Internal Medicine Section

Prevalence, Risk Factors of Deep Venous Thrombosis in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Cross-sectional Study

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ABSTRACT

Introduction: It is important to increase awareness and identify the predictors of Deep Vein Thrombosis (DVT) in Chronic Obstructive Pulmonary Disease (COPD) patients presenting with worsening dyspnoea, as they are at a high-risk for Venous Thromboembolism (VTE) due to immobility, inflammation, and comorbidities.

Aim: To determine the prevalence of DVT in hospitalised patients with acute exacerbation of COPD, as well as to identify associated risk factors for DVT in this group.

Materials and Methods: A cross-sectional study was conducted from March 2021 to June 2022 in the Department of Respiratory Medicine at Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, Karnataka, India. The sample population consisted of hospitalised patients with acute exacerbation of COPD who were aged over 40 years. All patients underwent routine blood investigations, Electrocardiograph (ECG), echocardiogram, arterial blood gas analysis, D-dimer test, chest radiograph, and lower-limb venous Doppler. Risk assessment was performed using the Modified Well's criteria for DVT, and pretest probability was determined for all patients. The Chi-square test was used as

a test of significance, with a p-value <0.05 considered statistically significant in all analyses.

Results: The mean age of the study population was found to be 60.80±10.21 years. Among the 74 patients included in the study, it was found that 3 (4.05%) patients had DVT. There was no statistically significant difference between the DVT and non DVT groups regarding age, sex, obesity, modified Medical Research Council (mMRC) grade of breathlessness, smoking status, severity of airflow obstruction in spirometry, COPD class, type of respiratory failure, and presence of comorbidities. However, there was a statistically significant difference between the DVT and non DVT groups in terms of elevated D-dimer (>500 ng/mL), history of immobilisation for more than three days, and Modified Wells' score (>2).

Conclusion: Patients with acute exacerbation of COPD, associated with a significant history of immobilisation and high D-dimer values, along with a high-risk pretest probability using clinical predictors such as the Modified Wells' score for DVT, should be considered for evaluation of VTE and early initiation of prophylactic anticoagulation therapy to prevent Pulmonary Thromboembolism.

INTRODUCTION

COPD is a pulmonary disease characterised by airflow limitation that is not fully reversible. Patients with COPD are at a high-risk for thromboembolism due to systemic inflammation, limited mobility, and co-existing comorbidities [1]. Risk factors such as a higher Body Mass Index (BMI), lower exercise capacity, use of oxygen, and severe dyspnoea have been found to be associated with VTE [2]. Keramidas G et al., reviewed the prevalence of venous thromboembolic disease in patients with chronic inflammatory lung diseases [3]. The prevalence of DVT in various studies was 4.8%, 6.4%, 10.5%, and 10.6% (CI: 95%) [1,4-6]. Although various studies have reported the incidence and prevalence of VTE in cases of Acute Exacerbation of COPD (AECOPD), there is limited data in the Indian subpopulation on the occurrence of DVT in patients with chronic lung diseases, which can contribute to the development of pulmonary vascular abnormalities [7-11]. The present study aims to determine the prevalence of DVT in patients with acute exacerbation of COPD, identify associated risk factors for VTE in such groups, and therefore reduce mortality due to pulmonary embolism through early detection.

MATERIALS AND METHODS

A cross-sectional study was conducted in the Department of Respiratory Medicine at Vydehi Institute of Medical Sciences and

Research Centre, Bengaluru, Karnataka, India from March 2021 to June 2022. Approval from the Institutional Ethics Committee (ECR/747/Inst/KA/2015/RR-18) was obtained.

Inclusion criteria: The study included all patients with COPD who were hospitalised due to acute exacerbation (diagnosed as per GOLD [12]) and were aged above 40 years.

Exclusion criteria: Patients with acute worsening breathlessness due to primary cardiac disorders, malignancy, stroke, coagulation disorders, chronic kidney disease, heart failure, those on regular anticoagulants, antiplatelet medication, antidepressants, and hormone replacement therapy, patients with a history of trauma or major surgeries in the past three months, and patients who were not willing to participate were not included in the study.

