

# Prevalence and Outcomes of Thrombophilia in Patients with Acute Pulmonary Embolism

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Munzir Obaid<sup>1</sup>  
Ayman El-Menyar<sup>1,2,3</sup>  
Mohammad Asim<sup>2</sup>  
Hassan Al-Thani<sup>1</sup>

<sup>1</sup>Department of Surgery, Hamad General Hospital (HGH), Doha, Qatar;

<sup>2</sup>Department of Surgery, Clinical Research, Trauma and Vascular Surgery Section, HGH, Doha, Qatar;

<sup>3</sup>Department of Clinical Medicine, Weill Cornell Medical School, Doha, Qatar

**Background:** We aimed to study the prevalence and outcomes of thrombophilia in acute pulmonary embolism.

**Methods:** A retrospective observational study was conducted to include patients with a radiologically confirmed diagnosis of PE screened for thrombophilia from May 2011 to February 2015. Data included patients' demographics; clinical presentation, risk factors, laboratory investigations, management, and outcome were analyzed and compared in patients with and without thrombophilia.

**Results:** A total of 227 cases of PE were included in the study, of which 108 (47.6%) had thrombophilia. The most frequent coagulopathic abnormality included deficiency of protein S, protein C, and antithrombin III and hyperhomocysteinemia. Only seven out of 79 patients were found to have factor V Leiden. PE patients diagnosed with thrombophilia were 10 years younger in age and peaked in the age range 30–39 years. Prior history of DVT ( $p=0.001$ ) and PE ( $p=0.001$ ) were the main significant risk factors in the thrombophilia group. The frequency of different risk categories of clinical probability scores did not differ significantly among those with and without thrombophilia. Pulmonary hypertension was a common complication in the thrombophilia group ( $P=0.009$ ). Medications used included warfarin (74.7%), enoxaparin (73.9%), and heparin (55.4%). The overall mortality rate was 8.4%, and was non-significantly higher in the non-thrombophilia group.

**Conclusion:** Deficiencies of protein S, protein C, and antithrombin III are the leading causes of thrombophilic defects. Patients with hereditary thrombophilia are at increased risk of acute PE, particularly among young individuals. Therefore, early detection of thrombophilic defects together with other unprovoked risk factors could reduce the risk of recurrent VTE.

**Keywords:** pulmonary embolism, thrombophilia, risk factors, thromboembolism, outcome

## Introduction

Acute pulmonary embolism (PE) is basically a detrimental form of venous thromboembolism (VTE) with an approximate 90-day fatality rate of 15–20%.<sup>1,2</sup> It occurs in about one-third of patients with VTE<sup>3</sup> and remains a cause of cardiovascular death.<sup>4</sup> Therefore, appropriate risk-stratification based on primary predisposing factors is crucial for the discrimination and aggressive management of high-risk individuals. It has been suggested that the occurrence of VTE necessitates interaction among various clinical, acquired, and inherited risk factors.<sup>5</sup> PE risk factors such as advanced age, cancer, immobility, recent trauma, surgery, or hospitalization can be identified in 50% of cases.<sup>6,7</sup> However, in as many as 20 to 50% of the idiopathic cases, unprovoked PE can be explained by inherited thrombophilia.<sup>8,9</sup>

Correspondence: Ayman El-Menyar  
Weill Cornell Medical College,  
Consultant Clinical Research, Trauma  
Surgery, Hamad General Hospital, Doha,  
Qatar  
Tel +974 44394029  
Fax +974 44394031  
Email aymanco65@yahoo.com

Inherited thrombophilia is a genetic predisposition to venous thromboembolism which may occur due to a single dominant abnormality or combinations of multiple milder defects.<sup>10</sup>

To date, various genetic traits are identified which influence the coagulation function and in turn contribute to the overall risk of VTE, namely protein C, protein S, and antithrombin deficiencies, and the point mutations in factor V Leiden.<sup>8</sup> Among the general population, the frequency of hereditary thrombophilia ranges from 4 to 5% for factor V Leiden, from 0.2 to 0.4% for deficiency of protein C, is 0.2% for protein S, and is 0.02% for antithrombin.<sup>11</sup>

Thrombophilic disorders are of two types which are characterized by coagulation abnormality with loss of function and the other with gain of function.<sup>12</sup> A metaanalysis showed that the VTE risk is increased in patients with natural anticoagulant deficiency.<sup>13</sup> Contemporary research suggests that thrombophilia might result from a combination of genetic and environmental risk factors.<sup>10</sup> The aim of the current study is to determine the frequency of thrombophilic risk factors in patients diagnosed with acute pulmonary embolism.

