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A retrospective cohort study on prognostic factors and anti-thrombotic therapy and its correlation with disease outcome in patients of COVID-19

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Abstract

Background Since the outbreak of coronavirus disease 2019 (COVID-19), many studies have been conducted on clinical features, laboratory parameters, treatment, and anticoagulation therapy. However, there is a scarcity of studies investigating the relationship between prognostic parameters, anti-thrombotic agents, and their impact on disease outcomes within the regional population. A complete analysis of all the factors related to the prognostic, risk, therapies are important to identify the possible interpretation of the disease progression. To find out the utilization of antithrombotic therapy in patients of coronavirus disease 2019 and to study the correlation of antithrombotic therapy and prognostic factors with survival and non-survival.

Methods In this retrospective study we included data of coronavirus disease 2019 positive patients who aged more than 18 with or without comorbidities, non-pregnant. We collected data of 768 patients from the medical record department of a tertiary care hospital. For the collected cohort data, we applied descriptive analysis and contingency analysis to find any difference between the surviving and non-surviving group of patients.

Results We found that compared to survivors, the age was higher in non-surviving patients. Non-surviving patients had higher D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), and Ferritin levels than survival. The coagulation profile was changed in the non-surviving group. Further conducting contingency analysis, we found the critical role of anti-thrombotic agents in the outcome of the disease. We found that one anti-thrombotic agent has a varied result over another. Co-morbidities were found to be a significant factor for the outcome of the disease; as we analysed, we found diabetes mellitus and hypertension in most non-survivors.

Conclusion We found that many prognostic factors were more important in finding the disease progression and can help in the administration of a particular anti-thrombotic therapy.

Keywords Coronavirus, COVID-19, Prognostic factors, Laboratory parameters, Survival, Non-survival, Anti-thrombotic agents, Enoxaparin (60 mg/0.6 ml), D-dimer, CRP, Co-morbidities

Introduction

In late 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in Wuhan city of China, which transmitted easily and affected 239 countries; by October 10, 2022, there were 617,597,680 confirmed cases which also included 6,532,705 deaths due to COVID-19 [1, 2]. A coronavirus

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is a distinct group of viruses which can infect a wide range of animals as well as humans with mild to severe respiratory illness. Previously in 2002 and 2012, two highly pathogenic zoonotic viruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), caused fatal respiratory illness in humans, which made the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) a new public concern in the twenty-first century. Patients infected with COVID-19 show clinical features like viral pneumonia, fever, cough and chest discomfort with shortness of breath and pulmonary infiltration in severe cases, which are similar to SARS and MERS [1]. In March 2020, WHO declared COVID-19 as a global pandemic which surpassed SARS and MERS devastatingly in terms of the number of infections and scope of epidemic areas [1, 3]. And this has given rise to a greater threat to global public health, which created immense challenges towards the countries [1, 4]. On January 30, 2020, India reported the first case of COVID-19 in Trissur, Kerala [5]. SARS-CoV-2 belongs to the Coronaviridae family and is the 7th CoV (after HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV) capable of causing different types of respiratory infections by targeting human respiratory systems leading to lethal disease COVID-19 represented a global health concern. The genome of viruses (MERS-CoV, SARS-CoV, and SARS-COV-2) encodes four different structural proteins, namely spike (S), nucleocapsid (N), membrane (M), and envelope (E) (Fig. 1) out of which the S protein recognizes the two receptors present in the lower respiratory system which are Angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP4). ≥ 70% of SARS CoV and SARS-CoV-2 genetic sequence is similar, yet there are differences in both their affinity towards ACE2 to which the SARS-CoV-2 binds 10–20 folds stronger, and that is one of the factors which is responsible for the quicker and easier transmission of SARS-CoV-2 in humans [6–8]. After the entry into the host alveolar cells, SARS-CoV-2 quickly replicates and gives rise to a strong immune response which leads to hypercytokinaemia (Cytokine storm syndromes) and pulmonary tissue damage. Acute respiratory distress syndrome (ARDS) and organ damage (heart, kidney, and liver, leading to multiple organ failure) are a result of pro-inflammatory cytokine production and chemokines by the immune effector cells, which is also a lead cause of death due to COVID-19 [6, 7].