Study Procedure

A total of 74 participants with acute exacerbation of COPD, fulfilling the inclusion criteria, were enrolled in the study. Data was obtained through a detailed clinical history, including age, sex, mMRC grade of breathlessness [12], previous episodes of acute exacerbation, smoking history, treatment history, and history of immobilisation. Thorough physical examination, including height, weight, BMI, pulse rate, blood pressure, and systemic examination, including examination for signs of DVT, was performed. Bedside Point of Care Ultrasound (POCUS) (4-point compression test) was performed on

all patients upon admission. Blood samples for arterial blood gas analysis, D-dimer, complete blood count, renal function test, and serum electrolytes were drawn immediately upon admission. ECG, echocardiogram, and chest radiographs were also obtained for all patients as part of routine COPD evaluation. Based on mMRC grade of breathlessness and history of exacerbations in the past, all the patients were classified using GOLD COPD assessment tool [12]. Risk stratification for DVT was calculated for each patient at admission using Modified Wells' criteria [13,14]. A Modified Wells' score below two was considered low risk, while a score of 2 or more considered as high-risk for DVT. Bilateral lower limb venous Doppler was performed on all participants using KT-LM200HDPE Siemens Ultrasound-Doppler machine by the faculty of radiodiagnosis. The presence or absence of deep vein thrombus, including its extent, was reported. Arterial blood gases were analysed for Type 1 (hypoxemic) and Type 2 (hypercapnic) respiratory failure. A complete blood picture was obtained to look for signs of infection. D-dimer was tested at the time of admission, and a value above 500 ng/mL was considered the cutoff [13-15].

STATISTICAL ANALYSIS

The data was entered into a Microsoft Excel datasheet and analysed using Statistical Packages for Social Sciences (SPSS) version 23.0 software (IBM SPSS Statistics, Somers NY, USA). Normally distributed data was represented as mean and standard deviation, while categorical data was presented as frequencies and proportions. The Chi-square test was used as a test of significance. A p-value less than 0.05 was considered statistically significant in all analyses.

RESULTS

Out of the 74 subjects with AECOPD, 60 (81.08%) were male, and 14 (18.92%) were female. The mean age of the study population was found to be 60.80±10.21 years. Among the AECOPD patients requiring hospitalisation, 28 (37.84%) were between 51 and 60 years of age. All patients were diagnosed cases of COPD on inhaler therapy with a post-bronchodilator FEV1/FVC ratio of ≤70%.

Among them, 39 (52.71%) patients belonged to GOLD Grade-3 Forced Expiratory Volume (FEV1) % predicted between ≥30-49, followed by 24 (32.43%) patients belonging to GOLD Grade-2 (FEV1 % predicted between ≥50-79), and 11 (14.86%) patients belonged to GOLD Grade-1 (FEV1 % predicted ≥80%). A history of smoking was present in 52 (70%) patients, whereas 22 (30%) patients were non smokers. Among smokers, the mean number of cigarettes/beedis smoked per day was found to be 11.4±9.56. The average number of years of smoking was found to be 17.64±14.16, and the mean smoking index was 244.01±232.37.

Among non smokers, the aetiology of COPD was attributed to various causes, of which 13 (17.57%) patients had a history of biomass fuel exposure, which was also found to be the most common aetiology for COPD among non smokers. Among the nine patients with occupation-related COPD, 6 (8.10%) were farmers, one patient was a beedi roller, one patient was a carpenter, and the other patient worked as a railway employee. A total of 54 (72.97%) patients had AECOPD secondary to infection, whereas 20 (27.03%) patients were non compliant with inhalers. The DVT was diagnosed in 3 (4.05%) out of 74 patients. Out of the 71 patients without DVT, 42 (59.2%) patients had a D-dimer level <500 ng/mL, and 29 (40.8%) patients had a D-dimer level >500 ng/mL. All patients with DVT had a D-dimer level >500 ng/mL. There was a statistically significant difference found between the two groups with respect to D-dimer.

Out of the 71 patients without DVT, 43 (60.6%) patients had a Modified Wells' score of less than 2, and 28 (39.4%) patients had a score of 2 or more. It was observed that in all patients with DVT, the Modified Wells' score was more than 2. There was a statistically

significant difference between the two groups with respect to the Modified Wells' score.

Out of the 71 patients without DVT, 52 (73.2%) patients had no history of immobilisation, and 19 (26.8%) had a history of immobilisation (>3 days). All three patients with DVT had a history of immobilisation for more than three days. There was a statistically significant difference between the two groups with respect to a history of immobilisation for more than three days [Table/Fig-1].

