

Prevalence of deep vein thrombosis in symptomatic COVID-19 patients presenting to the Emergency Department: correlation with inflammatory markers and acute respiratory distress syndrome

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ABSTRACT:

- **Objective:** To study the prevalence of deep venous thrombosis (DVT) in COVID-19 patients presenting to the Emergency Department of Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India and its association with inflammatory markers (C-Reactive Protein), D-dimer and severity of ARDS (pO_2/FiO_2 ratio).
- **Patients and methods:** Symptomatic adult patients diagnosed COVID-19 positive by RT-PCR for SARS-CoV-2 who presented to the Emergency Department of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India were screened for lower extremity deep vein thrombosis using compression venous ultrasonography and Doppler scanning. C-reactive protein (quantitative), D-dimer and arterial blood gas analysis for pO_2/FiO_2 ratio were obtained for all patients. The DVT and no DVT groups were compared with respect to C-Reactive Protein levels, D-dimer levels and pO_2/FiO_2 ratios and the continuous variables were analysed using Mann-Whitney U test. p -value <0.05 was considered significant.
- **Results:** 70 adult COVID-19 patients (SARS-CoV-2 positive by RT-PCR) presenting to the Emergency Department of a tertiary care hospital in north India were enrolled from April 1, 2021 to June 30, 2021. 3 (4.3%) out of 70 patients had DVT; of these, two had severe ARDS and one had moderate ARDS. The pO_2/FiO_2 ratios in the non-DVT group (Median [Quartiles]- 118 [74, 236.5]) did not differ significantly compared to the DVT group (Median [Quartiles]- 88 [64, 98.5]) (Mann-Whitney $U=152$, $p=0.139$). The C-Reactive Protein (CRP) values (mg/L) in the non-DVT group (Median [Quartiles]- 40 [23, 66]) did not differ significantly compared to the DVT group (Median [Quartiles]- 75 [59.5, 91.5]) (Mann-Whitney $U=44$, $p=0.104$). The D-dimer values in the non-DVT group (Median [Quartiles]- 369 [243, 642]) were significantly lower compared to the DVT group (Median [Quartiles]- 820 [790, 938]) (Mann-Whitney $U=7$, $p=0.007$).
- **Conclusions:** There is small but definitive risk of DVT in symptomatic COVID-19 patients presenting to the Emergency Department. The presence of DVT in COVID-19 patients was directly associated with raised D-Dimer levels, but did not show significant association with severity of ARDS and C-Reactive Protein (CRP) levels.



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- **Keywords:** COVID-19, Deep vein thrombosis, C-reactive protein, D-Dimer, Acute respiratory distress syndrome.
- **Abbreviations:** DVT- Deep Vein Thrombosis; CRP- C-Reactive Protein; P_{O_2} - Partial pressure of oxygen in arterial blood; FiO_2 - The Fraction of Inspired Oxygen; ARDS- Acute Respiratory Distress Syndrome.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), emerged in China in late 2019 from a zoonotic source¹. The majority of COVID-19 cases either are asymptomatic or result in only mild disease. However, in a substantial proportion of infected individuals a severe respiratory illness requiring hospitalisation develops, with requirement of hospitalisation being age-dependent, ranging from 1.1% in the 20-29 years age group, up to 18.4% in those 80 years and older patients; and such infections can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support²⁻⁶. Hypercoagulability^{7,8} and endotheliopathy⁹⁻¹¹ reported in patients with COVID-19 combined with immobilization due to Acute Respiratory Distress Syndrome (ARDS) may pre-dispose critically ill COVID-19 patients to an increased risk of venous thrombosis¹²⁻¹⁴. Our aim was to study the prevalence of deep venous thrombosis (DVT) in symptomatic COVID-19 patients presenting to the Emergency Department of a tertiary care hospital and its association with inflammatory markers (C-Reactive Protein), D-dimer and severity of ARDS (pO_2/FiO_2 ratio).

