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A high incidence of thrombosis in individuals with severe SARS-CoV-2 infection - A multicentre based prospective Cohort Study.

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Abstract: In COVID19 patients, there is little evidence of increased thrombotic risk. The goal of this study was to determine the risk of thrombosis in patients with severe SARSCoV2 infection.

Methodology: Between March 3rd and March 31st, 2021, all patients referred to four intensive care units (ICUs) from two centres of an Indian tertiary hospital for acute respiratory distress syndrome (ARDS) owing to COVID19 were included. Medical history, symptoms, biochemical data, and imaging data were all gathered prospectively. To compare the occurrence of thromboembolic events in non-COVID19 ARDS versus COVID19 ARDS patients, propensity score matching was used. The study included 150 COVID19 participants (122 men, median age 63 [53; 71] years, SAPSII 49 [37; 64] points).

Results: In 150 individuals, 64 clinically relevant thrombotic events were identified, the majority of which were pulmonary embolisms (16.7 percent). Circuit clotting occurred in 28 of 29 patients (96.6 percent) on continuous renal replacement treatment. In 12 patients (8 percent) who were on ECMO, three thrombotic occlusions of the centrifugal pump occurred (in two patients). D-dimer and fibrinogen levels were high in the vast majority of patients (> 95 percent). Disseminated intravascular coagulation did not develop in any of the patients. The activity of von Willebrand factor (vWF), vWF antigen, and FVIII were all significantly elevated, and 50 of the 57 individuals examined (87.7%) had a positive lupus anticoagulant. When compared to non-COVID19 ARDS patients (n = 145), COVID19 was found to be effective.

Conclusion: Despite anticoagulation, a significant number of patients with COVID19-related ARDS had life-threatening thrombotic events. Anticoagulation targets that are higher than those used in critically sick patients should most likely be recommended.

Keywords: COVID19, ARDS, Thrombosis, Lupus anticoagulant, Coagulopathy

Introduction

Patients admitted to intensive care units (ICUs) with severe acute respiratory syndrome (ARDS) caused by SARS-CoV-2 infection, commonly known as coronavirus disease 2019 (COVID19), mostly develop respiratory and digestive symptoms [1, 2]. Some patients, however, may develop coagulopathy, which is linked to a poor prognosis [3]. Tang et al. found that 71.4 percent of non-survivors and only 0.6 percent of survivors met the criteria for disseminated intravascular coagulation (DIC) in a retrospective study of 183 patients. Chen et al. [4] found aberrant "coagulation function" in 99 Chinese patients, including increased D-dimers in 36 (36%) patients, decreased prothrombin time (PT) in 30 (30%) patients, and increased activated partial thromboplastin time (aPTT) in 16 patients (16 percent).Wang et al. [5] found that prothrombin time and D-dimer level on admission were substantially greater in ICU patients than in non-ICU patients in a study of 13 patients admitted to ICU. Patients with severe COVID-19 may benefit from prophylactic anticoagulation, same as they do with sepsis [6].

The International Society of Thrombosis and Haemostasis (ISTH) has recently issued recommendations on coagulopathy management based on the monitoring of conventional coagulation markers (D - dimers, prothrombin time, fibrinogen, and platelet count) [7]. Tang et al. [8] suggested that heparin would reduce mortality in severe COVID-19 patients who met the SIC criteria or had considerably increased D-dimers in a retrospective analysis stratifying patients based on sepsis-induced coagulopathy (SIC) score or D-dimer level.

Despite mounting evidence of coagulation disorders, no data on the most severe patients, those admitted to ICU, is available based on this retrospective data from a small number of patients. Furthermore, none of the available publications discuss the clinical or radiological concerns associated with these coagulation disorders. [3-5]

The clinical significance of these findings is currently debatable.

We aimed to describe COVID-19-induced thrombotic complications and compare them to non-COVID-19 ARDS patients based on a comprehensive clinical examination, backed by biological and radiological data of a homogeneous prospective cohort of critically ill patients with ARDS due to SARSCoV2 infection, admitted to four intensive care units (ICUs) in two centres of a Indian tertiary hospital.