## Methods

Between May 2011 and February 2015, patients who presented with acute PE confirmed by CTPA were retrospectively identified from the radiology database, and the relevant clinical information was retrieved from the medical records at Hamad General Hospital. All adult patients admitted for the management of acute PE and screened for thrombophilia were included in the study. Clinically suspected patients with PE who were not confirmed by CT imaging or were not screened for thrombophilia markers were excluded from the study. The collected data from the patients' medical records included demographics, clinical presentation, predisposing factors, radiologic imaging, routine laboratory findings, D-dimers, cardiac troponin level, management, and detailed notes for in-hospital course, hospital length of stay, complications (leg pain, swelling, ulcers, and pulmonary hypertension), and outcome. Patients were followed up for routine clinical care as per the standard clinical practice. Screening for thrombophilia includes testing for deficiency of antithrombin (AT III), protein S (PS), and protein C (PC), hyperhomocysteine, antiphospholipid syndrome (APS), lupus anticoagulant, factor V Leiden, and systemic lupus erythematosus (SLE). PE was defined radiologically as the presence of an endoluminal central filling defect partially or completely occluding the pulmonary arteries. The severity

of clinical presentation in patients with PE was assessed by clinical probability scores such as the simplified Wells score, revised Geneva score, and simplified pulmonary embolism severity index (PESI). The Institutional Review Board (IRB# 15139/15) of the Hamad Medical Corporation has approved and granted exempt status for this retrospective study.

## Statistical Analysis

Data were reported as proportion, mean ( $\pm$ standard deviation), median, and range, when applicable. Patients were categorized into two groups based on the thrombophilia screening (non-thrombophilia vs thrombophilia). Comparison between the two groups was done using the Pearson chi-square test for categorical variables and Student's *t*-tests for continuous variables. Yates' corrected chi-square was used for categorical variables, if the expected cell frequencies were below 5. ANOVA test was used for different age groups in the cohort. In addition, descriptive statistics were also performed according to different thrombophilia tests to assess with respect to demographics, predisposing factors, and outcome. Data analysis was carried out using SPSS version 18 (SPSS Inc., Chicago, Illinois, USA).

## Results

During the study period, 227 consecutive patients with a radiologically confirmed diagnosis of PE were enrolled in the study. Of them, 108 (47.6%) patients were found to have a hypercoagulable state that had at least one marker positive for thrombophilia. There were 125 (55.1%) males and the mean age of the study cohort was  $50.6 \pm 16.9$  years.

## Characteristics and Clinical Presentation of PE Patients

PE patients diagnosed with thrombophilia were 10 years younger in age ( $45.2 \pm 13.9$  vs  $55.4 \pm 18.1$ ;  $p=0.001$ ) than those without thrombophilia (Table 1). In comparison to patients without thrombophilia, the vast majority of patients with thrombophilia were diagnosed with PE during an emergency department visit ( $p=0.001$ ), presented with dyspnea ( $p=0.02$ ) and chest pain ( $p=0.008$ ), and had a prior history of DVT ( $p=0.001$ ) and PE ( $p=0.001$ ). On the other hand, the non-thrombophilia group was more likely to have an in-hospital diagnosis ( $p=0.001$ ), have a history of surgery more than 24 h ( $p=0.01$ ), be bedridden ( $p=0.002$ ), and have coronary artery disease ( $p=0.001$ ), myocardial infarction ( $p=0.02$ ), trauma ( $p=0.008$ ), and long bone fracture ( $p=0.005$ ). There were no significant differences between