PATIENTS AND METHODS

Study Type

This is a prospective, observational study conducted from April 1, 2021 to June 30, 2021 at the Emergency Department of Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh (India), a tertiary care hospital in north India. The Independent Ethics Committee of the institute approved it.

Inclusion and Exclusion Criteria

Adult patients (age ≥ 18 years) were included if they were confirmed positive for COVID-19 by real-time reverse-transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 (Severe Acute Respiratory Syndrome- Coronavirus- 2), and symptomatic requiring Emergency Department admission. Multiplex real-time reverse-transcription polymerase chain reaction (RT-PCR) test was performed for qualitative detection of SARS-CoV-2 ribonucleic acid (RNA) in nasopharyngeal swab specimens using TaqPath COVID-19 Combo Kit (Applied Biosystems, Massachusetts, MA, USA).

Patients were excluded if they had a previous history of venous thromboembolic disease, required anticoagulant therapy prior to COVID-19 for any other condition, or refused to participate in the study.

Data Collection

Demographic data and need for respiratory support were recorded. C-reactive protein (quantitative), D-dimer, Arterial blood gas analysis with calculation of pO_2/FiO_2 ratio were done for all eligible patients. ARDS was defined as severe, if pO_2/FiO_2 was <100 , moderate if $pO_2/FiO_2 > 100$ but <200 , mild if $pO_2/FiO_2 > 200$ but <300 , and no ARDS if pO_2/FiO_2 was > 300 . In addition, all eligible patients were screened for deep venous thrombosis (DVT) using lower extremity compression venous ultrasound and Doppler scanning. Bedside ultrasound examinations were performed using a portable ultrasound scanner (Samsung My SonoU6 equipped with LN5-12 linear probe). Following veins were screened for presence of DVT: bilateral common femoral, deep and superficial femoral, popliteal and posterior tibial veins. All patients were given standard treatment as per institutional guidelines. Patients were treated with supplemental oxygen or non-invasive ventilation or invasive mechanical ventilation depending on the severity of illness. Patients hospitalized with COVID-19 received pharmacologic prophylaxis for venous thromboembolism with low-molecular-weight heparin (enoxaparin), acetaminophen for fever; and patients receiving supplemental oxygen or non-invasive ventilation or invasive mechanical ventilation were treated with low-dose dexamethasone at a dose of 6 mg daily for 10 days or until discharge, whichever was earlier, and remdesivir 200 mg intravenously on day 1 followed by 100 mg daily for 5 days total.

Statistical Analysis

The statistical analyses were performed with the help of OpenEpi program (Open Source Epidemiologic Statistics for Public Health) and JASP (JASP Computer Software Version 0.16.1, JASP Team). The DVT and no DVT groups were compared with respect to C-Reactive Protein levels, D-dimer levels and pO_2/FiO_2 ratios. Medians and quartiles were calculated for continuous variables and Box plots were constructed for graphical presentation of data. Assumption of normality was tested using Shapiro-Wilk test, and as the continuous variables deviated from the assumption of normality, they were an-

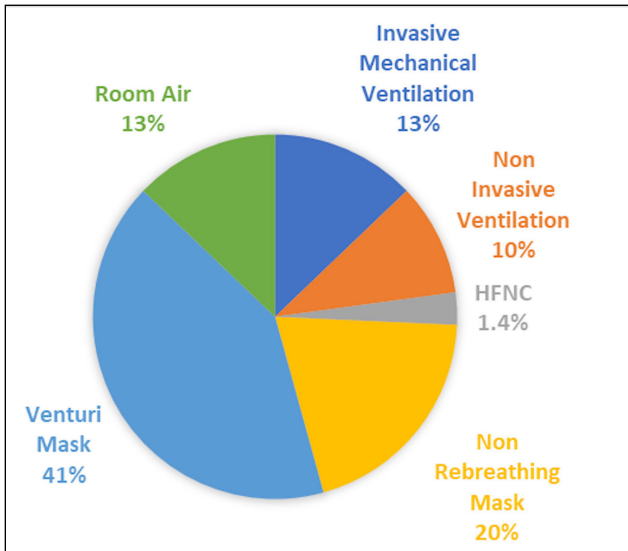


Figure 1. Requirement of respiratory support for included COVID-19 patients (percent). *HFNC- High Flow Nasal Cannula
**Total of Percentages not 100 because of rounding.

analysed using Mann-Whitney U test. *p*-value <0.05 was considered significant.