Patients and procedures

Patients

All patients referred for ARDS [9] owing to SARSCoV2 were prospectively admitted to four intensive care units (ICUs) in two sites of Moolchand hospital, Delhi, between March 3rd and March 31st, 2020. There was no criterion for exclusion. Patients were treated according to existing standards [6], but no special therapeutic intervention was used. All demographic parameters, medical history, clinical symptoms, biochemical, and imaging data are included in this study. The data was evaluated on April 7th, implying that the most current patients had at least 7 days of follow-up. Between 2014

and 2019, a prospective cohort of "non-COVID-19 ARDS" patients (NCT #02391792) was studied.

Population before matching (n=383)				Population after matching(n=222)		
	Non-COVID-19ARDS(n=233)	COVID-19ARDS (n=150)	p-value	Non-COVID 19ARDS(n=145)	COVID-19ARDS(n=77)	p-value
Age—median, IQR	74[63;81]	63[53;71]	<0.001	72[61;80]	68[61;75]	0.593
Male—n (%)	164(70.4)	122(81.3)	0.02	112(77.2)	63(81.8)	0.426
Medical history—n (%)						
Malignancies/hemopathies	31(13.4)	9(6.0)	0.02	14(9.7)	6(7.8)	0.678
Cardiovascular disease	143(61.4)	72(48)	0.01	85(58.6)	42(55.6)	0.753
Thrombo-embolic event	13(5.6)	8(5.3)	0.92	9(6.2)	7(9.1)	0.42
Cerebrovascular diseases	23(10)	7(4.7)	0.06	8(5.5)	5(6.5)	0.788
Immune diseases	13(5.6)	4(2.7)	0.17	7(4.8)	4(5.2)	0.951
Diabetes	51(21.9)	30(20)	0.66	29(20)	17(22.1)	0.589
Chronic liver disease	21(9)	4(2.7)	0.01	7(4.8)	3(3.9)	0.816
Chronic renal disease	38(16.3)	6(4.0)	<0.001	14(9.7)	5(6.5)	0.438
Respiratory disease	49(21.2)	21(14)	0.07	36(24.8)	11(14.3)	0.207
Baseline SAPSII—median, IQR	61[49;76]	49[37;64]	<0.001	54[45;69]	53[46;67]	0.560
Baseline SOFA—median, IQR	11[9,13]	8 [5,10]	<0.001	10[8,13]	9 [7,12]	0.204
PaO2/FiO2on ICU admission (mmHg)—median, IQR	142[93;195]	125[97;170]	<0.02	118[89;174]	135[99;181]	0.520
Invasive mechanical ventilation—n (%)	233(100)	150(100)	1	145(100)	77 (100)	1
Baseline heparin treatment—n (%)						
Prophylactic dosing	188(80.7)	105 (70)	0.27	110(75.9)	60(77.9)	0.768
Therapeutic dosing	45(19.3)	45(30)	0.02	35(24.1)	17(22.1)	0.697
ECMO—n (%)	10(4.3)	12(8.1)	0.124	7(4.8)	4(5.2)	0.952
ECMO duration(days)—median, IQR	8[5.3;10.8]	7[4.3;11]	0.642	10[7.0;11.5]	6.5[4.5;9]	0.527

Table 1: Characteristics of COVID-19 ARDS and non-COVID-19 ARDS

Outcomes

The primary outcome was to compare the occurrence of any thrombotic event (deep vein thrombosis, pulmonary embolism, myocardial infarction, mesenteric ischemia, lower limb ischemia, and cerebral ischemic attack) in patients with COVID-19 ARDS with those without COVID-19 ARDS. The secondary outcomes were to compare the occurrence of each of the a forementioned

thrombotic problems, RRT filter coagulation, the median longevity of each RRT circuit, ECMO oxygenator coagulation, hemorrhagic complications, and coagulation test findings.

Analyses in the lab

Platelet count and coagulation tests, including PT, antithrombin activity (AT), fibrinogen, D-dimers, and aPTT, were conducted daily during the ICU stay in order to calculate DIC scores. The researchers tested factor V (FV), von Willebrand factor (vWF) antigen, vWF activity, and factor VIII (FVIII) activity. When a coagulation issue was suspected, based on a prolonged aPTT at ICU admission or the occurrence of a thrombotic event during ICU stay, a lupus anticoagulant was searched. For more information, please see the supplementary material.