**Table I** Main Clinical Features and Risk Factors of Acute PE by Thrombophilia

	Overall (n=227)	Non-Thrombophilia (n=119)	Thrombophilia* (n=108)	P value
Age (mean±SD)	50.6±16.9	55.4±18.1	45.2±13.9	0.001
Males	125 (55.1%)	60 (50.4%)	65 (60.2%)	0.14
Body mass index (n=148)	32.6±9.9	31.8±8.9	33.7±11.1	0.26
Location of Diagnosis				
Emergency/ICU	155 (68.3%)	70 (58.8%)	85 (78.7%)	0.001 for all
In-hospital wards	57 (25.1%)	42 (35.3%)	15 (13.9%)	
Outpatient presented at ED	15 (6.6%)	7 (5.9%)	8 (7.4%)	
Frequency of admissions	1 (1–3)	1 (1–3)	1 (1–3)	0.09
Clinical Presentation				
Dyspnea (n=187)	147 (78.6%)	73 (72.3%)	74 (86.0%)	0.02
Chest pain (n=183)	114 (62.3%)	53 (53.5%)	61 (72.6%)	0.008
Shortness of breath (n=220)	51 (23.2%)	28 (25.0%)	23 (21.3%)	0.51
Syncope (n=165)	23 (12.9%)	12 (12.4%)	11 (13.6%)	0.81
Cardiogenic shock	7 (4.2%)	5 (5.4%)	2 (2.7%)	0.39
Number of CT scans	1 (1–11)	1 (1–11)	1 (1–8)	0.17
Comorbidities/Risk Factors				
Hypertension	78 (37.9%)	46 (40.7%)	32 (34.4%)	0.35
Diabetes mellitus	63 (37.9%)	41 (35.7%)	22 (23.7%)	0.06
History of DVT	54 (25.1%)	14 (12.8%)	40 (37.7%)	0.001
History of surgery (>24 h)	48 (22.6%)	32 (29.4%)	16 (15.5%)	0.01
Hypercholesterolemia	44 (21.0%)	22 (19.0%)	22 (23.4%)	0.43
Coronary artery disease	32 (15.6%)	24 (21.4%)	8 (8.6%)	0.01
History of PE	31 (14.8%)	7 (6.7%)	24 (22.9%)	0.001
Bedridden	20 (9.4%)	17 (15.5%)	3 (2.9%)	0.002
Trauma	17 (8.0%)	14 (12.7%)	3 (2.9%)	0.008
Leg fracture	15 (7.1%)	13 (11.8%)	2 (1.9%)	0.005
Neck central line	15 (7.1%)	11 (10.1%)	4 (3.9%)	0.07
Ventilation perfusion scintigraphy	14 (6.6%)	6 (5.5%)	8 (7.7%)	0.52
Myocardial infarction	10 (4.9%)	9 (8.1%)	1 (1.1%)	0.02
Congestive heart failure	8 (3.9%)	5 (4.5%)	3 (3.3%)	0.65
Pelvic fracture	7 (3.3%)	6 (5.5%)	1 (1.0%)	0.06
Femoral central line	5 (2.4%)	4 (3.7%)	1 (1.0%)	0.19
History of surgery (<24 h)	4 (1.9%)	4 (3.7%)	0 (0.0%)	0.04
Paraplegia	1 (0.5%)	1 (0.9%)	0 (0.0%)	0.32

**Note:** \*At least one marker positive for thrombophilia.

the two groups with respect to clinical presentation, comorbidities such as diabetes, hypertension, and congestive heart failure, and other predisposing factors like hypercholesterolemia, pelvic fracture, and paraplegia.

Table 2 compares the clinical probability scores. With respect to the clinical probability scores, the majority of subjects were in low probability (80.6%) using the simplified Wells score and of low risk using the revised Geneva score (94.3%) and simplified Pulmonary Embolism Severity Index (sPESI; 62.9%). The frequency of different risk categories of clinical probability scores did not differ significantly among those with and without thrombophilia.

## Hereditary Defects or Deficiency

The deficiencies of protein S (56.2%), protein C (51.7%), and antithrombin III (44.8%) and hyperhomocysteinemia (42.7%) were the most frequent hypercoagulopathic defects in our cohort. Only seven out of 79 patients (8.9%) were found to have factor V Leiden (Figure 1). The occurrence of thrombophilia according to different age groups in patients with acute PE is given in Figure 2. Thrombophilia showed an inverted bell-shaped curve with age groups which peaked in the age group of 30–39 years.

Table 3 shows the comparison of management and outcome based on thrombophilia status.

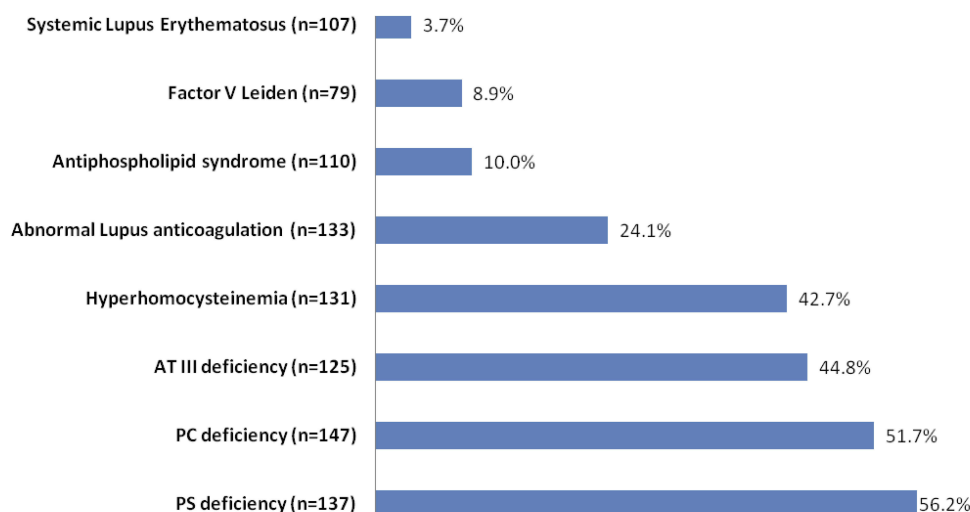
**Table 2** Comparison of Clinical Probability Scores