RESULTS

70 symptomatic patients who had tested positive for SARS-CoV-2 by RT-PCR were enrolled from the Emergency Department of PGIMER, Chandigarh (India) between April 1, 2021 to June 30, 2021. Of these, 39 (55.7%) were male and 31 (44.3%) female. On the basis of need for respiratory support, among these 70 patients, 9 (13%) required invasive mechanical ventilation, 7 (10%) non-invasive ventilation, 2 (1.4%) were on High Flow

Nasal Cannula, 14 (20%) needed non-rebreathing mask, 29 (41.4%) patients required Venturi mask, and 9 (13%) patients maintained oxygenation on room air (Figure 1). The distributions of patients according to age and severity of ARDS are given in Figure 2. In age group of 0 to 19, there was only 1 patient and she had moderate ARDS. In age group of 20 to 39, there were 15 patients, 12 male and 3 females and out of these 15 patients, 5 patients had severe ARDS, 3 had moderate ARDS, 4 had mild and 3 had no ARDS. The age group of 40 to 59 had a maximum number of patients (26), among them 14 were male and 12 were female, and out of these 26 patients, 13 patients had severe ARDS, 8 patients had moderate ARDS, 4 patients had mild and 1 patient had no ARDS. In age group of 60 to 79, there were total 24 patients, 11 male and 13 females, and among them 8 patients had severe ARDS, 7 patients had moderate ARDS, 6 patients had mild ARDS and 3 had no ARDS. In age group of 80 to 99, there were a total of 4 patients (2 male and 2 female) of whom 2 had severe ARDS, 1 had moderate ARDS, 1 had no ARDS.

3 (4.3%) out of 70 patients had lower extremity deep venous thrombosis (DVT) detected on compression venous ultrasound and Doppler scanning. Of these, 2 had severe ARDS and 1 had moderate ARDS (Figure 3). All 3 patients with DVT had D-Dimer levels >500 ng/mL.

The pO_2/FiO_2 ratios in the non-DVT group (Median [Quartiles]- 118 [74, 236.5]) did not differ significantly compared to the DVT group (Median [Quartiles]- 88 [64, 98.5]) (Mann-Whitney $U=152, p=0.139$). Figure 4 shows the box plot for pO_2/FiO_2 ratios in COVID-19 patients without DVT and with DVT. The C-Reactive Protein (CRP) values (mg/L) in the non-DVT group (Median [Quartiles]- 40 [23, 66]) did not differ significantly compared to the DVT group (Median [Quartiles]- 75 [59.5, 91.5]) (Mann-Whitney $U=44, p=0.104$). Figure 5 shows the box plot for C-Reactive Protein values in

