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ORIGINAL RESEARCH

A study of Incidence of Deep Venous Thrombosis in Post Covid 19 Patients.

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Abstract

Background: During the COVID-19 pandemic, investigations have reported a high incidence of venous thromboembolic (VTE) events in hospitalized patients with coronavirus disease 2019 (COVID-19) often despite thromboprophylaxis. However, the risk of Deep venous thromboembolism(DVT) extends from the time of admission and over the first 90 days post hospital discharge in COVID-19 patients to this regard, the actual post-discharge cumulative incidence of DVT events in patients hospitalized for COVID-19 pneumonia has not been clearly determined, limiting the formulation of clinical recommendations regarding the need for optimal duration of extended thromboprophylaxis strategies.

Methods: The study is a clinical prospective observational study all the eligible patients attending medicine department outpatient/ inpatient who matched the inclusion criteria. A detailed history thorough physical examinations were performed. Data were collected from the patients who admitted in COVID 19 block. Telephone contact numbers and detailed addresses were collected for follow-up.

Results: In our study prevalence of DVT in post COVID 19 patients is 7%, majority of subjects with DVT were in the age group 61 to 70 years (42.9%), males were in majority (85.7%).There is significant association with risk factor like systemic Hypertension, Diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, obesity, severity and length of hospital stay.Lab parameters like elevated D-dimer,CRP and alkaline phosphatase have ability to predict the DVT. There is significant association with thromboprophylaxis at discharge and incidence of DVT.

Conclusion: The findings of this study suggest that covid-19 is a risk factor for deep veinthrombosis. These results could impact recommendations on diagnostic and prophylactic strategies against venous thromboembolism after covid-19.

Keywords: DVT (Deepvenousthrombosis), VTE (Venousthromboembolism), Thromboprophylaxis.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been associated with significant morbidity and mortality globally. Importantly, elevated rates of macro vessel thrombotic events venous thromboembolism (VTE), such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial thromboembolism (ATE), such as stroke and myocardial

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infarction (MI) have been described especially in sick and critically ill hospitalized patients.[1]

During the COVID-19 pandemic, investigations have reported a high incidence of Deep venous thromboembolism(DVT) events in hospitalized patients with coronavirus disease 2019 (COVID-19) often despite thromboprophylaxis.[1,2] However, the risk of hospital-associated DVT extends from the time of admission and over the first 90 days post hospital discharge in COVID-19 patients.[2–5] Critically ill COVID-19 patients who do not have any predisposing risk factors for thrombosis can also manifest various thrombotic events including microvascular thrombosis, deep vein thrombosis (DVT) (25%), pulmonary thromboembolism, and acute arterial thrombosis (31%).[6,7] The reported incidence of thrombotic complications is between 16–49% in patients with COVID-19 admitted to intensive care.[2] However, data supporting routine screening for VTE using either lower limb ultrasound or computed tomography pulmonary angiography for all patients of COVID-19 is lacking, but the clinical suspicion for VTE should always be there. It might be possible that the reported prevalence of VTE and PE is far less since the access to imaging techniques may be limited in critically ill patients. To this regard, the actual post-discharge cumulative incidence of VTE events in patients hospitalized for COVID-19 pneumonia has not been clearly determined, limiting the formulation of clinical recommendations regarding the need for and optimal duration of extended thromboprophylaxis strategies.[8]

However, during the pandemic outbreak, limited healthcare resources resulted in a lack of examination of DVT. Thus, it is important to investigate the incident and risk factors of DVT particularly in patients with COVID-19. Herein, we aimed to assess the incident and risk factors of DVT in COVID-19 patients by comparing the clinical features and lab parameters of DVT patients with non-DVT patients.

Materials and methods

The study is a clinical prospective observational study all the eligible patients attending medicine department outpatient/ inpatient.