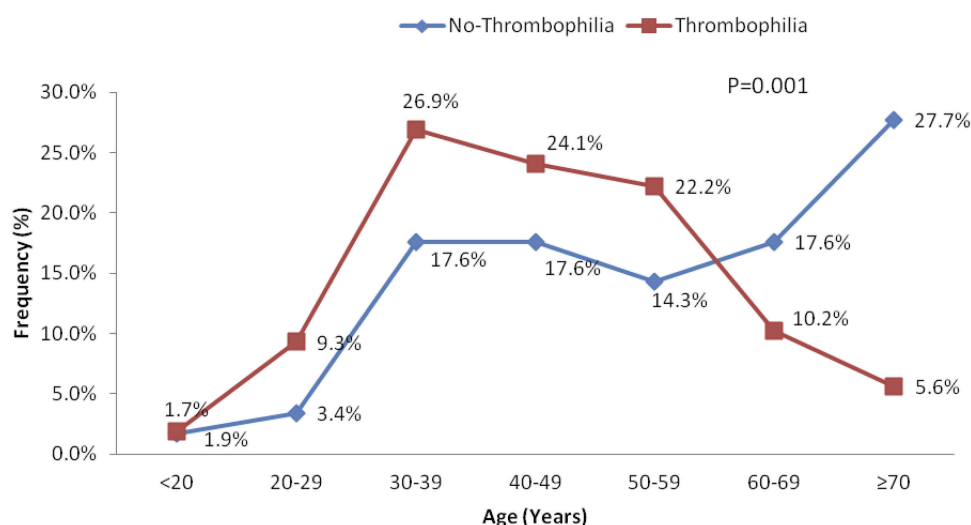
Clinical Probability Scores	Overall (n=227)	Non-Thrombophilia (n=119)	Thrombophilia (n=108)	P value
Simplified Wells Score	0.92±0.74	0.90±0.73	0.94±0.75	0.64
High probability (>6)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.72 for all
Moderate probability (score 2–6)	44 (19.4%)	22 (18.5%)	22 (20.4%)	
Low probability (<2)	183 (80.6%)	97 (81.5%)	86 (79.6%)	
Revised Geneva Score	1.79±1.09	1.85±1.08	1.73±1.10	0.42
Low risk (score 0–3)	214 (94.3%)	112 (94.1%)	102 (94.4%)	0.91 for all
Intermediate risk (score 4–10)	13 (5.7%)	7 (5.9%)	6 (5.6%)	
High risk (score ≥11)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Simplified Pulmonary Embolism Severity Index (sPESI)	0 (0–2)	0 (0–2)	0 (0–2)	0.14
Low risk (0 point)	157 (69.2%)	78 (65.5%)	79 (73.1%)	0.21 for all
High risk (≥1 point)	70 (30.8%)	41 (34.5%)	29 (26.9%)	

The median D-dimer value was lower among patients in the thrombophilia group as compared to those in the non-thrombophilia group ( $p=0.04$ ). Cardiac troponin was tested in 205 patients; of which 132 (64.4%) were found to have positive findings with no significant difference between the two groups. The most frequently used medications were warfarin (74.7%), enoxaparin (73.9%), heparin (55.4%), and aspirin (41.7%). PE patients with thrombophilia were frequently treated with enoxaparin (83.8% vs 65.0%,  $p=0.001$ ) and warfarin (86.9% vs 63.2%,  $p=0.001$ ) when compared to the non-thrombophilic group. A significantly higher proportion of patients with thrombophilia were treated with warfarin for more than 2 years ( $p=0.002$ ) as well as continued warfarin for their lifetime ( $P=0.001$ ). Antiplatelet treatment such as

aspirin (47.4% vs 35.3%;  $p=0.07$ ) and clopidogrel (14.5% vs 6.6%;  $P=0.05$ ) was non-significantly higher in the non-thrombophilia than thrombophilia group. Almost 50% of patients were treated with heparin, with no significant difference between the two groups. However, PE patients in the non-thrombophilia group were more likely to be treated with dalteparin as compared to the thrombophilia group (24.4% vs 9.6%;  $p=0.004$ ) respectively. Thrombolytic therapy was used only in 11 patients; 7 (6.5%) of them had thrombophilia.

