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Effect of metabolic syndrome on mean pulmonary arterial pressures in patients with acute pulmonary embolism treated with catheter-directed thrombolysis

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1.1 Introduction:

Metabolic syndrome (MetS) is a public health problem of great impact and significance. MetS is generally defined as a grouping of abdominal obesity, impaired glucose metabolism, dyslipidemia and hypertension and has an estimated national prevalence of approximately 34% (1–2). The presence of MetS has been previously found to confer numerous adverse long-term health consequences, including an increased risk for cardiovascular disease, the development of type 2 diabetes mellitus, fatty liver disease and cancer (3–6). We have previously demonstrated that patients with MetS with or without PE have prolonged clot lysis times compared with controls following the *in-vitro* addition of tissue plasminogen activator (tPA) to plasma samples (7). Increased accumulation of adipose tissue resulting in dysregulated secretion of adipokines has been shown to precipitate a pro-inflammatory state, both systemically and locally within blood vessels, leading to vascular remodeling, hypertension and thrombosis (8–10).

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Venous thromboembolism (VTE) is common, with approximately 600,000 new diagnoses in the U.S. annually, and carries with it significant morbidity and mortality (11–12). In addition to the approximate 10% short-term mortality rate for acute intermediate risk pulmonary embolism (PE), patients surviving the initial event go on to suffer an inordinately high rate of non-PE cardiovascular death in the years after PE diagnosis, with a recent study demonstrating 35% mortality from cardiovascular disease within 5 years (13). Nonfatal consequences of PE include persistent dyspnea due to the development of chronic thromboembolic pulmonary hypertension (CTEPH) and the risk of recurrent VTE, both of which may contribute to worsened patient quality of life (QoL) (14–16).

Although MetS has been previously shown to be associated with a procoagulant and hypofibrinolytic state, current data exploring the role of MetS in VTE are limited. An improved understanding of the role that MetS plays in this disease process could lead to better informed decision-making in the acute care setting regarding the effectiveness of fibrinolytic treatment and its impact on patient outcomes. The objective of this study was to measure the prevalence of MetS in patients with acute PE receiving catheter-directed thrombolysis (CDT) and to investigate its effect on mean pulmonary arterial pressure and overall treatment success.

1.2 Methods:

1.2.1 Overall study design

This was a secondary analysis of a multicenter, prospective registry of emergency department (ED) patients with acute PE with severity qualifying for activation of a Pulmonary Embolism Response Team (PERT), a multidisciplinary group comprised of representatives from emergency medicine (EM), pulmonary critical care, interventional radiology (IR) and interventional cardiology (IC). Patients qualifying for PERT activation include those with positive CT pulmonary angiography or high probability V/Q scan for PE with evidence of higher severity (hypotension, CT or echocardiography with RV strain, elevated troponin or BNP). Following PERT activation, the appropriate treatment pathway is selected through a multidisciplinary approach, based on severity and patient-specific clinical factors, and may include extracorporeal membrane oxygenation (ECMO), systemic fibrinolysis, pharmacomechanical catheter treatment or heparin anticoagulation alone. For this analysis, only those patients undergoing CDT with documented pre- and post-treatment pulmonary arterial pressures as measured invasively by right heart catheterization were included. In situations where patients did not have documented post-CDT pulmonary arterial pressures (n=28), pre-CDT mPAP values were still included in analysis of the pre-treatment group.

1.2.2 Technique for catheter-directed thrombolysis

All patients deemed necessary for CDT after PERT evaluation underwent urgent pulmonary arteriography, either in IR (n=118), or IC (n=16). Anticoagulation was maintained during and after CDT with weight-based intravenous heparin. Two separate venous accesses were obtained using standard, ultrasound-guided, technique to either the right internal jugular, or right common femoral vein at the operators' preference. For jugular access 6 French, 45cm

Flexor Ansel sheaths (Cook, Bloomington, IN) were placed and for femoral access 6 French, 10cm Pinnacle sheaths (Terumo, Somerset, NJ) were placed. Pulmonary arterial access was obtained using a variety of techniques: pigtail, or shaped catheters (cobra, angled pigtail, Montefiore, etc.), or flow-directed balloon catheters. Pulmonary arterial pressures where obtained using a Truwave pressure transducer (Edwards, Irvine, CA) applied to the angiographic catheter. Then pulmonary arteriograms were performed using Isovue 300 or 370 contrast (Iopamidol) (Bracco, Monroe, NJ), typically from the main pulmonary artery. Total contrast administered varied from 20 to 50 ml. Selective peripheral pulmonary arterial access was then obtained, most commonly to bilateral lower branches, and catheter exchanges were performed over guidewires for thrombolysis infusion catheters.

