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ORIGINAL ARTICLE **OPEN ACCESS**

Risk of pulmonary embolism and deep venous thrombosis in Covid and non-Covid ICU patients – retrospective study

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ABSTRACT
To compare the incidence of pulmonary embolism (PE) and deep vein thrombosis (DVT) in COVID-19 pneumonia and non-COVID patients admitted in the ICU.A retrospective case-control study was undertaken to compare the incidence of PE and DVT in COVID-19 pneumonia and non-COVID in the setting of ICU patients investigated with a computed tomography pulmonary angiogram (CTPA) and colour doppler ultrasonography (CDUS). Seventy-two patients were included; 36 cases (47% male; mean age 59 (±15) years), and 36 controls (56% male; mean age 58 (±20) years). PE was diagnosed in 25% of the cases versus 8.3% of the controls and DVT was diagnosed in 11% of the cases versus 5.5% of the controls. The adjusted odds ratio for PE and DVT was 3.23 (95% confidence interval [CI] in ICU patients with COVID-19 pneumonia compared with the control group.The odds of developing PE and DVT among ICU patients with COVID-19 pneumonia are thrice and twice the times higher than in those without COVID, respectively. Owing to the current pandemic situation, rather than doing CTPA and CDUS only on clinical suspicion basis, can be used as screening for all patients admitted to the ICU with COVID-19 pneumonia for the early detection of these complications and thereby reducing the morbidity and mortality.
Keywords: pulmonary embolism, deep vein thrombosis, COVID-19, pulmonary angiogram, colour doppler ultrasound, thrombus, pneumonia.

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INTRODUCTION

The novel coronavirus disease-2019 (COVID-19) illness is a global pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It belongs to family of viruses that cause illness starting from cold to more severe diseases such as MERS-CoV and severe acute respiratory syndrome (SARS)-CoV. At the onset of COVID-19, patients commonly present as respiratory tract infection with fever, cough, fatigue, and dyspnea. As the disease advances, there is deterioration into a severe systemic illness leading to multiorgan failure resulting in a hypercoagulable state and thromboembolic complications such as pulmonary embolism, deep vein thrombosis. Comorbidities and elderly age are major risk factors for the morbidity and mortality in patients with COVID-19[1]. Frequently emerging complications in critically ill patients with COVID-19 are hypercoagulable state and thromboembolism, and these complications contribute to morbidity and mortality. PE and DVT are common sequela of this hypercoagulability in patients with COVID-19. However, majority of thromboembolic events in COVID-19 is due to pulmonary embolism (PE) in particular [2], but the understanding of COVID-19 associated PE and DVT continues to evolve. Unlike other viruses, the marked affinity of the coronavirus for the angiotensin-converting enzyme 2 (ACE2) receptors is the cause for multi organ involvement [3]. Thus, tissues with high levels of ACE2 receptors such as lung alveolar epithelial cells, enterocytes of the small intestine, and vascular endothelium are susceptible to direct injury [4]. Covid19 is highly prothrombotic leading to alterations in the coagulation pathway that cause progressive elevation of D-dimer levels correlating with the extent and severity of thrombosis [5].The incidence of Venous thromboembolism was 17.46 per 10,000 admissions. Mortality in patients with confirmed pulmonary embolism was 13.5%.[6]Ng et al in a study, stated that the incidence of proximal and distal DVT was found to be 61.8% and 38.2%, respectively.[7]However, the prevalence of COVID-19 associated PE and/or DVT may be high and the incidence of PE among ICU patients have higher rates. Even among patients managed in ICU, COVID-19patients in a study on 107 patients had an absolute increased risk of Pulmonary embolism

compared with other ICU patients with similar illness. COVID-19 pneumonia when associated with PE or DVT may result in poor outcomes than either entity alone.

MATERIAL AND METHODS

A retrospective case-control study was undertaken to compare the incidence of PE and DVT in COVID-19 and non- COVID patients admitted to ICU. They were investigated with computed tomography pulmonary angiogram (CTPA) and colour doppler ultrasound. The primary outcome was to detect the risk of developing PE and DVT in both groups. This study was carried out in our department of Radiology. Ethical approval for this study was obtained from our institutional Research and Development Committee. Owing to the observational nature of our study, the need for informed consent was waived.