DIC scoring methods

Daily till day 7, the JAAM-DIC 2016 score [10], ISTH overt-DIC score [11], and SIC score [8] were calculated. If the ISTH overt-DIC score was 5 points or more, the JAAM-DIC score was also considered positive. If the ISTH overt-DIC score was 5 points or more, the JAAM-DIC score was 4 points or more, and the SIC score was 4 points or more, the results were judged positive.

Patients with suspected pulmonary embolism had a CT pulmonary angiography (CTPA) performed based on their clinical (worse PaO2/FiO2 despite inhaled nitric oxide or after prone positioning or hemodynamic impairment requiring fluid challenge and/or increased norepinephrine infusion rate, dilated right ventricle—even without acute cor pulmonale) or laboratory parameters evolution (a rapid elevation of D-dimer despite anti After injecting 50–75 mL of high concentration iodine contrast media, all CTPA were recorded on 64+ row scanners using a bolus-tracking approach and a threshold of 160 HU. If the ISTH overt-DIC score was 5 points or more, the JAAM-DIC score was 4 points or more, and the SIC score was 4 points or more, the results were judged positive.

Patients with suspected pulmonary embolism had a CT pulmonary angiography (CTPA) performed based on their clinical (worse PaO2/FiO2 despite inhaled nitric oxide or after prone positioning or hemodynamic impairment requiring fluid challenge and/or increased norepinephrine infusion rate, dilated right ventricle—even without acute cor pulmonale) or laboratory parameters evolution (a rapid elevation of D-dimer despite anti After injecting 50–75 mL of high concentration iodine contrast media, all CTPA were recorded on 64+ row scanners using a bolus-tracking approach and a threshold. Patients who had a non-contrast brain CT and/or a brain MRI with diffusion weighted imaging and 3D FLAIR acquisitions had a non-contrast brain CT and/or a brain MRI with diffusion weighted imaging and 3D FLAIR acquisitions. Consultant radiologists who specialise in emergency radiology read all CT and MR scans.

Statistic

Continuous variables were compared using non-parametric Wilcoxon tests and provided as median with first and third quartiles. Numbers and proportions were used to compare categorical variables, which were compared using Pearson's 2 tests or Fisher's exact tests. A propensity score analysis was done to compare the outcomes in this observational study. Propensity scores were calculated using a multivariable logistic regression model with the group (non-COVID-19 ARDS or COVID-19 ARDS) as the dependent variable and baseline characteristics that were unbalanced between groups or had clinical relevance as the independent

variables (age, sex, medical history of malignancies, cardiovascular diseases, cerebrovascular diseases, venous thrombo-embolic event, immune diseases, chronic liver diseases, chronic renal diseases, etc.) as the independent variables. On these propensity scores, the COVID-19 and non-COVID-19 patients were paired 1:3 with a calliper size of 0.1 logit [SD of the propensity score]. Variables were then compared using GEE (generalised estimating equation) models with an unstructured covariance matrix to account for the matching. For binary variables, the Binomial distribution was utilised, while for continuous variables, the Gamma distribution was employed. Histograms and quantile plots were used to evaluate the fit of the Gamma distribution. On the entire population, sensitivity analysis was performed using multivariable logistic regression models. The data is provided as an odds ratio with a 95% confidence interval. Statistical significance was defined as a p value of less than 0.05. R software version 3.6.0 was used for all of the analyses. (R Core Team) (2019).

Results

The patients' baseline features

The study comprised 150 patients who had positive real-time reverse transcriptase PCR tests for COVID-19 and were admitted to one of four participating ICUs. The average age was 63 [53; 71] years, with the median age being 63 [53; 71].122/28 was the male-to-female ratio (81.3 percent of men). Simplified acute physiology score (SAPS) II had a median of 49 [37; 64] points. The median length of stay in the ICU was 9.6 4.2 days, with an 8.7% mortality rate, when 101 patients (67.3%) were still intubated at the time of data analysis. By the time the data was analysed, 36 patients had been discharged from the ICU. Eighty-four patients (60%) received lopinavir + ritonavir, eight (5.3%) remdesivir, 49 (32.7%) hydroxychloroquine, and nine (7.5%) did not receive any treatment.

