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Original Research Article

Study of thrombotic complications in COVID-19

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ABSTRACT

Background: In December of 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) began to infect humans in the city of Wuhan and has rapidly become pandemic. Recent clinical trials suggested that COVID-19 related thromboembolic complications are the major cause for increased incidence of morbidity and mortality. We conducted a prospective observational study to evaluate the prevalence of vascular complications due to COVID-19 and to analyse the difference in the inflammatory markers before and after the events.
Methods: Prospective observational study, conducted at department of general medicine, Bangalore Medical College, Bangalore Karnataka from 3 months, 01 August 2021 to 30 October 2020. The incidence of thrombotic events was 70.7% (53/75). The incidence of arterial thromboembolic events was 48%, involving 36 patients of the overall study population. Of these 36 patients, majority of them were suffering from cerebrovascular accident (CVA) accounting for about 12 (16%) of the patients followed by 11 (14.7%) with ischemic heart disease (IHD). About 22.66% (17/75) of patients had developed venous thromboembolic events. Of which, 13 (17.3%) patients had developed deep-vein thrombosis (DVT).
Results: We observed that all the inflammatory markers had significantly increased after the onset of thrombotic events. Serum ferritin, lactate dehydrogenase (LDH), interleukin-6 (IL-6) and fibrinogen were almost raised by 50% of the pre-event values. We could not calculate the sensitivity, specificity, positive predictive value and negative predictive value for each parameter as the severity of the disease was widely distributed. Majority of these thrombotic events were observed among the patients aged >60 years and those with comorbid conditions. But there no statistically significant difference observed.
Conclusions: We concluded that COVID-19 causes significantly increased surge of inflammatory markers and thereby the significantly increased prevalence of arterial and venous thrombotic events.

Keywords: Thrombotic events, COVID-19, Arterial thromboembolic events, Venous thromboembolic events

INTRODUCTION

In December of 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) began to infect humans in the city of Wuhan in the Hubei province of China. Later it rapidly spread to the rest of the world and declared as pandemic by the World Health Organization (WHO) in March of 2020.[1]

At the time of this writing the burden of covid 19 in our country was 22,723,468 of the active cases and 22097 deaths.[2]

Clinical manifestations range from mild fever to severe pneumonia. Bilateral pneumonia is the main finding in hospitalized patients and at least 5% initially present in serious condition, requiring advanced medical support or intensive care.[3]

Recent clinical trials suggested that COVID-19 related thromboembolic complications are the major cause for increased incidence of morbidity and mortality. The probable cause might be the higher affinity of virus to angiotensin-converting enzyme-2 (ACE-2) which on binding of the virus will lead to release of inflammatory markers as a result of increased angiotensin I levels in serum.[4,5] Hence the further thrombotic events. Kolk et al observed 31% mortality due to vascular events in their patients COVID-19 among which 27% and 3.7% were due to venous and arterial thromboembolism.[6]

We conducted a study to evaluate the prevalence of vascular complications due to COVID-19 and to analyse the difference in the inflammatory markers before and after the events.

METHODS

Study type

The type of study was prospective observational study.

Study place

The study was conducted at the department of general medicine, Bangalore Medical College, Bangalore Karnataka.

Study duration

The study was conducted for 3 months, from 01 August 2021 to 30 October 2021 after obtaining the ethical committee clearance (IEC: BMCRI/PS/103/2021-22).

Inclusion criteria

Patients of either gender aged more than 18 years who were willing to participate in the study were included.

Exclusion criteria

The pregnant and lactating women, patients with known cases of cardiovascular disease, deep-vein thrombosis (DVT), varicose veins and those who had underwent any kind of cardiopulmonary surgery were excluded from the study.

Sample size calculation

We had recruited 75 patients by convenience sampling.

Methodology

After obtaining the ethical clearance, 75 study population were recruited based on the inclusion criteria. Basic demographic details of all the patients are recruited and their COVID-19 reverse transcriptase polymerase chain reaction (RTPCR) report is verified.