The most common post-thrombotic complications were leg edema (19.6%), pulmonary hypertension (16.6%), and calf pain (15.2%). Patients in the thrombophilia group were more likely to develop pulmonary hypertension (23.4% vs 10.3%;  $p=0.009$ ). Patients without thrombophilia were

**Figure 1** Distribution of thrombophilic disorders in patients with acute PE.



**Figure 2** Occurrence of thrombophilia according to different age groups in patients with acute PE.

found to have a prolonged median length of stay as compared to those with thrombophilia ( $p=0.02$ ). The overall all-cause mortality rate was 8.4% (19 patients), and the mortality rate was non-significantly higher in the non-thrombophilia group compared to the thrombophilia group.

**Table 3** Comparison of Management and Outcome

	Overall (n=227)	Non-Thrombophilia (n=119)	Thrombophilia* (n=108)	P value
D-Dimer (mg/L FEU), median, range (n=166)	4.5 (0.17–290)	6.6 (0.17–36.1)	3.9 (0.17–290)	0.04
Positive (>0.55 mg/L)	155 (93.4%)	74 (91.4%)	81 (95.3%)	0.30 for all
Negative	11 (6.6%)	7 (8.6%)	4 (4.7%)	
Troponin T/I positivity (n=205)	132 (64.4%)	70 (64.8%)	62 (63.9%)	0.89
SVC/IVC thrombosis (n=200)	4 (2.0%)	NA	4 (4.8%)	–
Treatment**				
Enoxaparin	164 (73.9%)	76 (65.0%)	88 (83.8%)	0.001
Warfarin	165 (74.7%)	72 (63.2%)	93 (86.9%)	0.001
Heparin	124 (55.4%)	69 (58.0%)	55 (52.4%)	0.40
Aspirin	91 (41.7%)	55 (47.4%)	36 (35.3%)	0.07
Dalteparin	39 (17.5%)	29 (24.4%)	10 (9.6%)	0.004
Warfarin for life	51 (22.6%)	16 (13.6%)	35 (32.4%)	0.001
Warfarin (<2 years)	86 (37.9%)	46 (38.7%)	40 (37.0%)	0.80
Warfarin (>2 years)	40 (17.6%)	12 (10.1%)	28 (25.9%)	0.002
Plavix	24 (10.8%)	17 (14.5%)	7 (6.6%)	0.05
Thrombolytic therapy	11 (4.9%)	4 (3.4%)	7 (6.5%)	0.28
Complications				
Leg edema	44 (19.6%)	21 (17.9%)	23 (21.5%)	0.50
Pulmonary hypertension	37 (16.6%)	12 (10.3%)	25 (23.4%)	0.009
Calf pain	34 (15.2%)	15 (12.8%)	19 (17.9%)	0.29
Leg ulcer	6 (2.7%)	4 (3.4%)	2 (1.9%)	0.48
Hospital stay (days)	8 (1–240)	9.5 (1–240)	7.5 (1–65)	0.02
Duration of follow-up (days)	45.2 (1–5488)	32 (1–1245)	73.3 (1–5488)	0.03
Mortality	19 (8.4%)	14 (11.8%)	5 (4.6%)	0.05

**Notes:** \*At least one marker positive for thrombophilia; \*\*There is an overlap as one can receive two different medications.