This study included hospitalized ICU patients with and without COVID-19 pneumonia and investigated for suspected pulmonary embolism and deep vein thrombosis with computed tomography pulmonary angiogram (CTPA) and colour doppler ultrasonography (CDUS) respectively. Cases were identified by doing a keyword search on Picture archiving and communication system (PACS) for CTPA and CDUS performed between 1 January 2021 to 30th June 2021, with reports having the keywords such as embolism", "occlusion", "COVID-19", "ground glass", "thrombus", "pulmonary emboli", "opacities". Cases were defined as patients admitted to the ICU with COVID-19 pneumonia confirmed by RT-PCR within the period of 1 January 2021 to 30th June 2021. The cases included are adults of ≥ 18years of age, confirmed diagnosis of COVID-19 pneumonia by RT-PCR, Hospitalized patients admitted to ICU, patients who underwent CTPA and Colour doppler USG between January 2021 to June 2021. All the patients who satisfy the eligibility criteria was included, which resulted in total of 36 eligible cases.

Controls were identified by performing exact same keyword search, except for "COVID-19". The first 36 patients were included.Controls were patients admitted to the ICU for severe systemic illnesses, who tested negative for COVID-19 pneumonia within a period of January 2021 to June 2021. This resulted in a total of 36 patients under each group, who met the eligibility criteria (Flow chart 1).

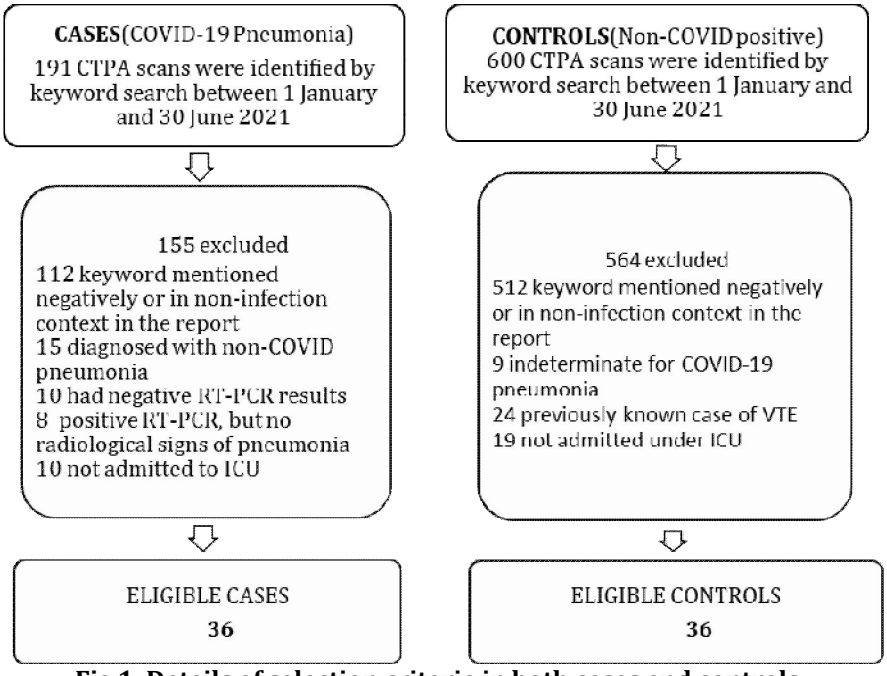

Fig 1. Details of selection criteria in both cases and controls

The primary aim was to determine the risk of developing pulmonary embolism and deep vein thrombosis in both groups. For both cases and controls, patients were selected within a same time frame, so as to minimize the differences in diagnostic criteria, healthcare teams, management protocol and imaging techniques.