For IR procedures 5 or 10 cm infusion length, 5 French UniFuse catheters (Angiodynamics, Latham, NY) were utilized and tPA (Alteplase) (Genentech, San Francisco, CA) was infused at a total rate of 1 mg/hour. Doses were typically split evenly (0.5 mg through each catheter) although at the discretion of the operator and based on laterality of clot burden, occasionally were varied (for example 0.7 mg to the right and 0.3 mg to the left). Patients returned for repeat angiography and pressure measurements at 18–26 hours. Most often lysis was halted and catheters and sheaths were removed at that time. On occasion, due to sufficient residual clot burden by angiography, pulmonary hypertension, and/or symptoms as determined by the operator, lysis was continued with or without catheter reposition (such as to the upper lobe). Total infusion times varied from 1 to 49 hours.

For IC procedures 12 cm infusion length, 5.4 French EKOS catheters (BTG, Bothell, WA) were utilized and, typically, a 2 mg tPA bolus was administered followed by tPA infusion at a total rate of 2 mg/hour for the first 4 hours, then 1 mg/hour until completion. Pressure measurements, cessation of lytic infusion and catheter removal were most often performed at the bedside without repeat arteriography. Total infusion times ranged from 4 to 28 hours.

1.2.3 Defining the metabolic syndrome criteria

The presence or absence of each of the four metabolic syndrome criteria for patients with acute PE undergoing CDT was defined based on explicit criteria. Obesity was defined as having a calculated BMI > 30 kg/m^2 at the time of PE diagnosis. Impaired glucose metabolism included any of the following criteria: 1) previous diagnosis of diabetes mellitus, 2) on anti-glycemic agent at time of diagnosis, 3) HbA1C > 6.5% recorded within the past two years. Hypertension was defined as either having a prior diagnosis of hypertension or taking an anti-hypertensive at the time of PE diagnosis. Dyslipidemia required any one of the following criteria: 1) previous diagnosis of hyperlipidemia, 2) on anti-lipid at time of diagnosis, 3) lipid panel recorded within the past two years with either triglyceride level >150 mg/dL or high-density lipoprotein level <40 mg/dL (17).

1.2.4 Calculating Miller scores

Two blinded EM physicians independently graded the severity of angiographic clot burden both pre- and post-fibrinolysis using the previously defined Miller score (18). This scoring system (ranging from 0 to 16) assigns points for each occluded segmental branch, with a saddle embolism receiving a maximum score of 16.

1.2.5 Statistical analysis

Statistical analyses were performed using SAS. The primary variable of interest was the mPAP values in patients with and without two or more MetS criteria, which were compared with the unpaired Student's T-test. A p-value <0.05 was considered significant. Additionally, we constructed a multivariate linear regression to test the independent predictive value of the components of MetS on the outcome variable of mPAP. Predefined independent predictor variables included in the regression equation were: age, sex, BMI, obesity, hypertension, diabetes mellitus, hyperlipidemia, active malignancy, CHF, COPD, MI, prior VTE and smoking history. In a post-hoc exercise, we added the amount of tPA administered (mg) and total hours of fibrinolysis to the regression model. We utilized Kendall's Tau rank correlation to compare mPAP values based on number of MetS components. We performed a subgroup analysis of IR vs. IC patients and compared results with the unpaired Student's T-test.

1.3 Results:

This study included 134 patients with acute PE receiving catheter-directed thrombolysis. There was a total of 300 PERT activations during the study period, with 166 excluded from this study as they did not undergo CDT. Table 1 contains specific demographic and comorbidity data of study participants. The average age of included patients was 57 years, and 49% were female. Obesity was the most common MetS criteria found in patients, with a prevalence of 71%. Hypertension was present in 49% of patients, while hyperlipidemia and diabetes mellitus were less prevalent, with measured rates of 37% and 25% respectively. The overall prevalence of the non-MetS comorbidities of interest included 10% with active malignancy, 4% with CHF, 4% with COPD, 4% with MI and 34% with a prior history of VTE. Table 1 also stratifies this data into groups based on the total number of MetS criteria patients were found to have, as follows: 15% of patients with 0 of the 4 components (85% had at least one criterion), 28% with 1 of 4, 24% with 2 of 4, 25% with 3 of 4, and 8% with all 4 components. Generally, demographic data including average age, sex and ethnicity as well as rates of comorbid conditions were similar amongst these stratified groups. However, those patients found to have all 4 components of MetS demonstrated significantly higher rates of certain comorbidities including 9% with CHF, 18% with COPD and 18% with MI.