Symptoms may appear 5–6 days on average and may take up to 14 days following exposure to the virus. Variety of symptoms are included from mild symptoms to severe illness. Frequent symptoms of COVID-19 include fever, cough, tiredness, and loss of taste and smell. Infrequent symptoms are sore throat, headache, ache and pain, diarrhea, skin rash, discoloration of fingers or toes, and red or irritating eyes. Severe symptoms include difficulty breathing or shortness of breath, loss of speech or mobility, confusion, and chest pain (Fig. 2) [9, 10]. COVID-19 cannot be precisely diagnosed with symptoms because they are nonspecific [11].

In the pathogenesis of infectious diseases, Toll-like receptors (TLRs), mainly TLR-2 and TLR-4, activation plays a significant role in the body's defense against microorganisms, including COVID-19 infection, where it can trigger the release of pro-inflammatory cytokines [12, 13]. Moreover, elevated levels of soluble PD-L1 (sPD-L1) in COVID-19 patients with a poor prognosis are indicative of an imbalance or disruption in the PD-1/PD-L1 immune regulatory pathway [14]. The PD-1/

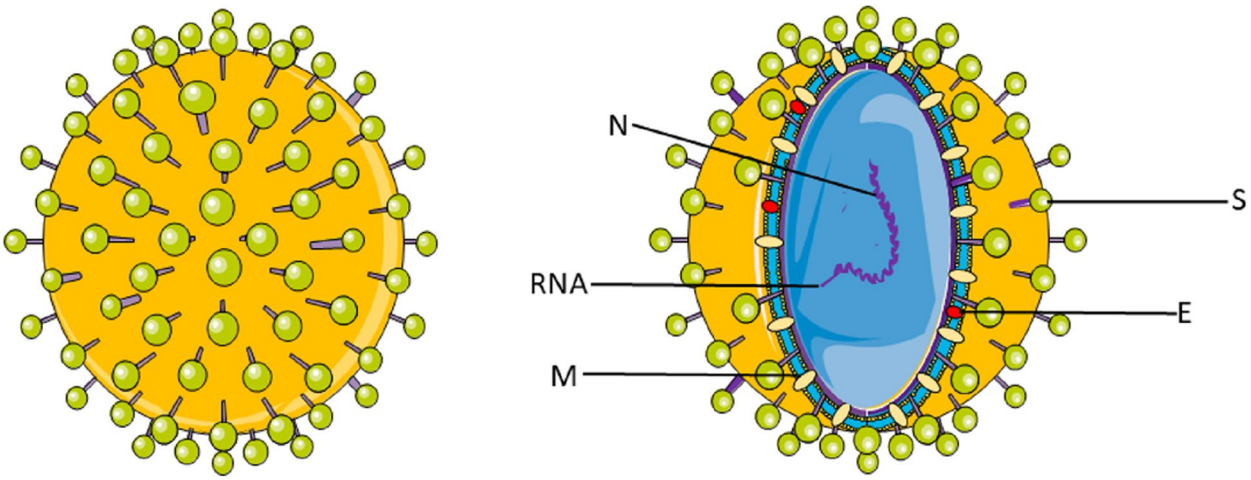

Fig. 1 Structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), There are 4 proteins as follows: Nucleocapsid (N), Spike (S) protein, Envelope (E) protein, and membrane (M) protein. (Ribonucleic acid (RNA) encased in N protein)