Further variables collected were patient details (age and sex), co-morbidities (such as diabetes mellitus, respiratory diseases, cardiovascular diseases, chronic kidney disease), prior venous thromboembolism, other predisposing factors (post-op/immobility, obesity, smoking), duration of hospitalization and patient outcome(death/discharged). CTPA was done using 16 SLICE MULTIDETECTOR CT (GE Revolution ACTs) with the patient in supine position. Images were reconstructed with section thickness of 1, 2 and 5 mm in the axial plane. Images were then reviewed for quality for confirmation of pneumonia findings and

for the presence or absence of pulmonary embolism. In cases with positive finding of PE, according to the site of filling defect, location of the clot was noted as subsegmental, segmental, lobar and central.
Both groups (cases and control) were then screened for deep vein thrombosis using bilateral lower limb venous doppler, performed with GE LOGIQ F8 Expert machine with the patient in supine and prone positions. Statistical analysis was performed using the SPSS (Statistical Package for the Social Sciences) version 26. When the data were normally distributed, continuous variables were presented as mean and Student's t-test was used for these variables. If the data were not normally distributed, it was expressed as median and Mann-Whitney test was used for these variables. Whereas categorical variables are expressed as numbers/percentages and chi-square test was applied for these categorical variables. The p value of <0.05 is considered as statistically significant. Multivariable logistic regression was used to calculate the adjusted odds ratio for PE.

RESULT

For the COVID positive ICU patient group, the keyword search identified a total of 191 patients during our study period. For the control group, the keyword search resulted 600 patients within the same time frame. Of these patients, 155 (%81) from cases and 564 (%94) from controls were excluded from the study, as they did not come under our study's eligible criteria.
The baseline characteristics of both cases and controls are mentioned in Table 1.

Variables	COVID-19 pneumonia group n = 36	CONTROL group n = 36	p- value
AGE	59(±15)	58(±20)	0.62
SEX, MALE	17(47%)	20(56%)	0.40
DIABETES MELLITUS	11(30%)	8(22%)	0.45
RESPIRATORY DISEASES[A]	9(25%)	15(41%)	0.07
CARDIOVASCULAR DISEASES[B]	17(47%)	10(14%)	0.04
CHRONIC KIDNEY DISEASE	5(14%)	5(14%)	NS
PREVIOUS VTE	2(5.6%)	3(8.3%)	0.74
PREVIOUS MALIGNANCY	2(5.6%)	3(8.3%)	0.74
ACTIVE MALIGNANCY	0(0%)	1(2.8%)	0.50
OBESITY	17(47%)	10(28%)	0.04
IMMOBILITY	2(5.6%)	1(4.0%)	NS
DURATION OF HOSPITALIZATION PRIOR TO CTPA(DAYS)	2.5(±7)	0.9(±3.5)	0.001

Table 1 Baseline characteristics of Cases and Controls
Data were entered as n (%) or mean (±SD). NS: non-significant
VTE - venous thromboembolism; CTPA - computed tomography pulmonary angiogram.
Arespiratory diseases included: asthma, chronic obstructive pulmonary disease (COPD) and interstitial lung disease.
B cardiovascular diseases included: hypertension, ischaemic heart disease, congestive heart failure and atrial fibrillation.

In our study, there was no significant difference in age and sex between the cases and controls (p= 0.62 and 0.40, respectively). Except for patients with cardiovascular diseases, which were more prevalent with COVID-19 pneumonia (p = 0.001); no significant difference was noted in most of the co-morbidities between the two groups.Both the groups have received VTE prophylaxis appropriately, who were later diagnosed to have pulmonary embolism.
Pulmonary embolism was confirmed in 9/36 (25%) of the cases and 3/36(8.3%) of the controls (p=0.005).DVT was confirmed in 4/36 (11%) of the cases and 2/36 (5.5%) of the controls. The crude odds ratio in the hospitalized patients with COVID-19 pneumoniacompared with those with Control group was 4.14 (95% CI).(Fig 1 - 5)