The average mPAP values across all patients were significantly lower following treatment with CDT (average pre-mPAP of 30.4 mmHg vs. post-mPAP of 21.4 mmHg, p<0.0001). Table 2 presents the pressure data as stratified by the number of MetS criteria and additional outcomes, including initial vital signs (HR and SBP) and biomarkers (troponin and BNP) at time of diagnosis, as well as overall length of stay and 30-day mortality. There were 9 deaths across all patients (7%). The mortality rate stratified by number of MetS criteria was as follows: 10% in those with 0 components, 3% with 1 component, 6% with 2 components, 6% with 3 components and 18% with all 4 components. Again, average mPAP values were significantly lower post-treatment across all groups compared to pre-treatment. Further, there appears to be a positive concordance between the number of criteria for MetS and the mPAP, both pre- (Kendall's Tau 0.15021, p=0.024) and post-treatment (Kendall's Tau 0.16174, p=0.028), as pressures tended to increase stepwise with each additional criterion. In

the pre-lysis group, patients with 0 components of MetS had an average mPAP of 26.7 mmHg, followed by 29.8 mmHg in those with 1 component, 32.7 mmHg in those with 2 components, 30.5 mmHg in those with 3 components and 33.1 mmHg in those with all 4 components (Supplemental Figure 1). This increase is more pronounced in the post-lysis group, where average mPAP values were as follows: 18.9 mmHg in those with 0 MetS criteria, 19.9 mmHg in those with 1 criteria, 22.6 mmHg in those with 2 criteria, 22.6 mmHg in those with 3 criteria and 24.6 mmHg in those with all 4 criteria (Supplemental Figure 1). When separated into two distinct groups ("- MetS": defined as those with either 0 or 1 component and "+ MetS": defined as those with 2, 3 or 4 components), there was a significant difference in both pre-mPAP (28.7 mmHg vs. 31.8 mmHg, p=0.045) and post-mPAP (19.6 mmHg vs. 22.7 mmHg, p=0.0145) values between those without and with MetS (Supplemental Figure 2). This "- MetS" group had a 29% decrease in mPAP values following fibrinolysis compared with a 25% decrease in the "+ MetS group" (p=0.428).

Table 3 compares pre- and post-mPAP values in those patients with or without each of the four components of MetS, in an effort to detect whether any particular component of MetS appeared to play a more contributory role in these pressure differences. In general, for each of the four disease processes, those with the condition of interest had higher mean pre- and post-mPAP values than those without. Obese patients had the highest average pre-treatment mean mPAP amongst all groups, (32.1 mmHg vs. 26.5 mmHg, p=0.0006). In addition, patients with a diagnosis of hypertension had significantly higher persistent mean mPAP values post-lysis compared to those without hypertension (23.0 mmHg vs. 19.9 mmHg, p=0.0226).

Multivariate regression with pre-treatment mPAP values as the dependent variable yielded an equation (F 2.71, p=0.0018) with an estimated R-squared value of 0.25, indicating that 25% of the variance in pre-mPAP was explained by the predictor variables listed in Table 1. Age (0.13726, p=0.0095), BMI (0.31931, p=0.0076), and hypertension (4.0655, p=0.0201) were all found to be significant independent predictors of pre-mPAP, with hypertension having the largest effect. Additionally, multivariate regression analysis with post-treatment mPAP values as the dependent variable was performed, yielding an equation (F 3.02, p=0.0007) with an Rsquared value of 0.32. Significant independent predictors of post-mPAP values were similarly determined to be age (−0.17308, p=0.0003), BMI (0.2181, p=0.026), and hypertension (3.84188, p=0.0099), again with hypertension having the largest magnitude of coefficient. Table 4 displays the results from these regression analyses. In a post-hoc analysis, we added both the amount of tPA administered and the total hours of fibrinolysis, separately, into the multivariate regression equations for pre-treatment and post-treatment mPAP. Neither was found to be a significant contributor (amount tPA: pre-mPAP [−0.05169, p=0.4545], post-mPAP [−0.00752, p=0.9008]; hours of lytics: pre-mPAP [0.02623, p=0.7178], post-mPAP [0.01581, p=0.7914]), and the addition of these variables into the regression models did not alter the significance of the results discussed above.