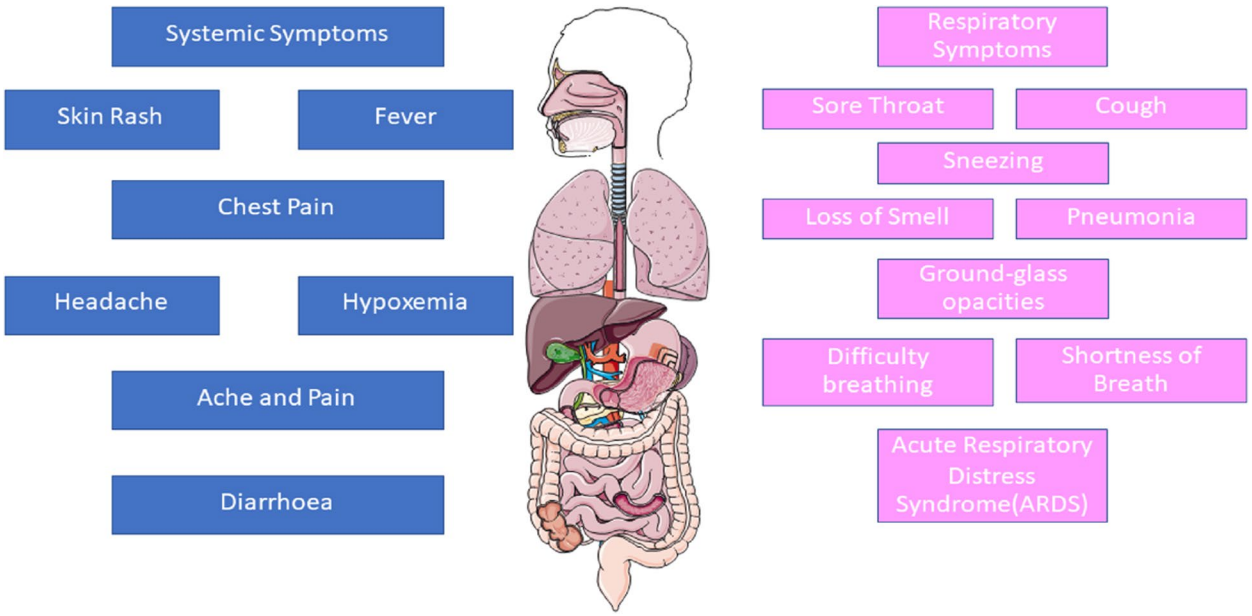

Fig. 2 Symptoms of COVID-19

PD-L1 axis, a significant constituent of the checkpoint molecule family, is implicated in the potential regulation of both the host immune response to SARS-CoV-2 and the pathogenesis of COVID-19 [14]. TGF-β1 and interleukin-10 (IL-10) are crucial immune regulators known for their anti-tumor effects in maintaining immune homeostasis [15, 16]. TGF-β serves as a prominent regulator of immune responses [17] and has been associated with the development of comorbidities in severe COVID-19 patients [18]. Prolonged viral stimulation can induce T cell exhaustion, characterized by the loss of cytokine production and impaired functional capabilities [18]. Elevated levels of mean platelet volume (MPV) and platelet distribution width (PDW) were observed in COVID-19 non-survivors. These platelet indices, MPV and PDW, also hold diagnostic significance in the identification of spontaneous bacterial peritonitis (SBP) [19, 20].

The release of inflammatory molecules leads to the macrophage activation syndrome, which is responsible for the tissue factor expression leading to pulmonary coagulopathy and microvascular thrombosis. This immunothrombosis caused by pulmonary intravascular coagulopathy is the reason for elevated D-dimer. PT and aPTT are most commonly elevated in DIC, and in COVID-19, they have prolonged in 5% and 6% of patients; otherwise, they are normal or near-normal. In addition, 36% of COVID-19 cases have elevated D-dimer levels, which is more frequent in severely ill patients and a steady and escalating rise in D-dimer was seen in non-survivors. This shows that D-dimer is highly prognostic, which corresponds with the severity and mortality of COVID-19 and differentiates those who require anticoagulant therapy [21]. Leukopenia, lymphocytopenia, high levels of CRP, high D-dimer, prolonged PT, and high fibrinogen levels had been previously mentioned during the early phase of COVID-19 [22]. One of the sensitive inflammatory markers of COVID-19 severity is LDH which also correlates with liver enzymes and cardiac biomarkers. Besides this, it also correlates with pneumonia severity index and computed tomography abnormalities [21]. The progression of SARS-CoV-2 infection and the ensuing inflammatory reactions are closely associated with the detrimental impact on the respiratory passages [23]. LDH release and cytokine-mediated tissue damage are two possible effects of severe infections like COVID-19. Since LDH (isozyme 3) is found in lung tissue, the host immune system's induction of inflammation causes infected cells to undergo apoptosis, which causes intracellular LDH to be released into the blood as a severe form of interstitial pneumonia, which frequently develops into acute respiratory distress syndrome which is the hallmark of the disease [24]. LDH can also assess the disease's progression by focusing on respiratory functions [21]. Chest CT scan is non-invasive and has a sensitivity of 86–98%; it also improves false negative rates more than RT-PCR [11]. In the majority of COVID-19 patients, chest CT shows characteristic radiologic signs, such as bilateral ground glass opacities (GGOs) in the lower lobes with a peripheral or posterior distribution, that again progresses to the crazy-paving pattern and subsequent consolidation.

CT score, a quantitative measurement used to assess the extent and severity of lung involvement in patients with various lung diseases, primarily derived from chest CT scans and provides a standardized approach to evaluate the severity and progression of lung abnormalities like GGOs, consolidation, etc. The severity of such abnormalities is often scaled from 0 to 5 or 0 to 25 [25].