Table 1 summarise the medical history, patient features, thrombotic/ischemic, and hemorrhagic problems experienced by COVID-19 and non-COVID-19 patients throughout their ICU stay.

Complications of thrombosis and ischemia

During their ICU stay, 150 patients were diagnosed with 64 clinically relevant thrombotic complications, the majority of which were pulmonary embolisms (Fig. 1). A total of 99 patients underwent CTPA to determine the aetiology of a respiratory re-aggravation or a large increase in D-dimers. Twenty-five (25%) of the participants (24 men, average age 62) had pulmonary embolisms: nine troncular, eight lobar, five segmental, and three subsegmental pulmonary embolisms. Pulmonary embolism was discovered 5.5 [2.8; 9.3] days after admission to the ICU.

Due to abnormal neurological examinations, fifteen brain CT scans and ten brain MRI scans were conducted in 25 individuals, with four patients receiving both.

4 of the patients had hemorrhagic or ischemic strokes. Two CT scans were performed after a fall in the setting of recent head trauma, but neither revealed any signs of ischemic stroke. There was a total obstruction of the right internal carotid artery in one patient, likely due to COVID-19 infection, although there was no sign of ischemic, stroke.

All patients (n=150)	
Baseline coagulation parameters	
Platelet count(109/L)—normalrange:150–400.109/L	200[152;267]
aPTT—normalrange:0.7–1.2	1.2[1.1;1.3]
PT (%)—normal range:>70%	84[73;91]
INR—normalrange:1.00–1.15	1.12[1.05;1.25]
D- dimers (mg/L) – normal range;	<0.5mg/L2.27[1.16;1.25]
Antithrombin activity (%)—normalrange:50–150%	91[78;102]
Factor V (%)—normal range:>70%	136[115;150]
Factor VIII (%) normal range: 60- 150%	341[258;416]
vW Factivity (%)	328[212;342]
vWFantigen (%)—normal range:	50–150%455[350;521]
Screen patient(s)	68.6[59.5;85.4]
Screen ratio—normal range:<1.2	1.63[1.43;2.04]
Confirm patient(s)	43.9[40.9;48.4]
Confirm ratio—normal range:<1.2	1.25[1.13;1.46]
Screen/confirm ratio—normal range:	< 1.21.4 [1.25; 1.48]
Fibrinogen(g/L)—normalrange:2–4g/L	6.99[6.08;7.73]
Lupus anticoagulant—n (%)	50/57 (87.7)
All results are giveninmedian [IQR], exceptifspecified otherwise aPTT, activated partial thrombo plastic time; INR, international normalized ratio; PT, prothrombin time; v WF, von Willebrand factor [a] Measured during ICU stay	

Table 2: CoagulationparametersofCOVID-19patients

Discussion

We found a high prevalence of clinically relevant thrombosis, primarily pulmonary embolisms (16.7 percent), in COVID-19 patients admitted to the ICU for hypoxemic acute respiratory failure in a prospective cohort. Despite prophylactic or therapeutic anticoagulation, several thrombotic consequences occurred.