Complete blood count (CBC), platelet, prothrombin time (PT), activated partial thromboplastin time (aPTT) and the COVID markers such as C-reactive protein (CRP), D dimer, interleukin-6 (IL-6), lactate dehydrogenase (LDH), and serum ferritin were tested at the time of admission and after the onset of thrombotic events were noted and tabulated for further analysis.

Statistical analysis

All the recruited data was tabulated in Microsoft (MS) excel and analysed using statistical package for the social sciences (SPSS) software version 2.0 with suitable statistical tests.

RESULTS

Based on the analysis, the average age of the recruited patients was 56.6±12.78 years. Forty-one patients were aged less than 60 years and the rest thirty-four were aged more than 60 years. There were 53 (70.7%) and 22 (29.3%) males and females respectively, which is illustrated in Figure 1.

Figure 2 illustrates the distribution of comorbid conditions. Out of 45 recruited study samples, 40 were suffering from the comorbid conditions. Of which, 17 (22.7%) were known cases of controlled hypertension (HTN) and diabetes mellitus (DM). 15 (20%) and 8 (10.7%) were suffering from HTN and DM. Majority of the patients were diagnosed with severe form accounting for about 35 (47%) followed by mild form in 22 (29%) and 18 (24%) were diagnosed with moderate form of COVID-19.

The incidence of thrombotic events was 70.7% (53/75). Table 2 and Figure 4 illustrates the number of patients developed thrombotic events. The incidence of arterial thromboembolic events was 48%, involving 36 patients of the overall study population. Of these 36 patients, majority of them were suffering from cerebrovascular accident (CVA) accounting for about 12 (16%) of the patients followed by 11 (14.7%) with ischemic heart disease (IHD). Three patients (4%) had developed mesenteric ischemia. Two patients (2.7%) each had developed acute infarcts, coronary artery disease (CAD), haemorrhagic stroke, and small vessel ischemia. One each (1.3%) had developed Fournier's gangrene and pulmonary embolism.

About 22.66% (17/75) of patients had developed venous thromboembolic events. Of which, 13 (17.3%) patients had developed DVT. The occurrence of DVT was statistically significant. Two patients had developed venous ulcer and one each had developed portal mesenteric vein thrombosis and complete thrombosis of cephalic vein.

The average values of inflammatory markers have been entered in Table 4. We observed that all the inflammatory markers had increased after the onset of thrombotic events with significant p value of <0.05. Serum ferritin, LDH, IL-

6 and fibrinogen were almost raised by 50% of the pre-event values. But there was no variation in the values between arterial and venous events. But we could not calculate the sensitivity, specificity, positive predictive value and negative predictive value for each parameter as the severity of the disease was widely distributed. Majority of these thrombotic events were observed among the patients aged more than 60 years and those with comorbid conditions. But there no statistically significant difference observed.

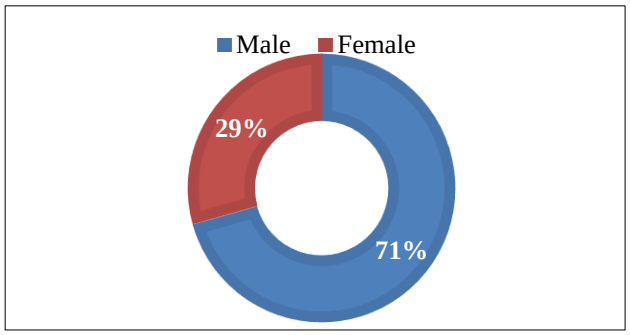

Figure 1: Pie chart representing the distribution of gender.