**Abbreviations:** NA, not applicable; ALA, abnormal lupus anticoagulation.

**Table 4** Presentation of Main Clinical Features of the Thrombophilic Defects

	<b>PC Deficiency (n=76)</b>	<b>PS Deficiency (n=77)</b>	<b>AT III Deficiency (n=56)</b>	<b>Hyperhomocysteinemia (n=56)</b>	<b>ALA (n=32)</b>	<b>APS (n=11)</b>	<b>FVL (n=7)</b>
Age (mean±SD)	44.1±13.8	44.5±13.7	45.5±13.8	45.4±12.9	43.2±12.8	38.2±11.7	51.4±14.3
Males	45 (59.2%)	45 (58.4%)	38 (67.9%)	40 (71.4%)	21 (65.6%)	7 (63.6%)	4 (57.1%)
Risk Factor/Comorbidity							
Hypertension	18 (28.6%)	19 (29.7%)	17 (37.8%)	14 (30.4%)	9 (34.6%)	2 (22.2%)	4 (57.1%)
Diabetes mellitus	13 (20.6%)	13 (17.6%)	10 (22.2%)	12 (21.4%)	6 (23.1%)	2 (28.6%)	1 (14.3%)
History of DVT	27 (36.5%)	28 (36.8%)	22 (40.0%)	22 (39.3%)	13 (40.6%)	6 (54.5%)	2 (28.6%)
History of surgery (>24 h)	13 (18.1%)	13 (17.6%)	10 (22.2%)	7 (13.0%)	1 (3.1%)	1 (11.1%)	2 (28.6%)
Coronary artery disease	5 (7.9%)	4 (6.3%)	4 (8.9%)	3 (6.5%)	2 (6.5%)	0 (0.0%)	0 (0.0%)
History of PE	17 (23.0%)	19 (25.0%)	13 (23.6%)	12 (21.4%)	9 (29.0%)	3 (30.3%)	1 (14.3%)
Bedridden	1 (1.4%)	1 (1.4%)	1 (1.9%)	2 (3.7%)	2 (6.5%)	1 (11.1%)	0 (0.0%)
Trauma	3 (4.2%)	3 (4.1%)	2 (3.7%)	2 (3.7%)	1 (3.1%)	0 (0.0%)	0 (0.0%)
D-Dimer level (mg/L FEU), median, range	3.9 (0.17–290)	3.9 (0.74–290)	3.6 (0.17–290)	4.5 (0.17–290)	3.05 (0.30–290)	2.5 (0.17–16.9)	4.6 (0.85–12.3)
Positive D-dimer	63 (98.4%)	65 (84.4%)	44 (95.7%)	44 (97.8%)	26 (96.3%)	8 (80.0%)	6 (85.7%)
Troponin T/I positivity	44 (62.9%)	44 (62.9%)	32 (64.0%)	32 (64.0%)	17 (63.0%)	4 (57.1%)	4 (80.0%)
Mortality	2 (2.6%)	2 (2.6%)	2 (3.6%)	0 (0.0%)	1 (3.1%)	1 (9.1%)	0 (0.0%)

**Abbreviations:** PC, protein C; PS, protein S; AT III, antithrombin III; ALA, abnormal lupus anticoagulation; APS, antiphospholipid syndrome; FVL, factor V Leiden.

Table 4 shows the presentation of the main clinical features of the thrombophilic group. Patients with APS were found to be the youngest with mean age  $38.2 \pm 11.7$  years, whereas patients with factor V Leiden were more likely to be older with mean age  $51.4 \pm 14.3$  years.

Male gender predominated among all of the groups with thrombotic disorders and was most frequent in patients with hyperhomocysteinemia (71.4%). History of DVT was most common in patients with AT III deficiency and hyperhomocysteinemia. Recurrent PE was more evident in those with lupus anticoagulant, antiphospholipid syndrome, and PS deficiency. However, thrombophilia defects were observed in less than 10% in bedridden, trauma and cardiac patients.

Positive D-dimer ( $>0.5$  mg/L) was observed in more than 80% and it reached up to 98.4% in PC deficiency. Moreover, cardiac troponin positivity was observed in more than 60% of patients with different thrombophilic defects (80% in FVL). There was no mortality in patients with hyperhomocysteinemia and FVL. However, the mortality was lower among groups with different thrombophilic defects.

## Discussion

The present study showed that nearly half of patients with acute PE had thrombophilic defects and the majority of them were diagnosed at an emergency department visit. The thrombophilic group was more likely to have a prior history of VTE. With respect to the clinical probability scores, the

majority of subjects fell under the low-risk group. The frequency of thrombophilia peaked in the age group of 30–39 years. The risk of pulmonary hypertension is high in our cohort (16.6%) with a significant difference between the study groups (23% in patients with thrombophilia vs 10% in non-thrombophilia). This finding needs further evaluation.

Table 5 shows the review of studies based on VTE and thrombophilia.<sup>14–22</sup> In the current literature, the frequency of hereditary thrombophilia varies possibly due to socio-ethnic diversity, and also depends upon the diagnostic modalities used in the different clinical settings.<sup>23</sup> It has been reported that almost 40% of VTE can be explained by activated protein C (APC) resistance which is caused by mutation in factor V (factor V Leiden).<sup>24,25</sup> Only 5–10% of the thrombophilic cases are associated with deficiency of AT, PC, and/or PS.<sup>21</sup> Contrary to the previous reports, deficiencies of AT-III, PC, and PS and hyperhomocysteinemia were the most frequent hereditary thrombophilia subtypes in our cohort. As shown in Table 5, the published data suggest inconsistency in the occurrence of VTE among males and females.<sup>3</sup> In the present study the proportion of males was slightly higher than females, which is consistent with an earlier study from our center and in the region.<sup>26,27</sup> Also, PE patients with thrombophilia were more likely to be younger and more frequently had a history of recurrent VTE than those without thrombophilia. Notably, there is a steep decline in