Parameters		No n	No %	Yes n	Yes %	p-value
Age (years)	41-50	11	15.5%	1	33.3%	0.529
	51-60	28	39.4%	0	0	
	61-70	20	28.2%	1	33.3%	
	Above 70	12	16.9%	1	33.3%	
Gender	Female	14	19.7%	0	0	0.393
	Male	57	80.3%	3	100.0%	
Obesity (BMI >30 kg/m²)	No	51	71.8%	3	100.0%	0.282
	Yes	20	28.2%	0	0	
mMRC grade of breath lessness	0	0	0	0	0	0.362
	1	0	0	0	0	
	2	20	28.17%	0	0	
	3	23	32.39%	0	0	
	4	28	39.44%	3	100.0%	
COPD class	A	7	9.86%	0	0	0.7235
	B	16	22.53%	1	33.33%	
	C	15	21.13%	0	0	
	D	33	46.48%	2	66.67%	
Smoker	No	21	29.6%	1	33.3%	0.889
	Yes	50	70.4%	2	66.7%	
Immobilisation >3 days	No	52	73.2%	0	0	0.007
	Yes	19	26.8%	3	100.0%	
Comorbidities	No	25	35.2%	1	33.3%	0.947
	Yes	46	64.8%	2	66.7%	
Hypertension	No	45	63.4%	2	66.7%	0.908
	Yes	26	36.6%	1	33.3%	
Diabetes	No	48	67.6%	3	100.0%	0.235
	Yes	23	32.4%	0	0	
IHD	No	53	74.6%	2	66.7%	0.757
	Yes	18	25.4%	1	33.3%	
Severity of obstruction (FEV1 % predicted)	>80%	11	15.5%	0	0	0.748
	50-79%	37	52.1%	2	66.7%	
	30-49%	23	32.4%	1	33.3%	
	<30%	0	0.0%	0	0	
ABG- respiratory failure	Type-1	26	36.6%	1	33.3%	0.908
	TYPE 2	45	63.4%	2	66.7%	
D-dimer (ng/mL)	< 500	42	59.2%	0	0	0.043
	> 500	29	40.8%	3	100.0%	
Modified Wells' score	<2	43	60.6%	0	0	0.037
	>2	28	39.4%	3	100.0%	

[Table/Fig-1]: Comparison of risk factors and clinical predictors for DVT betweeen the DVT and non DVT groups.
Chi-square test was used; IHD: Ischaemic heart disease; BMI: Body mass index; ABG: Arterial blood gas

DISCUSSION

In an observational trial conducted by Ilievska DK et al., in the Department of Pulmonology and Immunology at City General Hospital, Macedonia, 100 hospitalised patients with acute exacerbation of COPD were prospectively evaluated, and DVT

was diagnosed in 5% [7]. Pang H et al., performed a multi-centre, prospective, observational study involving 16 hospitals in China [8]. Over the course of one year, out of 1144 patients with acute exacerbation of COPD, 64 were diagnosed with DVT. Børvik T et al., aimed to investigate the association between COPD and the risk of VTE and mortality in a population-based cohort, where a total of 49.5% had DVT [9]. Park SH conducted a retrospective cohort study based on data collected from the Korean Health Insurance Review and Assessment Service (HIRA) national database [1]. The prevalence of DVT in men with COPD was about five times higher than that in men within the general population. In another study, by Chen CY and Liao KM, which aimed to estimate the influence of COPD on the development of VTE, the association between COPD and DVT was evaluated among the Asian population in a nationwide population-based cohort [10]. It was found that the risk of DVT was 38% higher in the COPD cohort than in the non COPD cohort. In the present study, the prevalence of DVT in hospitalised cases of AECOPD was observed to be 3 (4.05%). These results are similar to the aforementioned studies.

The probable association between DVT and AECOPD might be due to chronic inflammation as well as immobilisation among AECOPD patients. A systematic review and meta-analysis of 17 studies by Fu X et al., revealed a combined incidence of 7% of DVT in 3170 AECOPD patients [16]. In their study on 105 patients with COPD and acute exacerbation, Kamel MM et al., found that 28.6% of patients had PE and 26.7% had DVT [17]. It was also concluded that DVT of the lower limbs was not essential in all cases of proven pulmonary embolism. Wells' score and Geneva's score were helpful tools for bedside assessment of the occurrence of VTE. A systematic review and meta-analysis of 20 studies, including 5854 patients, found the prevalence of DVT to be 9% (95% CI) [18]. In a retrospective study of 116 patients with pulmonary embolism, 66 patients were diagnosed with COPD. The incidence of DVT in patients with combined PE and COPD was found to be 33% [19].