Subgroup analysis comparing IR and IC groups found included patients to have a similar average number of MetS criteria (1.9 vs. 1.6, p=0.4594). IR procedures had a significantly longer average duration of fibrinolysis compared to IC procedures (25 hours vs. 15 hours,

p<0.0001). However, the total amount of tPA administered was equal between groups (24 mg with IR vs. 23 mg with IC, p=0.5710).

For a subset of 53 patients, angiographic clot burden was independently calculated by two EM physicians using the Miller score (mean of two graders). Pre-CDT Miller scores were similar in those 3 or 4 MetS criteria vs. those with less than 3 (13±2 vs. 13±2, p=0.56), while post-CDT scores were higher in those with 3 or 4 MetS criteria (9±2 vs. 7±2, p<0.01). Interobserver agreement between graders was very low (95% limits of agreement [pre: −7.95 to 1.76] vs. [post: −12.11 to 10.153]).

1.4 Discussion:

1.4.1 Overall discussion

This study was the first to collect and evaluate the impact of the components of MetS on catheter measured mPAP values at time of diagnosis of acute PE as well as following treatment with catheter-directed fibrinolysis. These disease processes were relatively common comorbid conditions in patients presenting with acute PE, with 85% of patients included in this study having at least one of these conditions. Many recognized guidelines describing the necessary criteria for a clinical diagnosis of MetS suggest that at least 3 of the 4 risk factors must be present (1). Thirty-three percent of patients in this study had either 3 or 4 components of MetS, which is in close agreement with the reported national prevalence for MetS, ranging between 30 and 35%. Moreover, patients with 2 or more MetS components had higher pre- and post-mPAP values compared with patients with 0–1 criteria (Supplemental Figure 2).

This study reports an important novel finding regarding the role of MetS in PE, as it suggests a positive concordance between the increasing number of MetS criteria and mPAP, a widely used marker of both PE severity and treatment success (19). In both pre- and post-CDT groups, mPAP values were highest in those with all four components of MetS and lowest in those without any of these comorbidities. In a post-hoc exercise, we compared initial vital signs and biomarkers at time of diagnosis, as well as overall length of stay and 30-day mortality. The presence of all 4 components of MetS was associated with a trend toward a higher 30-day mortality rate compared to the total mortality rate across all patients (18% vs. 7%, 95% difference of 10%= −5% to 28%), but this difference was not significant (t 1.38, p=0.1697), perhaps secondary to the overall low number of patients in the group with all 4 MetS criteria (n=11). Further investigation is needed to help elucidate whether patients with MetS are at risk of more severe PE as determined by patient-centered clinical outcomes such as VTE recurrence and death.

Further, of the four MetS criteria, obesity was the most common finding, present in 71% of patients. Obese patients had the highest pre-treatment mPAP values (32.1 mmHg) across all groups, significantly higher than their non-obese counterparts. In addition to this finding, multivariate regression analysis identified BMI as an independent predictor of mPAP both at time of diagnosis and following treatment, with higher pressures associated with patients with elevated BMIs. In this context, a previous analysis exploring patient quality of life after submassive PE found obesity to have the greatest negative influence on quality of life

outcomes 3 months post-treatment, as measured by the physical component summary of the Short Form 36 instrument (20). Accordingly, obese patients could be at higher risk for persistent dyspnea from the development of CTEPH due to higher remaining mPAP values following treatment, leading to progressive pulmonary hypertension and eventual right ventricular (RV) failure.