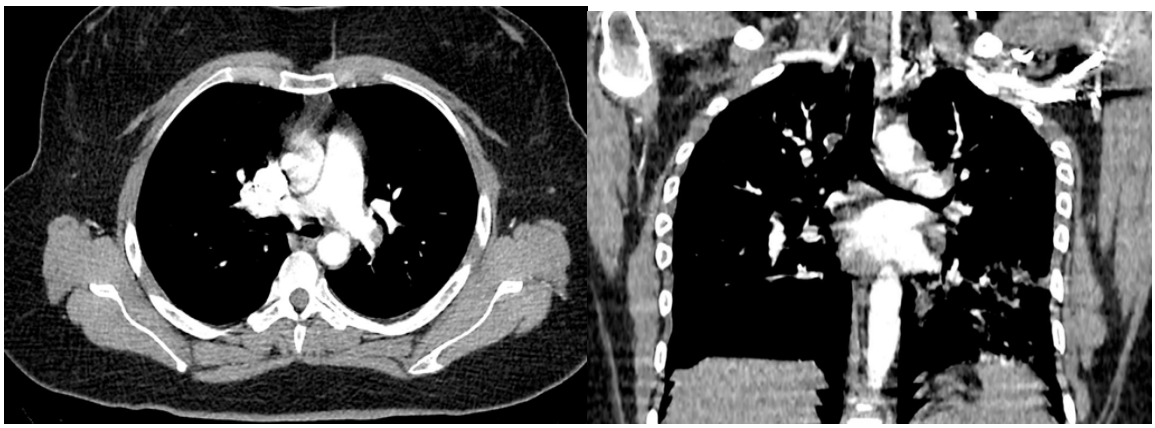

Fig 2(A & B) A case of 35yr old female with moderate COVID-19 pneumonia, admitted to the ICU. Image showing CT-PA axial and coronal sections depicting a thrombus (red arrow) at the left main pulmonary artery - lobar type.

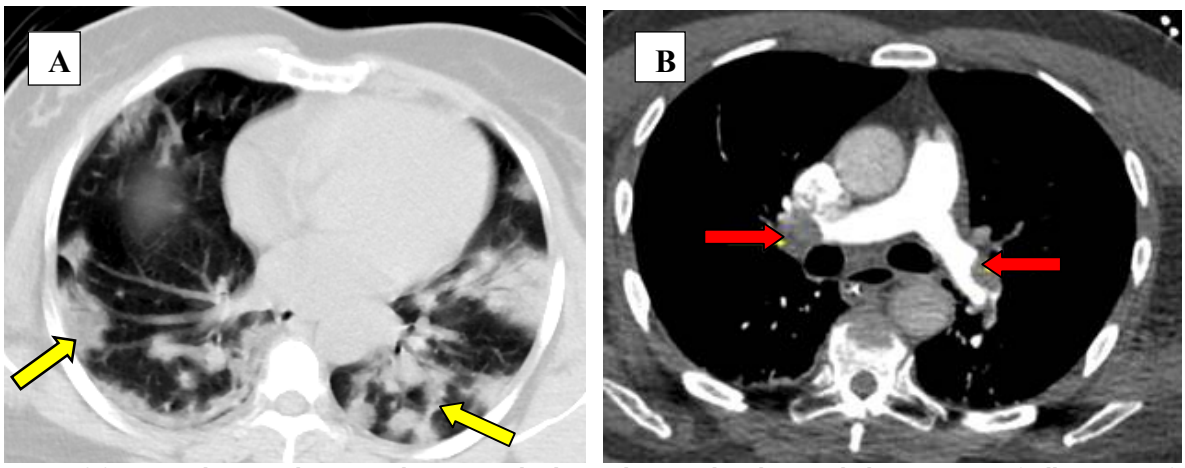

Fig – 3(A) HRCT-Chest axial section showing multiple patchy peripheral ground glass opacities (yellow arrows) in bilateral lung fields **(B)** CTPA of the chest in the axial projection at the level of the main pulmonary artery bifurcation shows large filling defects of the right and left pulmonary arteries (red arrows)