**Table 5** Review of Literature for VTE and Thrombophilia

Author	Year	Population	Age	Sex M/F	AT III	PC	PS	FVL	Hyp-Hcy	Double/Multiple	VTE/PE	Outcome
Lee et al <sup>14</sup>	2017	222 (66)	50 (41–63)	109/7	14	12	4	NA	NA	NA	VTE	The prevalence of HT (unprovoked VTE) was 15%. Family history of VTE and young age (<45 years) were independent predictors for unprovoked VTE due to HT
Brüwer et al <sup>15</sup>	2016	144 688 Adult 321 Children 367	Age of the first VTE	Male children (58.8%); male adolescents (47.6%); male adults (55.9%)	23 child 23 adult	29 child 13 adult	33 child 23 adult	NA	NA	NA	VTE	Children and adults differ with respect to i) thrombotic locations, ii) percentage of unprovoked versus provoked VTE, and iii) different rates of positive VTE family histories
Bucciarelli et al <sup>16</sup>	1999	746	39.5 (1–95)	232/281	129	145 309 APCR	138	NA	NA	25	VTE	AT III deficiency seems to have a higher risk for VTE than the other genetic defects. There is a relationship between age and occurrence of thrombosis for both men and women
Lee et al <sup>17</sup>	2011	384	PC: 50.5 (23–76) PS: 44 (20–76) AT: 59.5 (23–83) FV: 30	151/233	14	4	31	I	NA	NA	VTE	In Singapore and countries with similar demographics, hereditary thrombophilia screening should be confined to testing for protein C, protein S and AT III
Brouwer et al <sup>18</sup>	2009	130 (90)	49 (21–89)	50/80	12	40	39	25 (19)	24 (20)	NA	VTE	Patients with a PS, PC, or AT III deficiency appear to have a high absolute risk of recurrence
Rossi et al <sup>19</sup>	2008	920 (198) DVT + PE 242 DVT 678	37 (1–85)	146 (16)	8 (3)	11 (3)	10 (3)	62 (19%)	NA	12 (4)	PE	Higher risk of symptomatic PE in patients with AT deficiency or PT G20210A. Risk decreased in those with FV Leiden in comparison with those with no known inherited defect
De Stefano et al <sup>20</sup>	2006	538 (64)	0–68	29/35	14	28	22	NA	NA	NA	VTE	Deficiency of AT, PC, or PS has a 1.5-fold increased risk of recurrent VTE; in particular, symptomatic patients with AT deficiency require indefinite anticoagulation

(Continued)

Table 5 (Continued).

Author	Year	Population	Age	Sex M/F	AT III	PC	PS	FVL	Hyp-Hcy	Double/Multiple	VTE/PE	Outcome
Martinelli et al <sup>21</sup>	1998	723 (39%)	40±19	332/391	85 (12%)	64 (9%)	41 (6%)	200 (28%)	NA	6 (1%)	VTE	Factor V Leiden is associated with smaller risk of thrombosis (less severe thrombotic manifestations), than that for AT III, protein C, or protein S deficiency
Simioni et al <sup>22</sup>	1999	405 (793)	41 (2–80) 42 (6–95) for factor V	80/101 105–119	34	73	74	224	NA	NA	VTE	Screening family members of symptomatic carriers of AT III, PC, and PS deficiency is needed. For family members of symptomatic carriers of factor V Leiden, screening does not seem to be justified except for women of fertile age
Current study	–	227	50.6±16.9	125/102	56	76	77	7	56	–	PE	A total of 108 (47.6%) patients were found to have thrombophilia. Deficiency of protein S, protein C, and antithrombin III are the leading causes of thrombotic defects. Patients with hereditary thrombophilia are at increased risk of acute PE, particularly among young individuals (<40 years)

Abbreviations: NA, not available; HT, hereditary thrombophilia.

the frequency of hereditary thrombophilia with age in our cohort, which is also evident from findings of the MAISTHRO registry suggesting that this could be attributed to the decrease in frequency of genetic defects and deficiency of PC or PS in individuals that developed an initial VTE event at an advanced age.<sup>28</sup>

Evidence suggests that around 10% of in-hospital mortalities are related to PE which often remains undiagnosed prior to death.<sup>13</sup> Therefore, it is necessary to initiate early thromboprophylaxis in high-risk patients. In the present study, there is a higher predilection between PE diagnosed in the emergency department or in the ICU and thrombophilia.

Although hereditary thrombophilia and mainly deficiencies of PC and PS are known to have higher risk for myocardial infarction (MI),<sup>29</sup> in our study the incidence of MI was significantly lower in the thrombophilia group. Notably, comorbidities were more frequent in the non-thrombophilia group.