The results of this study raise important questions concerning the most appropriate management of patients diagnosed with acute PE found to carry one or more of the comorbid risk factors of MetS. From the perspective of multidisciplinary PE response teams, patients with multiple MetS components may benefit from mechanical clot removal as opposed to infusion of plasminogen activators such as tPA. A combined phenotype and biomarker-based selection approach may assist in this decision (7). Optimal transition in care at discharge might include systems-based efforts directed toward the implementation of exercise programs, dietary education or targeted pharmacologic agents in patients with the components of MetS diagnosed with VTE. Exercise affords a strong antithrombotic effect and may provide long-term benefits through reduced platelet activity, decreased circulating inflammatory agents and reduced venous stasis (21–29). Nonsteroidal anti-inflammatory agents and statins have been suggested as methods of acutely attenuating the post-PE inflammatory response and could be of particular benefit in this subset of patients (30–31).

1.4.2 Limitations

There are several potential limitations of this study. First, 28 of the 134 patients did not have recorded post-mPAP values. Although multifactorial, this was most commonly due to the individual reporting preferences of the clinician performing post-initiation pressure check. The use of mPAP values as surrogate markers of disease severity and treatment success, although a commonly cited practice, may not be fully representative of the true outcomes of interest. We abandoned the computation of angiographic occlusion because of the extraordinarily low interobserver agreement and the authors' unanimous gestalt interpretation that it was impossible to reliably grade the perfusion defect with planar angiography images. This precluded our ability to correlate pre- and post-mPAP values with anatomic obstruction and its clearance, and it is possible that those with higher mPAP may have elevated pressures at baseline, independent of acute thrombus load. Alternatively, this could represent chronic thrombus that is less amenable to fibrinolysis.

Although patients undergoing CDT typically had catheters in place for an approximate period of 24 hours, this was not standardized and varied somewhat based on overall clinical picture and findings at 24-hour catheter recheck. Further, although IR and IC groups consisted of a similar proportion of MetS patients and were given a similar mean amount of fibrinolytic agent, this was administered over a significantly shorter time period in the IC cohort. It is possible that methodological differences between IR and IC procedures could be a contributory factor in differences in mPAP values obtained. As the process for defining the MetS criteria was determined by retrospective chart review, it is possible that patients actually meeting the criteria but not yet diagnosed for the conditions comprising MetS may have been missed. The overall small sample size resulted in relatively low numbers of

patients in each of the MetS subgroups, and, consequently, the study may have been underpowered to detect significant differences.

The lack of data comparing left ventricular diastolic function is an additional limitation, as diastolic dysfunction could cause increased pulmonary wedge pressure. Although we did not record left ventricular end diastolic pressure (LVEDP), we did compare left atrial size on echocardiography as an indirect sign of increased LVEDP and found a similar proportion of left atrial dilatation in patients with 3 or 4 and 0–2 MetS criteria (19% vs. 16%, p=0.7). Further, the higher proportion of patients with COPD in the subgroup with 4 MetS criteria (18%) is a potential limitation, given its association with pulmonary hypertension. However, within this subgroup of COPD patients (n=6), those with 3 or 4 MetS components (n=3) tended to have higher pre-mPAP (40 vs. 23, p=0.2) and post-mPAP (31 vs. 20, p=0.2) values than those with 0–2 components (n=3). Finally, we restricted this analysis to patients undergoing CDT, as these were the only patients with available pressure data. These results may not be generalizable to all PE patients across the heterogeneous disease spectrum.

1.5 Conclusion:

Metabolic syndrome was relatively common in patients who underwent CDT treatment as part of a multidisciplinary PE response team; MetS was associated with higher mPAP values before and after CDT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Metabolic syndrome is common in patients with acute pulmonary embolism
- Metabolic syndrome is associated with increased mean pulmonary arterial pressures
- These increased pulmonary pressures remain following catheter-directed thrombolysis
- Presence of metabolic syndrome may lead to increased resistance to fibrinolysis

Table 1.

Clinical characteristics stratified by number of MetS criteria

	0	1	2	3	4	All
Total # of patients	20	38	32	33	11	134
Average age (yrs)	54	50	59	65	61	57
Average BMI (kg/m^2)	25.7	36.6	37.4	36.6	38.0	35.3
Female (%)	30	47	56	48	55	49
Caucasian (%)	90	82	78	82	73	81
Obesity (%)	0	79	72	94	100	71
HTN (%)	0	5	66	97	100	49
DM (%)	0	3	22	45	100	25
HLD (%)	0	13	38	64	100	37
Active malignancy (%)	15	5	13	12	0	10
CHF (%)	5	3	3	3	9	4
COPD (%)	5	5	0	3	18	4
MI (%)	0	3	3	3	18	4
Prior VTE (%)	30	39	32	36	18	34
Smoking history (%)	25	26	19	18	27	22

Abbreviations: BMI-body mass index; HTN-hypertension; HLD-hyperlipidemia; DM-diabetes mellitus; CHF-congestive heart failure; COPD-chronic obstructive pulmonary disease; MI-myocardial infarction; VTE-venous thromboembolism

Table 2.