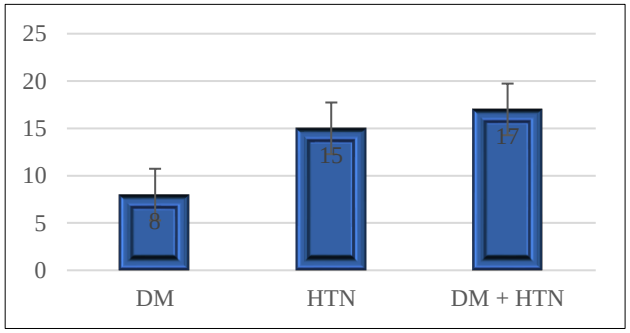

Figure 2: Distribution of comorbid conditions.

Table 1: Distribution on age.

Age (years)	N (%)
<60	41 (54.66)
>60	24 (46.44)

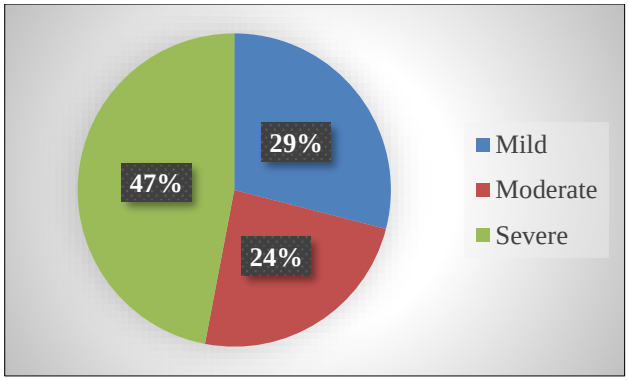

Figure 3: Pie chart illustrating the distribution of severity of COVID-19 in recruited patients.

Table 2: Distribution if arterial thromboembolism events among the recruited population.

Arterial thromboembolic events	N	%
Acute infract	2	2.7
CAD	2	2.7
CVA	12	16.0
Fourniers gangrene	1	1.3
Haemorragic stroke	2	2.7
IHD	11	14.7
Mesentric ischemia	3	4.0
Pulmonary embolism	1	1.3
Small vessel ischemia	2	2.7
Total	36	48.0

Table 3: Distribution if venous thromboembolism events among the recruited population.

Venous thromboembolic events	N	%
DVT	13	17.3
Portal and mesenteric vein thrombosis	1	1.3
Venous ulcer	2	2.7
Complete thrombosis of cephalic vein	1	1.3
Total	17	22.66

Table 4: Comparison of laboratory parameters before and after the thrombotic events.

Parameters	At the time of admission	After the thrombotic event	P value
TC	12.7±5.14	14.3±5.67	0.072
PLT	1.9±0.46	2.3±0.79	0.002
PT	12.5±1.62	16.5±3.55	<0.0001
INR	1±0.12	1.4±0.22	<0.0001
aPTT	34.8±4.6	43.4±6.97	<0.0001
D dimer	1.3±0.61	2.9±0.97	<0.0001
Fibrinogen	255.2±41.21	427±79.51	<0.001
CRP	31.3±21.85	58.4±19.81	<0.0001
Ferritin	443.3±214.81	1212.7±415.95	<0.0001
IL-6	13.3±4.19	54.9±15.74	<0.0001
LDH	224.9±45.71	490.8±185.27	<0.0001