Among various prognostic scorings, the sPESI is considered the most useful and validated tool to predict mortality in patients with PE.<sup>30</sup> With respect to clinical probability scores, the majority of subjects were in low probability or risk and often have a better prognosis and there is no observed association of thrombophilia with the predicted risk of mortality in PE patients in the current study.

Moreover, in patients with acute PE, increased levels of cardiac troponin indicate the right ventricular strain which might be related to the higher risk of severe PE.<sup>31</sup> In the current study, elevated cardiac troponin showed no significant association with thrombophilia and the risk of mortality.

Douketis et al<sup>32</sup> suggested that PE patients are four times more likely to die due to recurrent VTE. Notably, in our cohort, patients with hereditary thrombophilia had longer treatment course due to increased risk of recurrence and about one-third continued to use anticoagulant for their lifetime. For unprovoked PE, the optimal treatment duration remains unknown and treatment could be extended beyond 3 months of duration.<sup>33</sup> Lifetime continuation of anticoagulant in patients with low risk of bleeding was also recommended by some authors; particularly in males with second unprovoked PE and/or positive D-dimer testing after 1 month of stopping anticoagulant therapy.<sup>34</sup>

Chronic thromboembolic pulmonary hypertension is one of the serious complications of acute PE, which is observed in 16.6% of cases in our cohort. Also, we observed a significant association of pulmonary hypertension with hereditary



thrombophilia. Our findings are in accordance with an earlier prospective study of 314 cases with acute PE.<sup>35</sup>

An earlier study suggested that deficiencies of PC or PS and AT III, and antiphospholipid antibodies are associated with an increased risk of recurrent VTE.<sup>28</sup> In our study, 38% of patients presented with recurrent DVT and 23% had a prior history of PE; this is in agreement with earlier studies which demonstrated that patients with thrombophilia are at increased risk of recurrent VTE, which ranges between 36% and 62%.<sup>20,36</sup> There is no association between family history of thrombosis and the risk of recurrent thrombosis in patients without protein C, protein S, or antithrombin deficiency.<sup>37</sup>

The overall mortality rate in our cohort was 8.4%, and the mortality rate was non-significantly higher in the non-thrombophilia group compared to the thrombophilia group. Consistent with our findings, a European Prospective Cohort on Thrombophilia identified no association of familial thrombophilia with the risk of mortality, irrespective of prior history of thrombosis.<sup>38</sup> This could be explained by the fact that patients with familial thrombophilia are better aware of the symptoms of VTE, which increases the chances of early diagnosis and management; thereby conferring lower risk of complications and mortality.

## Limitations

One limitation is the retrospective design which might influence the generalizability of our results and also the data obtained from a single center which limits the sample size. Another potential limitation is the timing of testing for thrombophilia. It is known that PS, PC, and AT III values can be misleadingly reduced due to consumption during the acute episode of VTE or during anticoagulant therapy.<sup>39</sup> It is not clearly stated when blood samples were drawn, in particular, or the duration of symptoms and therapy used as this may overestimate or underestimate the prevalence of thrombophilia. However, based on our institutional guidelines we believed that all of the tests were performed after the initial presentation and in the absence of the anticoagulant, when possible. The analysis in our study was done based on the second result after 6 months. Finally, some of our patients were partially screened for thrombophilic defects, so there might be a possibility of underestimation of the true incidence of multiple thrombophilic risk factors. However, we believe that not every test that is

available is necessary and thrombophilic testing should be customized on an individual basis.

In conclusion, deficiency of protein S, protein C, and antithrombin III is the leading cause of thrombophilic defects in our cohort; however, the timing of measurement is crucial. Patients with hereditary thrombophilia are at increased risk of acute PE, particularly young individuals (<40 years). Importantly, one-third and one-fifth of DVTs and PEs respectively reoccur in the presence of thrombophilic risk factors and could therefore be prevented, if individuals are appropriately screened after a first VTE episode. Therefore, early detection of thrombophilic defects together with other unprovoked risk factors could reduce the risk of VTE in high-risk individuals. Furthermore, larger prospective studies are needed to confirm the findings of the present study.

## Ethics Approval and Consent to Participate

This observational study has received expedited review and was approved by the Institutional Review Board (IRB#15139/15) at the Medical Research Center, Hamad Medical Corporation, Doha, Qatar. A waiver of consent was granted as there was no direct contact with subjects and data were anonymously and confidentially retrieved with compliance with the Declaration of Helsinki.

## Consent for Publication

Approved by the Institutional Review Board (IRB#15139/15).

## Data Sharing Statement

Data will be available upon request after approval and signing agreement with the medical research center.

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## Author Contributions

MMO, AE, MA, and HA: all authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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