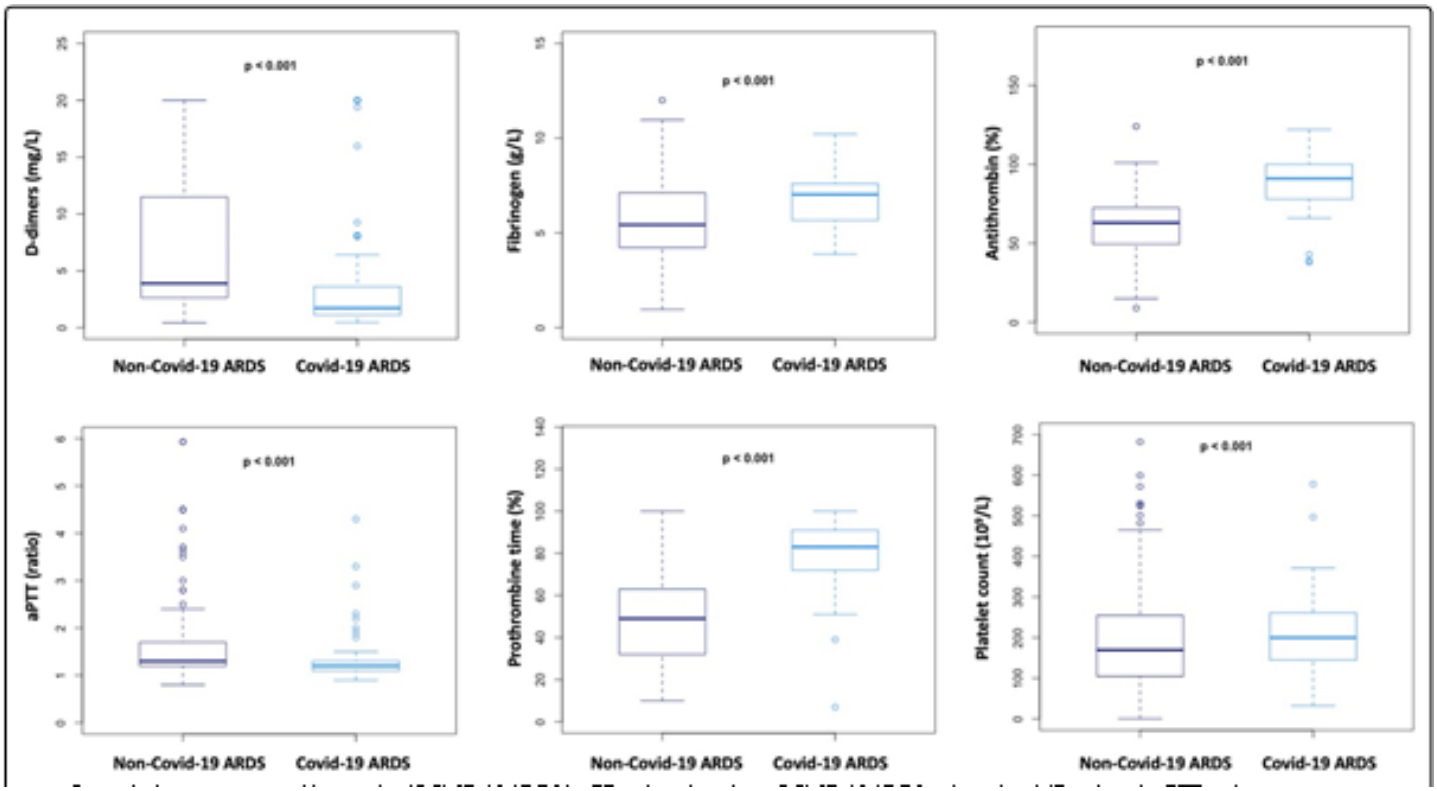
All patients had a systemic inflammatory response syndrome, which was detected by high fibrinogen levels and was responsible for blood coagulation activation.

Populationbefore matching (n=383)					Populationafter matching(n=222)			
	Non-COVID-19-	COVID-19-ARDS(n=150	OR[95%IC]	p-value	Non-COVID-19-	COVID-19-	OR[95%IC]	p-value

	ARDS (n=233)	)			ARDS (n=145)	ARDS(n=77)		
hrombo-emboliccomplica-tions—n (%)	14(6)	27(18)	3.4[1.7–7.3]	<0.001	7(4.8)	9(11.7)	2.6[1.1–6.1]	0.04
Pulmonary embolisms—n(%)	3(1.3)	25(16.7)	15.2[4.5–80.4]	<0.001	3(2.1)	9(11.7)	6.2[1.6–23.4]	0.01
Deepveinthrombosis—n(%)	3(1.3)	3(2)	1[0.1–9.2]	1	2(1.4)	0(0)	–	–
Myocardial infarction—n(%)	6(2.6)	0(0)	0[0–1.3]	0.09	2(1.4)	0(0)	–	–
Cerebral ischemic attack—n(%)	1(0.4)	2(1.3)	3.1[0.2–185.5]	0.68	0(0.0)	0(0)	–	–
Limb ischemia—n (%)	0(0)	1(0.7)	Inf[0.0–Inf]	0.78	0(0.0)	0(0)	–	–
Mesenteric ischemia—n(%)	3(1.3)	1(0.7)	0.5[0.0–6.5]	0.98	2(1.4)	1(1.3)	0.96[0.09–9.8]	0.97
lbofRRTfilterperdialyzedpatient—median, IQR	1[2–1]	3[2–7]	–	<0.001	2.0[1.0–2.5]	3.0[2.0–6]	–	0.03
NbofRRTfilterperdayof RRT—median, IQR	0.3[0.3;0.5]	0.7[0.5;1]	–	<0.001	0.3[0.3;0.4]	0.7[0.5;1]	–	<0.001
ECMO oxygenator thrombo-sis —n (%)	1/10(10)	2/12(16.7)	–	0.59	1/7 (14.3)	0/4(0)	–	–
Hemorrhagic complications— n (%)	1(1.8)	4(2.7)	–	2.4[0.27–28.5] 0.6	2(1.4)	0(0)	–	–