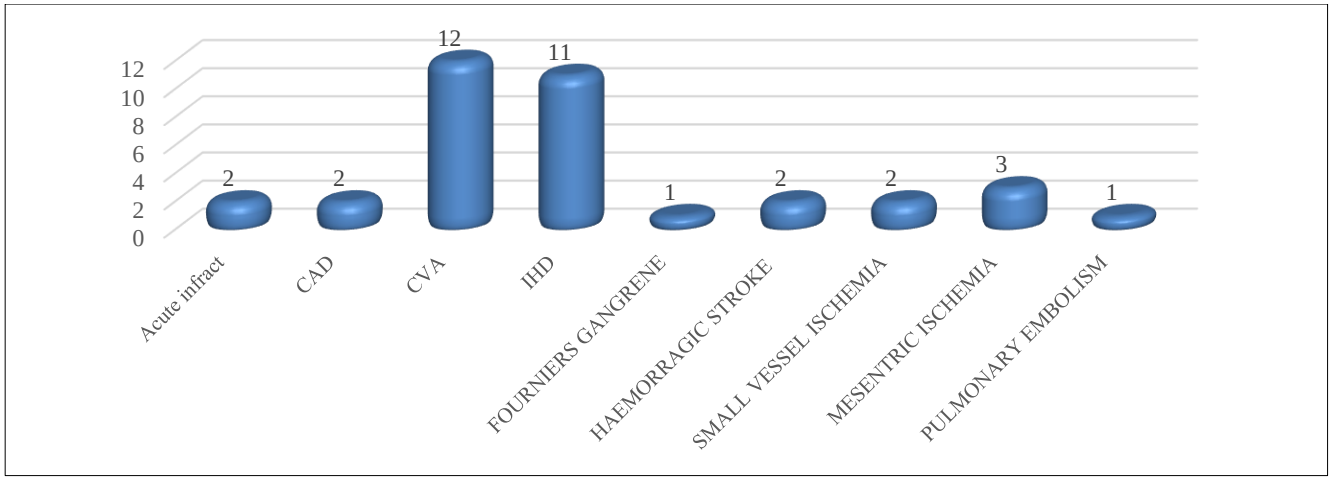

Figure 4: Distribution of thrombotic events in studied samples.

CAD: Coronary artery disease, CVA: cerebrovascular accident, and IHD: ischemic heart disease

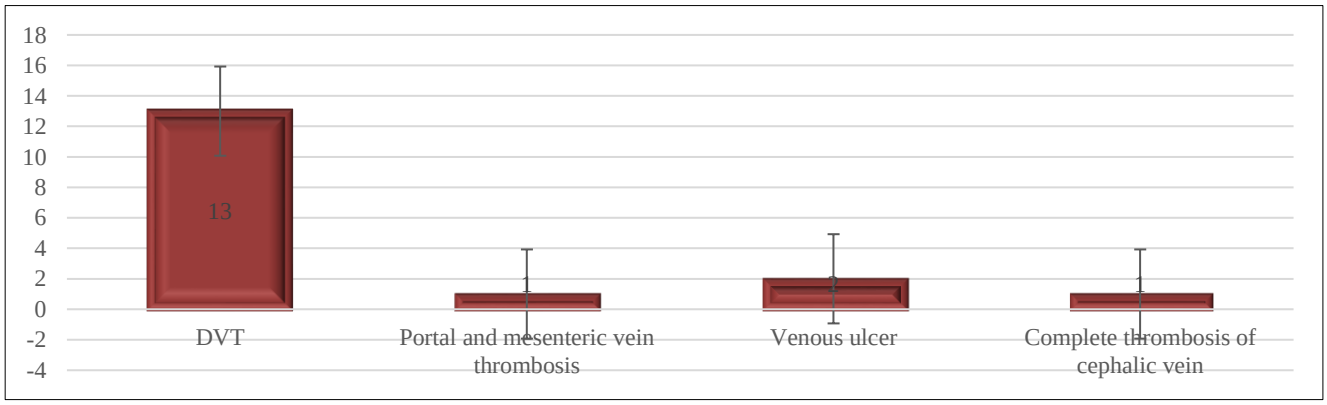

Figure 5: Venous thromboembolic events.

DISCUSSION

Majority of the RCTs identified that the rate of thrombosis in admitted COVID-19 patients was relatively high and attributed to a pro-thrombotic state. The rate of thrombosis appeared to be dependent on the severity of illness.[8] Hence we conducted a prospective study to analyse the pattern of distribution of risk factors causing thromboembolic events.