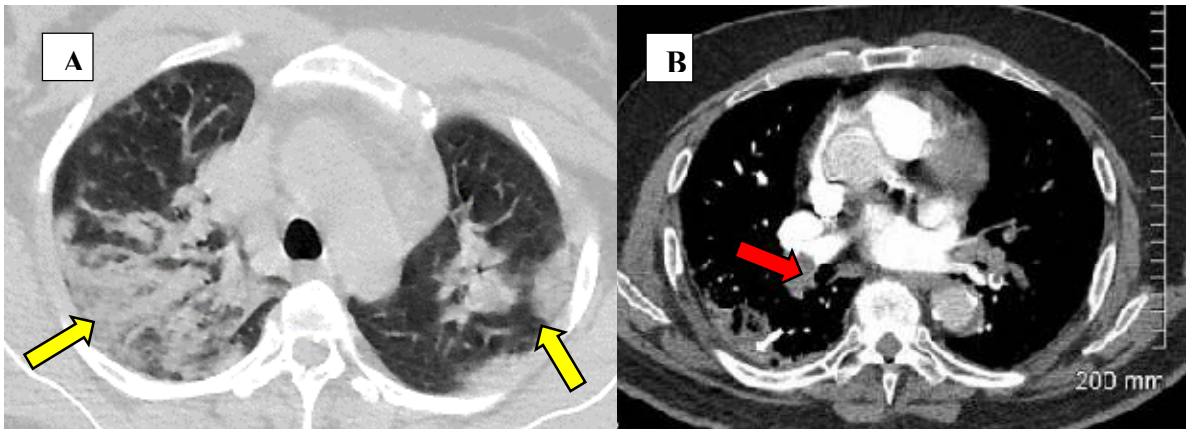

Fig – 4 (A) Shows HRCT-Chest of a 48-year-old male with confluent areas of ground glass opacity (yellow arrows) in bilateral upper lobes (admitted in the ICU with severe COVID-19 pneumonia) **(B)** Shows CTPA in the axial plane with a large filling defect in the right pulmonary artery (red arrow) with resultant opacification (white arrow) representing wedge shaped pulmonary infarct of the right lower lobe.

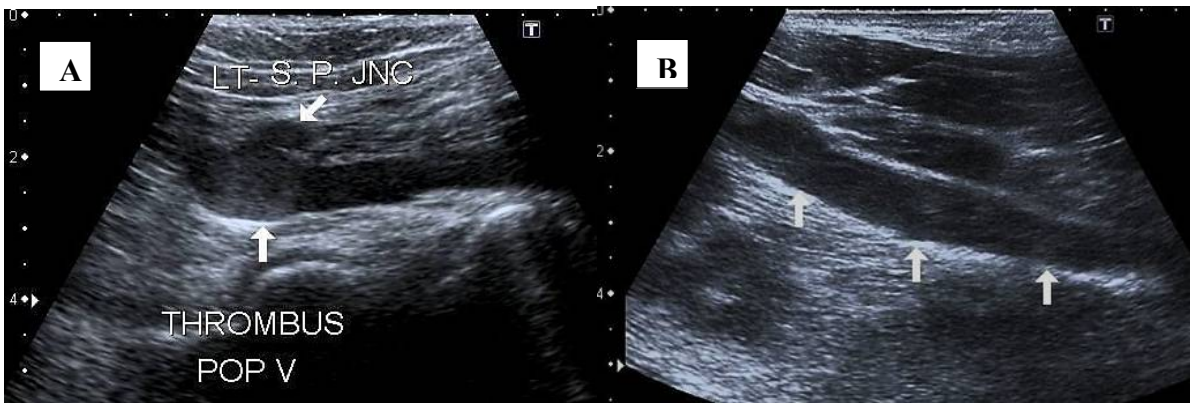

Fig – 5(A & B) A case of 52-year-old male with severe COVID-19 pneumonia with acute onset of lower limb pain. Leftlower limb doppler **(A)** axial image showing thrombus in the popliteal vein (white arrow) at the level of sapheno-popliteal junction **(B)** longitudinal section of the same thrombus filled left popliteal vein (white arrow).