Outcome data stratified by number of MetS criteria shown as mean (±SD)

	0 (n=20)	1 (n=38)	2 (n=32)	3 (n=33)	4 (n=11)	All (n=134)
Pre-mPAP (mmHg)	26.7 (±8.0)	29.8 (±7.5)	32.7 (±10.3)	30.5 (±7.2)	33.1 (±10.6)	30.4 (±8.6)
Post-mPAP (mmHg)	18.9 (±6.1)	19.9 (±4.5)	22.6 (±7.3)	22.6 (±8.7)	24.6 (±8.3)	21.4 (±6.9)
Troponin (ng/ml)	0.45 (±0.44)	0.36 (±0.38)	0.27 (±0.33)	0.34 (±0.34)	0.44 (±0.83)	0.36 (±0.42)
BNP (pg/ml)	272 (±300)	273 (±247)	489 (±507)	311 (±320)	186 (±138)	345 (±352)
Initial HR (bpm)	114 (±20)	114 (±15)	107 (±27)	105 (±19)	111 (±18)	110 (±21)
Initial SBP (mmHg)	120 (±26)	129 (±21)	126 (±26)	136 (±28)	129 (±26)	129 (±25)
Length of stay (days)	7.49 (±6.4)	5.40 (±5.0)	7.77 (±6.1)	5.72 (±4.1)	5.35 (±3.7)	6.35 (±5.3)
# of deaths	2 (±0.31)	1 (±0.16)	2 (±0.25)	2 (±0.24)	2 (±0.40)	9 (±0.25)

Abbreviations mPAP-mean pulmonary arterial pressure; BNP-brain natriuretic peptide; HR-heart rate; SBP-systolic blood pressure

Table 3.

mPAP values stratified by presence or absence of each MetS condition

	Pre-mPAP	Post-mPAP	p-value*
No obesity (n=39)	26.50	20	0.0002
Obesity (n=96)	32	22	<0.0001
p-value*	0.0006	0.198	
No HTN (n=68)	29	20	<0.0001
HTN (n=67)	32	23	<0.0001
p-value	0.0835	0.0226	
No HLD (n=85)	31	21	<0.0001
HLD (n=50)	30	22	<0.0001
p-value	0.6306	0.3094	
No DM (n=100)	30	21	<0.0001
DM (n=35)	31	22.5	0.0007
p-value	0.7983	0.329	

Abbreviations: mPAP-mean pulmonary arterial pressure; HTN-hypertension; HLD-hyperlipidemia; DM-diabetes mellitus

*p-values in rows compare pre- to post-mPAP values and p-values in columns compare mean mPAP values for presence or absence of the metabolic syndrome component

Table 4.

Multivariate linear regression analysis for pre- and post-mPAP

	Pre-mPAP		Post-mPAP	
Variable	**Parameter estimate**	**p-value**	**Parameter estimate**	**p-value**
Age	−0.13726	0.0095	−0.17308	0.0003
Sex	−0.77830	0.5922	−0.97769	0.4296
BMI	0.31931	0.0076	0.21810	0.0260
Obesity	0.17862	0.9360	−1.76762	0.3483
HTN	4.06550	0.0201	3.84188	0.0099
DM	−0.72604	0.6914	1.50012	0.3329
HLD	−0.96598	0.5806	1.00877	0.5109
Active malignancy	−0.80847	0.7476	−2.37462	0.2649
CHF	4.95772	0.2852	0.72956	0.8403
COPD	0.99588	0.7879	0.17351	0.9560
MI	2.08212	0.6746	4.83828	0.2198
Prior DVT	−2.04515	0.3268	0.35770	0.8510
Prior PE	−0.35071	0.8825	−2.61270	0.1945
Smoking history	−1.07729	0.5487	1.15740	0.4764

Abbreviations: mPAP-mean pulmonary arterial pressure; HTN-hypertension; HLD-hyperlipidemia; DM-diabetes mellitus