Source of data

All patients attending post COVID clinic were enrolled for study. Their detailed clinical history, physical examination and relevant investigations required for the study were done. Patient were selected based on clinical examinations, biochemical tests were done. Patients were subjected to routine investigation work up and data was recorded. The tests included CBC, RFT, LFT, D-dimer, LDH, CRP, Venous Doppler study.

Study design

The present study was a prospective observational study.

Study period

The study was conducted for a period of 18 months.

Sampling method

Purposive sampling method was followed for sampling.

Sample size

100

The sample size required for the study was estimated based on the incidence of DVT among POST COVID 19 patients which was found to be about 2.5%-14%. (based on previous studies and hospital experience).

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Method of collection of data

- All the data was collected from the patients admitted in the department of general medicine and those patients who attended in-patients and out-patient department with detailed history and thorough physical examinations.
- It included age, sex, nationality, complaints and duration of symptoms.
- Telephone contact numbers and detailed address were collected for follow up.
- After obtaining the clinical details, examination of the patient was done.
- The tests included CBC, RFT, LFT, D-dimer, LDH, CRP, serum ferritin, Venous Doppler study (when indicated).

Statistical analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Normality of the continuous data, was tested by Kolmogorov–Smirnov test and the Shapiro–Wilk test. Independent t test was used as test of significance to identify the mean difference between two quantitative variables.

Graphical representation of data: MS Excel and MS word were used to obtain various types of graphs such as bar diagram, Pie diagram.

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

Results

Table 1: Association of Age, Gender, Disease severity and length of hospital stay with DVT

		Diagnosis of DVT				P value
		Yes		No		
		Count	%	Count	%	
Age	<50 years	0	0.0%	9	9.7%	0.845
	51 to 60 years	2	28.6%	23	24.7%	
	61 to 70 years	3	42.9%	40	43.0%	
	>70 years	2	28.6%	21	22.6%	
Sex	Female	1	14.3%	35	37.6%	0.215
	Male	6	85.7%	58	62.4%	
Disease Severity	Mild	1	14.3%	16	17.2%	0.952
	Moderate	1	14.3%	16	17.2%	
	Severity	5	71.4%	61	65.6%	
Length of Hospital stay	<15 days	1	14.3%	61	65.6%	0.007*
	>15 days	6	85.7%	32	34.4%	

Pearson Chi-Square Test

In the study majority of subjects with DVT were in the age group 61 to 70 years (42.9%), males were in majority (85.7%).

Among subjects with DVT, 14.3% had mild and moderate disease and 71.4% had severe disease. However there was no significant association of DVT with age, sex and disease severity.

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Among subjects with DVT, 14.3% had duration of hospital stay for <15 days and 85.7% had >15 days stay. Length of Hospital stay was significant factor associated with DVT.

Table 2: Association between Risk factors and DVT

		Diagnosis of DVT				P value
		Yes		No		
		Count	%	Count	%	
HTN	Yes	5	71.4%	16	17.2%	0.001*
	No	2	28.6%	77	82.8%	
DM	Yes	5	71.4%	24	25.8%	0.01*
	No	2	28.6%	69	74.2%	
Thyroid	Yes	0	0.0%	22	23.7%	0.145
	No	7	100.0%	71	76.3%	
CKD	Yes	4	57.1%	20	21.5%	0.033*
	No	3	42.9%	73	78.5%	
CAD	Yes	2	28.6%	10	10.8%	0.162
	No	5	71.4%	83	89.2%	
Atrial fibrillation	Yes	2	28.6%	0	0.0%	<0.001*
	No	5	71.4%	93	100.0%	
COPD	Yes	3	42.9%	6	6.5%	0.001*
	No	4	57.1%	87	93.5%	
ICU Admission	Yes	3	42.9%	60	64.5%	0.252
	No	4	57.1%	33	35.5%	
Previous H/o of thromboembolism	Yes	1	14.3%	5	5.4%	0.338
	No	6	85.7%	88	94.6%	
Obesity (>35kg/m2)	Yes	3	42.9%	75	80.6%	0.02*
	No	4	57.1%	18	19.4%	

Among subjects with DVT 71.4% had Hypertension (HTN) and Type 2 Diabetus mellitus(T2DM) respectively, 57.1% had Chronic kidney disease (CKD), 28.6% had Atrial fibrillation, 42.9% had Chronic obstructive pulmonary disease (COPD), 42.9% had obesity. There is significant association with HTN, T2DM, CKD, COPD, atrial fibrillation and obesity.