Table 3: OutcomesofCOVID-19ARDSandnon-COVID-19ARDS

Fig 2: Coagulation parameter soft he matched COVID-19 ARDS (n=77patients); and non - COVID-19ARDSpatients (n= 145 patients); aPTT: ACTi- vatedpartial thrombo plastin time, PT: pro thrombin time.



As evidenced by progressive D-dimers elevation in practically all COVID-19 patients. The pattern of coagulation activation in our group of non-COVID-19 ARDS patients, on the other hand, was not the same. D-dimers levels were lower (2.27 mg/L vs. 4.30), PT, aPTT, and AT were all within normal ranges, and fibrinogen was higher (7.0 g/L vs. 5.6) compared to septic shock without DIC [12]. Although 30–40% of septic shock patients develop DIC [13], no COVID- 19 patient was diagnosed with DIC with the ISTH "overt" score, and only 6 with the JAAM-DIC score. Only 22 patients had a positive SIC score, which should reveal people at risk of developing DIC.

As a result, we can safely anticipate that the mechanisms causing DIC in COVID-19 patients differ from those commonly documented in ICU patients. Then there's the possibility that the mechanisms leading to localised thrombosis (PE, stroke, or mesenteric infarction) or circuit device thrombosis (either RRT or ECMO) aren't the same. Indeed, despite systemic anticoagulation with continuous infusions of heparin and/or citrate [14], RRT circuit thrombosis may be explained by both the extremely high level of fibrinogen and ultrafiltration, which results in higher concentrations inside the dialyzer capillaries, rather than contact phase activation by the circuit itself [15]. Prothrombin and other traditional coagulation markers

The procoagulant condition is not detected by the activated thromboplastin time or platelet count [16].

According to our findings, pulmonary embolism was the most common type of pulmonary embolism. According to our findings, pulmonary embolism was most commonly discovered a few days after ICU admission. As compared to non-COVID-19 patients, the incidence

of pulmonary embolism was considerably higher in COVID-19 ARDS patients (11.7 vs. 2.1 percent). Only 1.3 percent of critically sick individuals had PE in another prospective cohort [17].

The mechanisms that cause thrombosis are unknown. With very high levels of vWF: Ag and FVIII, endothelial inflammation was visible. Vasoconstriction, which reduces blood flow and promotes vascular occlusion, may occur as a result of severe hypoxemia in the pulmonary capillaries [18]. Hypoxia also causes hypoxia-inducible factors to become active (HIFs). HIFs are heterodimeric transcriptional factors that include the HIF subunit, which is expressed by all nucleated cells, as well as the HIF1 and HIF2 subunits (for HIF1 and HIF2, respectively).

Hypoxia causes HIF2 subunits to be produced and hydroxylation to be reduced, resulting in the induction or repression of several genes, including tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) [19, 20]. We didn't measure PAI-1 in our patients, but it's likely that it's quite high because it's secreted by endothelial cells like vWF.

Conclusion

Despite anticoagulation, a high number of patients with ARDS caused by COVID-19 have life-threatening thrombotic complications, according to this study. Because of the variations in normal hemostasis measures in this condition, anti-Xa testing should be used to monitor anticoagulant medication. Although Tang et al. [3] suggested that anticoagulant therapy primarily with LMWH is associated with a better outcome in severe COVID-19 individuals who meet SIC criteria or have a markedly elevated D-dimer, larger anticoagulation targets than usual should most likely be considered.

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