Previous studies show that patients with co-morbidities have significantly increased ferritin levels than those who do not [26]. Furthermore, co-morbid conditions play a significant role in disease outcomes which is an increase in death [27]. The primary objective of this study is to examine the utilization of antithrombotic therapy in individuals diagnosed with COVID-19. Additionally, it aims to explore the association between the administration of antithrombotic therapy, prognostic factors, and the likelihood of survival or non-survival in these patients.

Methodology

Patients and data collection

This study is a single-centre retrospective observational study of hospitalized COVID-19 patients approved by the Institutional Review Board and conducted for six months. Patients with COVID-19 infection and patients of all age groups were included. Data were obtained retrospectively from the medical record department of Parul Sevashram Hospital by manual chart review of patient files. Patient data included laboratory parameters like D-dimer, aPTT, and Blood glucose levels. Other data collected included age, demographic details of the patients, name, sex, date of admission, date of discharge, diagnosis, reason for admission, medical history, medication history, prescription, and other information.

Ethical consideration

This study was approved by the Parul University-Institutional Ethics Committee on Human Research (PU-IECHR). Approval Number: PUIECHR/PIMSR/00/081734/3908.

Statistical method

Data are represented graphically, and statistical data like mean, SD, and paired *t* test (*p* value) were found using online Prism GraphPad. The data were statistically represented as mean ± standard deviation using a *t* test. *P* value < 0.05 was considered significant statistically.

Result

This study encompassed data from patients of all age groups who had a confirmed diagnosis of COVID-19 infection. Patient files lacking any crucial data necessary for analysis and evaluation were carefully excluded from the study. Data from a total of 768 admitted patients were collected from the medical record division of a tertiary care institution based on inclusion criteria with a positive polymerase chain reaction test. The study included a total of 6855 patient days. Of all the patients, the mean age was 53.65 years, and the median was 55 years, with an IQR of 43–65. Out of a total, 468 were males, and 300 were females. In demographic data analysis, it was found that the median age was higher in the non-surviving group. A significant difference was found between the elderly (≥ 65 years) and other than the elderly group in the surviving and non-surviving groups. Gender does not conclude any significant factor for the outcome.

The blood test results were obtained and analysed, and it was found that D-dimer, LDH, CRP, Ferritin, PT, aPTT, CT-score etc., were carried out throughout their hospital stay. We found elevated D-dimer levels, CRP, LDH, ferritin, high CT score and prolonged PT and aPTT in the non-surviving group. Overall, the D-dimer levels in the non-surviving group show an increasing pattern to the surviving group, and there was a significant difference between both the groups, as shown in (Table 1). CRP was found, with a significant difference between both the groups (surviving and non-surviving). LDH was found in 495 patients out of 768, where we found no significantly different in surviving and non-surviving groups. Ferritin was found in 195 patients' files, with a mean of 393.6 and 588.1 in surviving and non-surviving groups, which shows no significance. Out of the total number of subjects, 584 (76%) patients are currently undergoing anticoagulant therapy, whereas 184 (24%) patients are not receiving anticoagulant therapy. Enoxaparin (60 mg/0.6 ml) is the primary treatment received by the majority of patients, followed by Aspirin (75 mg/150 mg), Heparin (35,000 IU to 50,000 IU), and Clopidogrel (75 mg). Besides that, the relation between comorbidity and survival status indicates that with comorbidity, 161 patients survived and 95 did not, but without comorbidity, 407 survived and 105 did not, as shown in (Table 1). Further analysis shows that there is a significant difference between surviving and non-surviving groups, those who have comorbidities and those who do not, with a *p* value of 0.0087 (Fisher's exact test). The per cent for surviving was 71% for those without comorbidities and 29% for comorbidities, and for non-surviving was 48% with comorbidities and 52% without comorbidities. Patients with comorbidities like diabetes mellitus (DM) and hypertension (HTN) were more prone to adverse outcomes than those who did not. We found a significant difference in both groups who had DM and HTN and those who did not.