Table 4: Laboratory parameters with respect to DVT

	Diagnosis of DVT						P value
	Yes			No			
	Mean	SD	Median	Mean	SD	Median	
WBC 1000/mcl	13.51	1.61	14	9.87	2.13	10	<0.001*
Serum creatine (mg/dl)	2.43	0.56	2	1.45	0.62	2	<0.001*
D Dimer (ng/ml)	5377.57	1365.28	5550	1870.39	1958.29	999	<0.001*
CRP (mg/dl)	42	10.2	156	19	21	11	0.07*
LDH (mcg/l)	658.86	130.39	668	554.09	239.24	563	0.256
ESR (mm/hr)	82	20	78	62	31	64	0.93
ALP (IU/L)	110	78	90	72	24	62	0.009

Mean WBC Count in subjects with DVT was 13.51±1.61 1000/mcl and among subjects without DVT was 9.87±2.13 1000/mcl. There was significant difference in mean WBC Count between two groups.

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Mean Serum Creatinine in subjects with DVT was 2.43±0.56 mg/dl and among subjects without DVT was 1.45±0.62 mg/dl. There was significant difference in mean Creatinine between two groups.

Mean D Dimer in subjects with DVT was 5377.57±1365.28 ng/ml and among subjects without DVT was 1870.39 ± 1958.29 ng/ml. There was significant difference in mean D Dimer between two groups.

Mean CRP in subjects with DVT was 156.86 ± 51.42 mg/dland among subjects without DVT was 64.27 ± 48.28 mg/dl. There was significant difference in mean CRP between two groups.

Mean LDH in subjects with DVT was 658.86 ± 130.39 mcg/l and among subjects without DVT was 554.09 ± 239.24 mcg/l. There was significant difference in mean LDH between two groups.

Mean ESR in subjects with DVT is 82 ±20 and among subjects with out DVT62±31mm/hr.

Mean ALP in subjects with DVT is 110±78 and among subjects with out DVT is 72±24, there is significant difference in mean ALP between two groups.

Table 3: Prevalence of DVT on thromboprophylaxis

		Diagnosis of DVT				P value
		Yes		No		
Thromboprophylaxis at admission	Yes	3	42.9%	66	71.0%	**0.121**
	No	4	57.1%	27	29.0%	
Thromboprophylaxis at discharge	Yes	1	25%	48	51.6%	
	No	6	75%	45	48.4%	**0.05**

In the study among subjects with DVT, at admission 42.9% were on thrombophylaxis and among subjects without DVT, 71% were thrombophylaxis at admission.

Among subjects with DVT, at discharge 25% were on thrombophylaxis and among subjects without DVT, 51.6% were thrombophylaxis at discharge. There was significant association between DVT and thromboprophylaxis at discharge.

Table 5: Association between DVT and Mortality

		Diagnosis of DVT			
		Yes		No	
		Count	**%**	**Count**	**%**
Death	**Yes**	**2**	28.6%	7	7.5%
	No	**5**	71.4%	86	92.5%
	Total	**7**	100.0%	93	100.0%

$\chi 2 = 3.520$, df =1, p = 0.061 [Chi-square test]

In the study among subjects with DVT, 28.6% had mortality and among subjects without DVT, 7.5% had mortality. Mortality rate was high in Subjects with DVT. However statistically it was no significant.

Discussion

It is by now well recognized that COVID-19 induces a prothrombotic state resulting from interactions between the immune, inflammatory, and coagulation systems in sick, hospitalized patients that lead to a multifold increased risk of DVT.