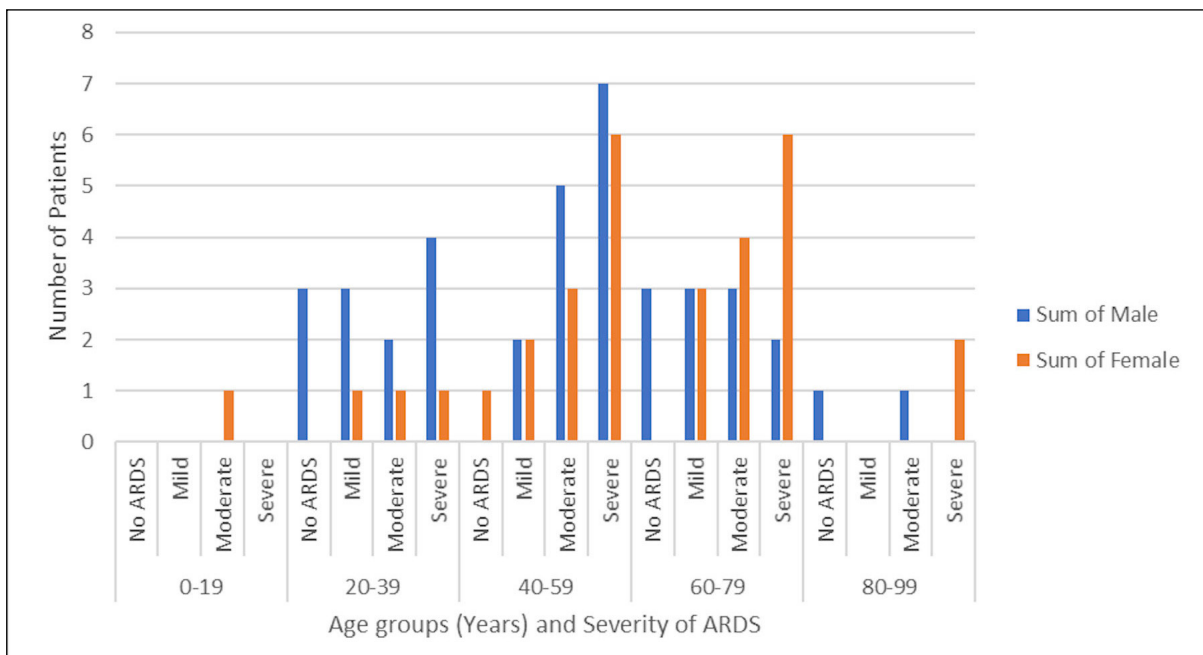


Figure 2. Severity of acute respiratory distress syndrome (ARDS) in COVID-19 patients according to age group and sex.

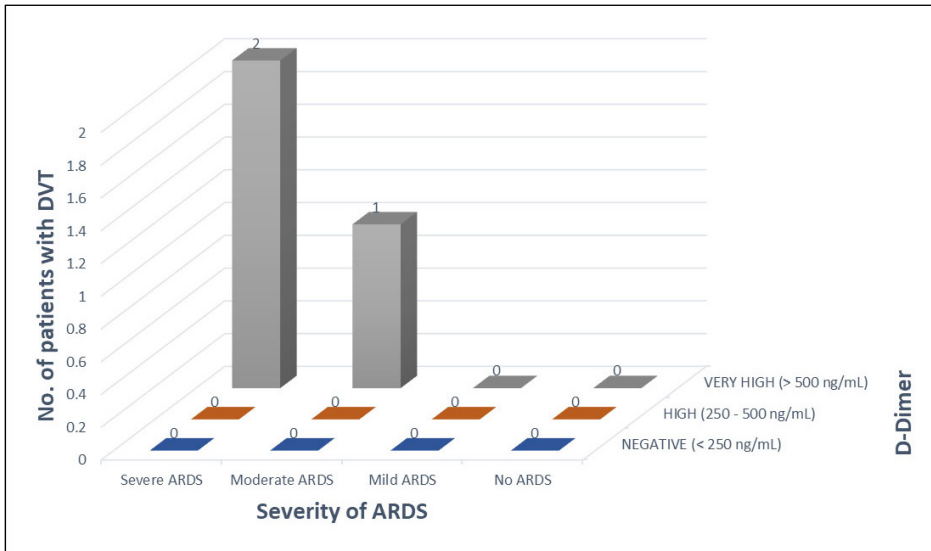


Figure 3. Correlation of Deep Venous Thrombosis (DVT) in COVID-19 patients with severity of Acute Respiratory Distress Syndrome (ARDS) and D-Dimer levels.