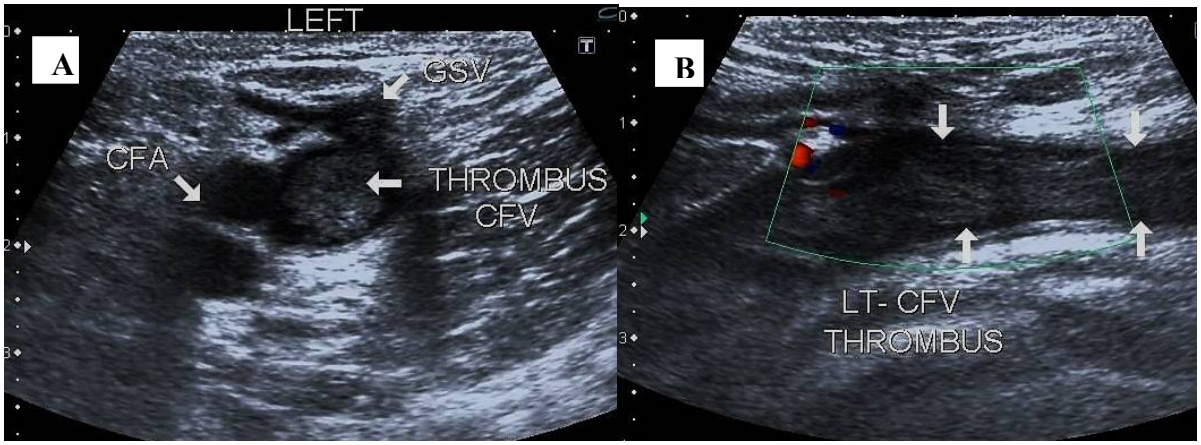

Fig – 6(A & B) A 58-year male (chronic smoker), post-operative case of left intertrochanteric fracture admitted to the ICU. Leftlower limb doppler **(A)** axial image showing thrombus in the common femoral vein (white arrow) at the level of sapheno-femoral junction **(B)**longitudinal section of the same thrombus filled common femoral vein (white arrow) with absence of flow.

After adjustment for potential confounding factors, the odds ratio among hospitalized patients with COVID-19 pneumonia was 3.23 (95% CI).The was no significant contribution to the logistic regression model by other confounding variables, which depicts that COVID-19 pneumonia was an independent risk factor for causing PE.By the end of the data collection period on 30 June 2021, all the patients in the study had been discharged from hospital either alive or died. The mortality rate was higher in the COVID-19 pneumonia group (19%) compared to the Control group (11%); however, this did not reach statistical significance (p=0.17). Those patients with confirmed PE showed no significant difference in the mortality rate between the case and control groups (p=0.87). Furthermore, there was no significant difference in the mortality rates amongst patients with COVID-19 pneumonia whether they had PE or not (p=0.63) Table 2. When there was a confirmed diagnosis of PE, both groups showed the proximal filling defect commonly in the lobar vessels, followed by the segmental vessels. Only 22% of the positive scans in patients with COVID-19 pneumonia showed PE in the central vessels, whilst none of the patients among control group developed central PE; this difference was statistically insignificant (p=0.41) Table 2.

Table 2 Clinical outcome among cases and control group

	COVID-19 pneumonia group n = 36	CONTROL group n = 36	p- value
DEATH			
TOTAL	7/36(19%)	4/36(11%)	0.17
PE POSITIVE GROUP	2/9(22%)	0/3(0%)	0.40
PE NEGATIVE GROUP	5/27(18%)	4/36(11%)	0.24
LOCATION OF PE IN CONFIRMED CASES			
CENTRAL	2/9(22%)	0/3(0%)	0.41
LOBAR	4/9(44%)	2/3(66%)	0.61
SEGMENTAL	3/9(33%)	1/3(33%)	NS
SUBSEGMENTAL	0/9(0%)	0/3	NS
PRESENCE OF DVT	4/36(11%)	2/36(5.5%)	0.8

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Data were entered in n (%); NS - non-significant.
PE – Pulmonary embolism.

DISCUSSION

Even before the COVID-19 pandemic, pneumonia is one among the known risk factors for causing PE [8]. Pulmonary embolism (PE) is a major health issue, but has the greatest preventable cause of hospital mortality and is one of the most commonly missed diagnosis in clinical practice.Recent studies [9,10] had reported the high incidence of PE in patients with COVID-19 infection. However, owing to the present pandemic situation with heavy case load, comparison with a control group without COVID-19 pneumonia would provide more confirmation regarding whether the obtained high incidence is true.