An important observation in our study is that anticoagulants (either LMWH or a DOAC), mainly at prophylactic doses and prescribed at hospital discharge, were significantly associated with a reduction in the composite outcome in our prospective observational study conducted in 100 patients with mean follow up of 90 days.

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In our study majority of subjects with DVT were in the age group 61 to 70 years (42.9%), males were in majority (85.7%). However there was no significant association of DVT with Age and sex among subjects with DVT.

This study is comparable with study done by et al Salisbury i.e., the cohort had a mean age of 61.7 +/- 17.5 years, was predominantly male (53.7%).In present study Prevalence of DVT is 7%. However, this finding resulted from very heterogeneous rates described in individual studies, which may have been due to differences in VTE screening strategies and should carefully interpreted. Indeed, it is possible that differences in follow-up strategies and presence of an immune thrombosis may have led to "overdiagnosis" of VTE in critically ill COVID-19 patients.

The cumulative post-discharge rate of VTE in COVID-19 patients ranged between 0.2 and 14%.

This study is comparable with study done by Salisbury[1] et al 1.5%.In this study among subjects with DVT, 14.3% had mild and moderate disease and 71.4% had severe disease.

This study is comparable with study done by et al Engelene et al. [(2)] Most of the VTE events collected in this analysis were diagnosed early after hospital discharge, indicating that their onset depends on the changes during acute COVID-19 and on hospitalization-related risk factors. In present study 14.3% had duration of hospital stay for <15 days and 85.7% had >15 days stay. Length of Hospital stay was significant factor associated with DVT.

This study is comparable with study done by Engelenet al.[(2)] Incidence of DVT is increased in patients with risk factors like HTN, T2DM , atrial fibrillation, COPD, CAD, PVD and obesity. In this study subjects main risk factors included with DVT are 71.4% had HTN and DM respectively, 57.1% had CKD, 28.6% had Atrial fibrillation, 42.9% had COPD, 42.9% had obesity. There is significant association with HTN, DM, CKD, COPD, Obesity.

This study is comparable with study done by Salisburyet al.[(1)] That is main risk factor included hypertension in 38.6%, diabetes mellitus in 25.1%, body mass index more than 35 kg/m2 in 18.9%, ICU admission at index hospitalization in 11.8%, coronary artery disease in 6.9%, heart failure in 4.5%, atrial fibrillation in 6.5%.

In this study mean WBC Count in subjects with DVT was 13.51±1.61 1000/mcl and among subjects without DVT was 9.87±2.13 1000/mcl. There was significant difference in mean WBC Count between two groups.

This study is comparable with study done by Lund et al. [(4)] In this study mean Serum Creatinine in subjects with DVT was 2.43±0.56 mg/dl and among subjects without DVT was 1.45±0.62 mg/dl. There was significant difference in mean Creatinine between two groups.

This study is comparable with study done by Salisburyet al. [(1)]In this study mean D Dimer in subjects with DVT was 5377.57±1365.28 ng/ml and among subjects without DVT was 1870.39 ± 1958.29 ng/ml. There was significant difference in mean D Dimer between two groups.

This study is comparable with study done by et al Giannis et al. [(2)]This study is comparable with study done by Salisbury et al. where D-dimer greater than sixfold the ULN was predictive of our primary outcome in univariate analysis, but it lost significance in the multivariate analysis. However, the IMPROVE-DD VTE score, which incorporates elevated D-dimer, was a significant predictor of post discharge cardiovascular events and death, with an OR of 1.5 in the multivariate analysis.

In this study mean CRP in subjects with DVT was 156.86 ± 51.42 mg/dland among subjects without DVT was 64.27 ± 48.28 mg/dl. There was significant difference in mean CRP between two groups.

