, the authors observed an underestimation of PE-related mortality using existing PE prognostic models. [42] Therefore, the utility of age or chronic cardiopulmonary disease in PE prognostic models may need further evaluation.

Active cancer has not been consistently associated with massive PE. [6,17,37,43] In our study, while most active cancer patients (>85%) had active cancer treatment, they had similar proportions of massive PE and PEACE compared to the entire cohort. However, neither active cancer nor active cancer treatment was significantly associated with our massive PE or PEACE, though there was a suggestion of an association between active cancer treatment (RR = 2.5, 95% CI: 1.0 to 6.7, $p = 0.07$) with PEACE. The association of active cancer treatment and its interaction with other risk factors for massive PE or PEACE needs further evaluation.

Table 2
Multivariate model for massive PE ($n = 364$).

Variables	Massive PE[a] ($n = 48$)		Massive PE with interaction term[b] ($n = 48$)	
	p	OR (95% CI)	p	OR (95% CI)
Recent invasive procedure	0.08	2.0 (1.0 to 4.6)	0.007	7.4 (1.7 to 33.7)
Recent hospitalization	0.01	3.2 (1.4 to 8.3)	0.002	7.3 (2.2 to 28.6)
Idiopathic	0.008	4.0 (1.5 to 11.7)	0.003	6.5 (2.1 to 25.1)
Active cancer treatment	0.08	2.0 (1.0 to 4.4)	0.09	2.0 (0.9 to 4.3)

[a] Final model after backward selection. Baseline included following risks: Recent invasive procedure, Recent hospitalization, Idiopathic, Active cancer treatment, and CVD.
[b] Model with interaction term: Recent invasive procedure, Recent hospitalization, Idiopathic, Active cancer treatment, and Recent invasive procedure*Recent hospitalization.

Table 3
Multivariate Model for PEACE ($n = 364$).[a]

Variables	PEACE ($n = 32$)	
	p	OR (95% CI)
Recent invasive procedure	0.22	1.9 (0.7 to 5.3)
Recent hospitalization	0.12	2.4 (0.8 to 7.6)
Idiopathic	0.005	5.7 (1.8 to 21.1)
Active cancer treatment	0.07	2.5 (1.0 to 6.7)

[a] PEACE (Massive PE related adverse clinical events). Final model after backward selection: Recent invasive procedure, Recent hospitalization, Idiopathic, Active cancer treatment.

4.1. Limitations

We obtained risk factor information based on chart review, and while our list was extensive, it was not exhaustive. In this study, data-abstractors were blind to the study design and outcomes to limit information bias. Moreover, we screened data for integrity after initial abstraction and amended inconsistencies, thereby limiting measurement bias. In our study, comparisons for risk variables like recent trauma, chronic liver, kidney disease, chronic bedbound, and heparin-induced thrombocytopenia were limited by low prevalence. However, prior studies have reported associations between some of these variables and massive PE or PEACE. [6,10,37,44] Also, we did not assess the association of comorbidities with bleeding events as used in some prognostic models. We acknowledge that can have implications for clinicians utilizing these models for ambulatory PE management. [25] Because PEACE in our study was largely driven by the use of thrombolytic interventions for PE, any association between recent surgery or invasive procedures may have been attenuated, as thrombolysis is less likely to be performed on patients who have had recent procedures. We defined idiopathic PE based on lack of transient or persistent provoking risk factors, but patients in both groups may be subject to misclassification due to unmeasured risks for VTE, like the effects of prior treated malignancy or infections. [32] Our study was conducted before the onset of the SARS-COV2 pandemic, and the effect of SARS-COV2 on acute PE prognosis is a matter of further investigation [5].

MGH is a tertiary referral center, and PERT activations are based on a referral process; therefore, the enrolled cohort may be subject to selection bias with a higher incidence of massive PE. However, we observed that the baseline frequencies of risk variables, outcomes, and mortality after massive PE physiology accounting were comparable to prior reported studies. [6,45,46] While the massive PE and PEACE were defined temporally after acute PE events, we did not control all other active medical conditions. Among all patients enrolled, we excluded 127 (26%) patients due to a lack of radiologic diagnosis or other reasons (Fig. 1). In this process, we may have excluded some massive PE and patients with cardiopulmonary collapse of multifactorial etiology, and those later diagnosed with PE outside the time window for enrollment (e.g., at autopsy).

5. Conclusions

As a take-home message, recent invasive procedure, recent hospitalization, and idiopathic PE were associated with massive PE, and only idiopathic PE was associated with PEACE. Simultaneously, comorbidities like age or chronic cardiopulmonary disease seem not to be associated

with massive PE or PEACE. These observations underscore the need for continued vigilance for modifiable PE risks and thromboprophylaxis.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.01.057.

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