In a meta-analysis recently performed by Jimenez *et al* [17] involving 49 studies had reported a VTE incidence of 17% in COVID-19 patients. (12.1% DVT and 7.1% PE).

A meta-analysis performed by Suh YJ et al [20] reported that the pooled incidence rates of PE and DVT in patients with COVID-19 pneumonia were 16.5% and 14.8%, respectively. This meta-analysis demonstrated that greater disease severity and universal screening with CTPA were significantly associated with increased incidence of PE. More than half of the patients diagnosed with PE lacked DVT. Furthermore, 42.4% of patients with PE had DVT, and PE was more frequently located in the peripheral portion of the pulmonary arteries than in the central portion (60.4% vs 39.0%). In our study, frequent location of PE was in the lobar vessels with 44% among cases and 66% among controls (p=0.61).

The present study supports other published data [18,19] that patients with COVID-19 pneumonia who develop PE are more likely to require critical care management. Therefore, these patients may require close monitoring. Further study conducted among 184 ICU patients in France and Italy, by Klok FA et al [14] showed similar observations with the incidence of 31% of venous thromboembolism; among that Pulmonary embolism was reported as the common complication (81%). This study substantiates that COVID-19 patients admitted to ICU are at higher risk of developing thrombotic complications.

Cui S Et al [13]conducted a study of 184 ICU patients, where LMWH (low molecular weight heparin) was given as thromboprophylaxis, 68 (37%) patients had VTE, with a cumulative incidence (CI) of 49%.In a study conducted by Helms J et al, in COVID-19 ICU patients, where thromboprophylaxis was given as a standard of care, reported venous thromboembolism in 35/75 (47%), with a CI of 59% [15,16]. Initiation of a screening approach, partially explains the high incidence among ICU patients.

At our hospital, all inpatients undergo a risk assessment for VTE on admission and again 24 h later. In the present study, all the PE events occurred despite the appropriate standard care of VTE prophylaxis. This supports that COVID-19 pneumonia may be an independent risk factor for PE [11,12]. It shows that standard doses of thromboprophylaxis may not be effective, and higher dose regimens may be efficacious.

An interesting finding in the present data is that there was no difference in the mortality rates between the COVID-19 pneumonia and Control groups, in patients with confirmed VTE. Especially, whether the patients had VTE or not, there was no difference in the mortality rates amongst patients with COVID-19 pneumonia. In our study, COVID-19 patients who underwent CTPA were only assessed, it suggests that PE in COVID-19 pneumonia may not adversely impact upon mortality rate, as long as it is managed promptly. Even though the number of patients in the present study is too small to confirm this finding, there is no effective treatment for COVID-19 pneumonia to date. Whereas the treatment for PE, is effective and so the diagnosis should not be missed.

Our study showed that the odds of developing PE and DVT in the ICU patients with COVID-19 pneumonia are thrice and twice higher than in hospitalized patients without COVID-19, respectively. The study results may help the healthcare teams to weigh the risk of PE and DVT in patients with COVID-19

pneumonia. Among all the predisposing factors for VTE, in our study cardiovascular diseases and obesity, were more prevalent in the COVID-19 pneumonia group. Despite that, COVID-19 pneumonia remained an independent risk factor causing PE and DVT in those hospitalized patients.

The present study has limitations and strengths. Regarding limitations, the study was retrospective. Imaging was performed only in those patients with clinical signs and symptoms suggestive of PE; therefore, it is possible that the risk of PE/DVT has been underestimated and patients with subclinical features of PE may not have been imaged further. The results of this study may not be generalisable to the community setting as the incidence of PE was studied only among hospitalised patients admitted under ICU with COVID-19 pneumonia. The study has many strengths as the diagnoses of COVID-19 pneumonia, DVT and PE were confirmed objectively. To conclude, the risk of PE and DVT in the hospitalized (ICU) patients with COVID19 pneumonia is more in those without COVID-19 pneumonia. This shows the impact of morbidity and mortality of this widespread illness on the hospitalized patients.