COVID-19 patients without DVT and with DVT. The D-dimer values in the non-DVT group (Median [Quartiles]- 369 [243, 642]) were significantly lower compared to the DVT group (Median [Quartiles]- 820 [790, 938]) (Mann-Whitney U=7, $p=0.007$). Figure 6 shows the box plot for D-dimer values in COVID-19 patients without DVT and with DVT.

DISCUSSION

The main goal of this study was to evaluate the prevalence of deep venous thrombosis (DVT) in COVID-19 patients presenting to the Emergency Department of a tertiary care hospital and to determine whether pO_2/FiO_2 ratio, C-Reactive Protein (CRP) and D-dimer are predictors of DVT in COVID-19 patients in acute care setting. We enrolled 70 patients who were diagnosed with COVID-19 in this study. Among them 62 [88.5%] had ARDS as per the pre-defined criteria. The limitations were that this was a single centre study with relatively small sample size and a single ultrasound scan

was used to screen for DVT in all patients, which may have led to underestimation of the prevalence of DVT. In a systematic review and meta-analysis of 33 studies¹⁵, including a total of 4009 patients with COVID-19 hospitalized in the medical ward and/or Intensive Care Unit, the incidence of major venous thrombo-embolism was 9%. The incidence of proximal lower limb DVT was 3% and the incidence of pulmonary embolism was 8%. The 4.3% prevalence of DVT in our study population of emergency department patients was lower in comparison to patients hospitalized in ward or Intensive Care Unit probably because hospitalized patients undergo prolonged immobilization and may require neuromuscular blockade for mechanical ventilation. While all the three COVID-19 patients with deep venous thrombosis (DVT) in our study had moderate to severe ARDS, the association of DVT with pO_2/FiO_2 ratios and C-Reactive Protein (CRP) levels was not statistically significant. This may be because of the relatively small sample size of the study. The presence of DVT in COVID-19

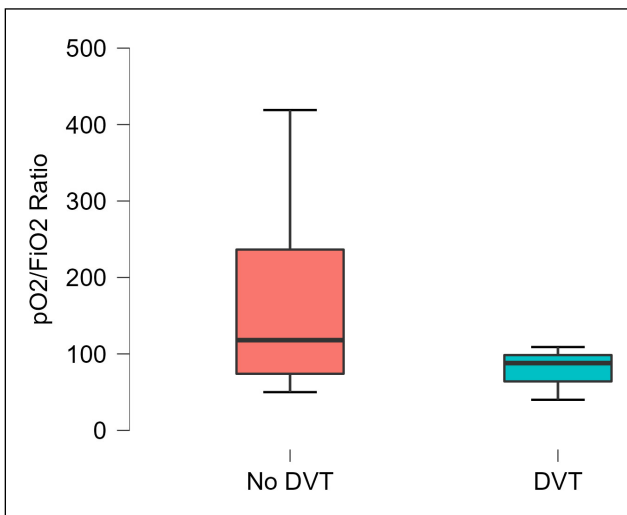


Figure 4. Box plot for pO_2/FiO_2 ratio in COVID-19 patients without deep venous thrombosis (DVT) and with DVT.

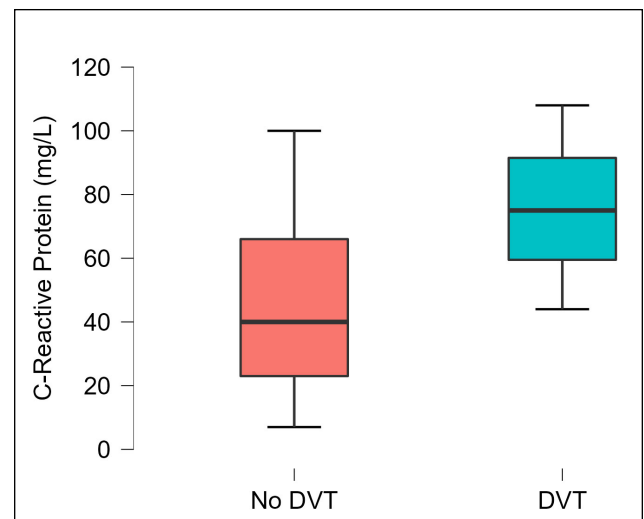


Figure 5. Box plot for C-Reactive Protein (CRP) values (mg/L) in COVID-19 patients without deep venous thrombosis (DVT) and with DVT.