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This study is comparable with study done by Salisbury et al.[1] In this study Mean LDH in subjects with DVT was 658.86 ± 130.39 mcg/l and among subjects without DVT was 554.09 ± 239.24 mcg/l . There was significant difference in mean LDH between two groups. This study is comparable with study done by et al Giannis et al.[2] Mean ESR in subjects with DVT is 82 ±20 and among subjects with out DVT62±31mm/hr. This study is comparable with study done by Giannis et al.[2] Mean ALP in subjects with DVT is 110±78 and among subjects without DVT is 72±24, there is significant difference in mean ALP between two groups.

This study is comparable with study done by Salisbury et al.[1] That is In-hospital laboratory parameters included mild leucocytosis (white blood cell count, 11.0 +/- 6.7 * 103/mL), mildly increased serum creatinine (1.8 +/-2.5 mg/dL) markedly increased D-dimer (3373+/-7113.2 ng/mL)pg/mL), C-Reactive protein (138.7+/- 99.1 mg/L) and lactate dehydrogenase (469.1+/- 541.7 m/L), ESR is 82 ±20, ALP is 110±78.

In the study among subjects with DVT, 57.1% had femoral vessel involvement, 14.3% had Femoral + Popliteal vessel involvement and 28.6% had Popliteal vessel. This study is comparable with study done by Salisbury et al. [1] In the study 9% had mortality.

This study is comparable with Engelen et al.[2] An important observation in our study is that anticoagulants (either LMWH or a DOAC), mainly at prophylactic doses and prescribed at hospital discharge, were significantly associated with a reduction in the composite outcome. As thromboprophylaxis was prescribed to a proportion of patients therefore, our estimate may represent an underestimation of the background risk of post-discharge VTE in patients hospitalized with COVID-19.

In the study among subjects with DVT, at admission 42.9% were on thromboprophylaxis and among subjects without DVT, 71% were thromboprophylaxis at admission. Among subjects with DVT, at discharge 25% were on thromboprophylaxis and among subjects without DVT, 51.6% were thromboprophylaxis at discharge. There was significant association between DVT and thromboprophylaxis at discharge.

This study is comparable with study done by A.C. Spyropoulos et al.[4] that is Previous high-quality data from randomized trials revealed a 28% to 38% risk reduction for major and fatal thromboembolic events (including ATE and VTE) using extended post–hospital discharge thromboprophylaxis with a DOAC.

This study is comparable with study done by R Salisbury et al.[1] that is that anticoagulants(either LMWH or a DOAC), mainly at prophylactic doses and prescribed at hospital discharge, were significantly associated with a reduction in the composite outcome of ATE, VTE, or ACM by 46% in hospitalized patients with COVID-19.

Conclusion

Venous thromboembolism is one of the most common preventable causes of death in hospitals. Early recognition and appropriate management of deep venous thrombosis helps to save human lives and hospital resources. Although, this entity was initially described among surgical patients, recent studies have shown that the risks are similar among medical patients, but arising from interplay of factors different from those in the former.

Post discharge VTE, ATE, and ACM occurred frequently after COVID-19 hospitalization. Advanced age, cardiovascular risk factors, CKD, and ICU stay increased risk. Post discharge anticoagulation reduced risk. Most of the VTE events collected in this analysis were diagnosed early after hospital discharge, indicating that their onset depends on the changes during acute COVID-19 and on hospitalization-related risk factor.

Risk factors like length of hospital stay, HTN, T2DM, CKD, Atrial fibrillation and obesity associated with increased risk of DVT. Lab parameters like elevated D-dimer, CRP, alkaline phosphatase have ability to predict the DVT. In the study among subjects with DVT,

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at admission 42.9% were on thrombophylaxis and among subjects without DVT, 71% were thrombophylaxis at admission.

Among subjects with DVT, at discharge 25% were on thrombophylaxis and among subjects without DVT, 51.6% were thrombophylaxis at discharge. There was significant association between DVT and thromboprophylaxis at discharge. The findings of this study suggest that covid-19 is a risk factor for deep vein thrombosis. These results could impact recommendations on diagnostic and prophylactic strategies against venous thromboembolism after covid-19.

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