CONCLUSION

The odds of developing PE and DVT in ICU patients with COVID-19 pneumonia are thrice and twice the times higher than in those patients without COVID, respectively. The study results provide quantitative assessment about the risk of PE and DVT in COVID-19 pneumonia in ICU patients, when compared to other patients in ICU with various morbidities.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Yang X, Yu Y, Xu J et al. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med 2020;8(5):475–481 [Published correction appears in Lancet Respir Med;8(4):e26.].*
2. Klok FA, Kruip MJHA, van der Meer NJM et al. (2020). Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res *;191:145–147.*
3. Hamming I, Timens W, Bulthuis M et al (2004). Tissue distribution ofACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. *J Pathol 203:631–637 Cross Ref Medline*
4. Zou X, Chen K, Zou J, Han P, et al(2020).. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med. ;http://dx.doi. org/https://doi.org/10.1007/s11684-020-0754-0.*
5. Chen J, Wang X, Zhang S, et al. (2020). Findings of acute pulmonaryembolism in COVID-19 patients. 2020. *Available at SSRN: https://ssrn.com/abstract=354 8771 or https://doi.org/102139/ssrn3548771 .*
6. Jimenez D, Garcia-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, Le Mao R, Rodriguez C, Hunt BJ and Monreal M. I, (2020). Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: *A Systematic Review and Meta-analysis. Chest. 12-23.*
7. A.D. Lee, E. Stephen, S. Agarwal, P. Premkumar, (2009). Venous Thrombo-embolism in India, *European Journal of Vascular and Endovascular Surgery,Volume 37, Issue 4, 482-485, , https://doi.org/10.1016/j.ejvs.2008.11.031.*
8. Ribeiro DD, LijferingWM, Van Hylckama Vlieg A, et al. (2012). Pneumonia and risk of venous thrombosis: results from the MEGA study. *J Thromb Haemost ;10(6):1179e82.*
9. Klok FA, Kruip MJHA, van der Meer NJM, et al. (2020). Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res ;191:145e7.*
10. Middeldorp S, Coppens M, van Haaps TF, et al. (2020). Incidence of venous thromboembolism in hospitalised patients with COVID-19. *J Thromb Haemost ;18(8):1995e2002.*
11. Thomas W, Varley J, Johnston A, et al. (2020). Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom. *Thromb Res;191:76e7.*
12. Poyiadji N, Cormier P, Patel PY, et al. Acute pulmonary embolism and COVID-19. *Radiology 2020;297(3):E335e8.*
13. Cui S, Chen S, Li X, Liu S, Wang F. (2020). Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost. ;18(6):1–4.*
14. Klok FA, Kruip MJHA, van der Meer NJM, et al. (2020). Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res. :113391.
15. Helms J. (2020). High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 11; 9-23
16. Lodigiani C, Iapichino G, Carenzo L, et al. (2020). Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan. *Italy. Thromb Res*. 191:9-14.
17. Jiménez D, García-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, Le Mao R, Rodríguez C, Hunt BJ, Monreal M. (2021). Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. *Chest. 159(3):1182-1196. doi: 10.1016/j.chest.2020.11.005. Epub . PMID: 33217420; PMCID: PMC7670889.*

18. Poyiadji N, Cormier P, Patel PY, et al. (2020). Acute pulmonary embolism and COVID-19. Radiology 297(3):E335e8.
19. Grillet F, Behr J, Calame P, et al. (2020). Acute pulmonary embolism associated with COVID-19 pneumonia detected by pulmonary CT angiography. *Radiology;296(3):E186e8.*
20. Suh YJ, Hong H, Ohana M, Bompard F, Revel MP, Valle C, Gervaise A, Poissy J, Susen S, Hékimian G, Artifoni M, Periard D, Contou D, Delaloye J, Sanchez B, Fang C, Garzillo G, Robbie H, Yoon SH. (2021). Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. *Radiology. 298(2):E70-E80. doi: 10.1148/radiol.2020203557. Epub. PMID: 33320063; PMCID: PMC7745997.*

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