Ilievska DK et al., and Pang H et al., noted a positive correlation between COPD severity and DVT [7,8]. Immobility and obesity were significantly higher among these patients. After adjusting for co-variates, it was observed that a venous thrombosis history, prolonged immobility (≥3 days), and lower limb pain before hospitalisation were independently associated with the development of VTE, as per the above studies. In a population-based cohort conducted by Børvik T et al., patients with COPD stage III/IV (C/D) had a 1.6-times higher risk of VTE than those without COPD [9]. Among the numerous factors predisposing to DVT, prolonged immobilisation, especially during hospitalisation, was found to be a major risk factor. Immobility increases the possibility of a pro-thrombotic state when the duration is more than 24 hours. It will be a risk factor if the duration exceeds three days [11]. Therefore, patients with frequent episodes of exacerbation leading to immobilisation and COPD patients on long-term oxygen therapy are at high-risk for DVT. A significant association has been reported between smoking and COPD exacerbation in various studies [20,21]. Therefore, patients who have smoked for a long duration are at a higher risk for exacerbation and repeated hospitalisation leading to prolonged immobilisation.

Dentali F et al., Ilievska DK et al., Pang H, et al., and Dong W et al., have all found a positive correlation between elevated D-dimer levels and the prevalence of VTE in their respective studies [4,7,8,11]. A negative D-dimer is a valuable laboratory index for excluding VTE [11]. It has been reported that high D-dimer levels were found in 95% of COPD patients experiencing acute exacerbation with VTE [11]. Since, 72.97% of the patients in the present study had an infective exacerbation, the relevance of elevated D-dimer as an independent marker of thromboembolism in this clinical setting cannot be definitively concluded. However, the present study

did find a significant association between high D-dimer values (>500 ng/mL) and VTE.

Clinical predictors for VTE, such as Modified Wells' criteria, are frequently used to assess the likelihood of DVT in patients with prolonged immobilisation, such as post-operative or trauma cases, due to their high sensitivity and specificity. In the present study, the Modified Wells' score for DVT was found to be highly statistically significant and may therefore be a useful tool in determining the pretest probability. Both physicians and patients are highly concerned about the diagnosis, treatment, and prognosis of COPD, especially due to its increasing global incidence [22]. In patients with COPD exacerbation, VTE is considered an independent risk factor for poor prognosis. The mortality rate among AECOPD cases is also higher when combined with VTE [22]. Due to their similar clinical presentation, PE is more likely to be misdiagnosed or ignored in COPD cases [22]. Therefore, prompt diagnosis and early initiation of anticoagulation therapy become integral parts of the prevention of pulmonary embolism and improvement of outcomes in AECOPD cases with a high-risk for VTE [22].

Limitation(s)

Firstly, the sample size was relatively small. Secondly, not all AECOPD patients had their lung function tested during hospitalisation, few cases were diagnosed based on Pulmonary Function Test (PFT) reports available with the patients, ranging from three years to two months prior to presentation. This could have potentially affected the results when comparing the severity of airflow obstruction with the incidence of VTE. Finally, follow-up was not conducted to evaluate mortality.

CONCLUSION(S)

As pulmonary physicians, our goal is to reduce the incidence of VTE in COPD cases and to enhance the prognosis and survival rate of COPD patients with VTE. Based on the results of the present study, we can conclude that all hospitalised patients with acute exacerbation of COPD, who have risk factors such as a history of immobilisation for more than three days, high D-dimer values (>500 ng/mL), and those with a high pretest probability of VTE, should be actively evaluated for thromboembolism and treated accordingly. Initiating prophylactic anticoagulant therapy early among high-risk groups of AECOPD may help in reducing the incidence of VTE. Furthermore, early initiation of chest physiotherapy, limb exercises, and pulmonary rehabilitation to improve the quality of life in AECOPD patients can contribute to reducing the incidence, morbidity, and mortality associated with VTE.

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