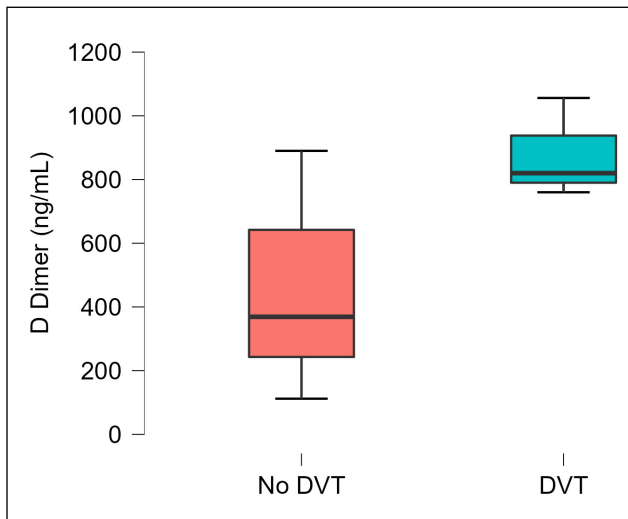


Figure 6. Box plot for D- dimer values (ng/mL) in COVID-19 Patients without deep venous thrombosis (DVT) and with DVT.

patients was directly associated with raised D-Dimer levels. These findings are similar to the meta-analysis of six retrospective observational studies by Loomba et al¹⁶, who found that COVID-19 patients with a DVT had significantly higher D-dimer levels; however, there was no significant difference in CRP levels. In a retrospective study of 81 COVID-19 patients by Cui et al¹⁷, the incidence of venous thrombo-embolism was 25% (20/81) and a D-dimer cut-off of 1000 ng/mL had sensitivity of 85% and specificity of 77% for diagnosis of venous thrombo-embolism. In another study of 143 hospitalised patients by Zhang et al¹⁸, 62.1% patients with D-dimer more than 1000 ng/mL had DVT, whereas 15.9% with D-dimer <1000 ng/mL had DVT. The aetiology of DVT in COVID-19 includes presence of hypercoagulability and endotheliopathy due to activation of the inflammatory cascade⁷⁻¹¹. D-dimer is a molecular marker that results from the dissolution of cross-linked fibrin and is often elevated in thrombotic conditions. Higher D-dimer levels may suggest hyper-inflammation and pro-thrombotic state and possibly, are associated with more extensive endothelial damage and activation of the coagulation cascade that leads to deep vein thrombosis. Elevated D-dimer levels are a sign of excessive coagulation activation and hyperfibrinolysis, and have high sensitivity for detection of venous thrombo-embolism.

CONCLUSIONS

There is small but definitive risk of deep venous thrombosis (DVT) in COVID-19 patients presenting to the Emergency Department. The presence of DVT in COVID-19 patients was directly associated with raised D-Dimer levels, but did not show significant association with severity of ARDS and C-Reactive Protein. Further studies are required to investigate protocols for DVT screening in COVID-19 patients based on optimal D-Dimer cut-offs.

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AUTHOR CONTRIBUTIONS:

MSB, SCS and RA conceived and designed the study. All authors contributed to data collection. MSB checked the completeness of data. SCS performed the statistical analysis. MSB drafted the manuscript, and all authors contributed substantially to its revision. All authors take the responsibility for the paper as a whole.

PATIENT CONSENT:

Obtained.

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ETHICS APPROVAL:

The study was approved by the Institute Ethics Committee, PGIMER, Chandigarh, India.

CONFLICT OF INTEREST:

The authors declare that they have no conflicts of interest.

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None.

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