The average age of the recruited patients in our study was 56.6±12.78 years. 54.7% and 45.3% of the patients where patients were aged <60 years and >60 years respectively. There were 53 (70.7%) and 22 (29.3%) males and females respectively in our study. Middeldorp et al also observed the average age of their patients being 61 years with male predominance.[9]

Piazza et al in their retrospective cohort study had found that 44.8±16.2 years were found to be having major thrombotic changes. Out of 1114 patients, 715 patients did not have any thrombotic complications.[10]

Out of 45 recruited study samples, 40 were suffering from the comorbid conditions. Of which, 17 (22.7%) were known cases of controlled HTN and DM. 15 (20%) and 8 (10.7%) were suffering from HTN and DM. Majority of the patients were diagnosed with severe form accounting for about 35 (47%) followed by mild form in 22 (29%) and 18 (24%) were diagnosed with moderate form of COVID-19.

The overall incidence of thrombotic events was 70.7% (53/75). The incidence of arterial thromboembolic events was 48%, involving 36 patients of the overall study population. Of these 36 patients, majority of them were suffering from CVA accounting for about 12 (16%) of the patients followed by 11 (14.7%) with IHD. Three patients (4%) had developed mesenteric ischemia. Two patients (2.7%) each had developed acute infarcts, CAD, haemorrhagic stroke, small vessel ischemia. One each (1.3%) had developed Fournier's gangrene and pulmonary embolism.

In the study by Middeldorp et al who had aimed at analysing the venous thromboembolism only had reported 20% of the recruited samples were diagnosed with VTE of which 13% were symptomatic even after administration of routine thrombosis prophylaxis.[9] They had compared the incidence of VTE between ward versus ICU patients and

found that patients admitted in ICU had higher incidence than in the ward. Hence, we can understand that as the prevalence of severe form is more in our study, the incidence of TVE and AVE also have raised. Also similar to our study, Middeldorp et al found higher incidence of DVT.[9] Rey et al and Fournier et al found comparatively higher incidence of arterial thrombosis in covid patients than non-COVID.[11,12]

About 22.66% (17/75) of patients had developed VTE. Of which, 13 (17.3%) patients had developed DVT. The occurrence of DVT was statistically significant. Two patients had developed venous ulcer and one each had developed portal mesenteric vein thrombosis and complete thrombosis of cephalic vein. In contrast to our findings, Hill et al reported only 0.9% incidence of VTE. But the recruited study population in their study had a greater number of young patients.[13] Bilaloglu et al reported 29% incidence of thrombosis of which comprising of PE (6.2%), DVT (9.4%), stroke (3.7%) and myocardial infarction (13.9%), with an overall mortality rate of 54%.[14] Other study by Jenner et al 56.3% developed thrombosis, and 34% of ICU admitted patients were found to have thrombotic complications, where 16.1% were reported with deep vein thrombosis and 12.6% with pulmonary embolism.[15]

Almost all the inflammatory markers had increased by 50% of the pre-event values. The severity of the disease was widely distributed among these patients hence the sensitivity specificity could not be calculated. Majority of these thrombotic events were observed among the patients aged >60 years and those with comorbid conditions with no statistical significance. Similar to the present study Hanif et al also observed that majority of their patients with thrombotic complications were aged >65 years with significant association and also the patients with higher D dimer were found be at higher risk of developing the ATE and VTE.[16]

Similar to our study Alonso-Fernandez et al who had carried out screening CTPA on COVID-19 patients with d-dimer > 1 µg/ml identified the complications of PE in almost 50% of the patients.[17] Samkari HA et al also has found that increased D dimer was statistically associated increased inflammatory markers both at the time of admission and after the event.[18]

Limitation of this study was, we have had not compared the increase in inflammatory markers between the patient developed complications and those who had not. And the sensitivity, specificity of each parameter is also not analysed as there was wide distribution in severity of the disease.

CONCLUSION

COVID-19 causes significantly increased surge of inflammatory markers and thereby the significantly increased prevalence of arterial and venous thrombotic events. There is almost >50% raise in serum ferritin, LDH, IL-6 and fibrinogen among the patients after development thrombotic events. 22.6% and 17.3% were the prevalence of venous and arterial thrombotic events respectively.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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