Table 1 Demographic and laboratory test results

Parameter	Total (mean/number)	Surviving	Non-surviving	*p* value
Age	55 (43–65)	52 (40–87)	60 (51–68)	
Elderly ≥ 65	71.52	122 (22%)	76 (38%)	0.0202*
Other than elderly < 65	47.45	444 (78%)	126 (62%)	
Gender (Fisher's exact test)	Male	336 (59%)	132 (65%)	0.4665*
	Female	230 (41%)	70 (35%)	
D-dimer (mean)	2546.25	446 (1736.33)	154(3356.167)	0.0066 †
CRP (mean)	63.21125	422 (46.015)	172 (80.4075)	0.0042 †
LDH (mean)	1343.83	378 (798.6667)	120 (1889)	0.1117 †
Ferritin (mean)	490.85	184 (393.6)	59 (588.1)	0.2971 †
PT-time (mean)	16.57	230 (15.41)	111 (17.73)	0.5124 †
aPTT (mean)	43.205	217 (40.15)	108 (46.26)	0.5356 †
CT score (mean)	15.29	173 (14.07)	89 (16.51)	
Anti-coagulant				
Given	584	414 (71%)	170 (84%)	0.0414*
Not given	202	170 (29%)	32 (16%)	
Anti-coagulant (Fisher's exact test)				
Enoxaparin	491	357(73%)	134 (27%)	
Heparin	90	34 (38%)	56 (62%)	
Aspirin	131	88 (67%)	43 (33%)	
Clopidogrel	5	4 (80%)	1 (20%)	
Enoxapari	491	357 (74%)	134 (57%)	0.017*
Other than Enoxaparin	226	126 (26%)	100 (43%)	
Comorbidities				
Present	256	161 (28%)	95 (48%)	0.0087*
Absent	512	407 (72%)	105 (52%)	
DM	160	97 (17%)	63 (31%)	0.0307*
Other than DM	608	469 (83%)	139 (69%)	
HTN	167	104 (18%)	63 (31%)	0.0479*
Other than HTN	601	462 (82%)	9%)	

Data are mean (IQR), mean (Percentage), number (mean) obtained by using descriptive statistics. *P* values comparing patients are from Student's t test or Fisher's exact test, where, (†) suggest application of student t-test and (*) suggests Fisher's exact test

PT partial thromboplastin time, *APTT* activated partial thromboplastin time

Discussion

COVID-19 became a global threat and challenged the healthcare system in terms of management and transmission of disease. All this time, the diagnosis and prognosis depended on the clinical features, laboratory parameters, and other prognostic factors like D-dimer and LDH. In this study, we found different parameters that remained a key factor throughout the disease, like age; we found that elderly patients were more prone to adverse outcomes of the disease, which also correlates with other studies [1, 28–31]. The lack of significant disparity in mortality across the gender groups, as corroborated by relevant studies, suggests that there are several factors contributing to gender-specific mortality outcomes [32]. In this study, various factors were investigated, including the coagulation profile. The findings indicated that the non-surviving group showed elevated levels of PT, aPTT, and D-dimer [33]. Notably, significant changes were observed in D-dimer levels among the non-surviving group, which is consistent with findings reported in previous studies [4, 29, 33]. The non-surviving group exhibited heightened levels of inflammatory markers, including CRP, LDH, and Ferritin which is also similar to the findings of Chaomin Wu et.al in their study [29, 33]. Despite the existence of COVID 19, elevated levels of ferritin also persist in cases of tumour, rheumatic disease, diabetes, etc. Therefore, COVID-19 patients with one or more comorbidities had a considerably greater level of ferritin than those without comorbidities, indicating poor prognosis in such individuals [26]. These results suggest

the presence of active inflammation and infection when considering the patients' clinical condition. Notably, our study found that CRP stood out as a statistically significant indicator (shown in the Table 1) [28, 34]. In this study, we find no significance of CT score in surviving and non-surviving group, which contraindicate the previous study [35]. Together with laboratory parameters, our objective was to analyse the impact of anti-thrombotic agents in survival and non-survival, so we analysed Anti-thrombotic agents within both groups of outcomes. Moreover, as a result, we found four anti-thrombotic agents prescribed to the entire study cohort (Enoxaparin (60 mg/0.6 ml), Aspirin (75/150 mg), Heparin (35,000 IU to 50,000 IU), and Clopidogrel (75 mg)). When we compared patients receiving anti-thrombotic agents with the other group (not receiving group), we found that many patients receiving anti-thrombotic agents were survivors (as shown in Table 1) which is consistent with studies [36]. We also compared all the anti-thrombotic agents within, and we found that Enoxaparin (60 mg/0.6 ml) receiving group has the most survivors. During the study, we found that along with all factors for disease outcome, co-morbidities had played a significant role. We found that 33% of the total cohort had single or multiple past medical histories (co-morbidities). Previous studies have consistently shown that patients with co-morbidities face a reduced likelihood of survival [37]. Another study conducted on 201 patients concluded that co-morbidities were not a factor responsible for death in COVID-19 patients [29]. In our analysis of co-morbidities among the 768 patients included in the study, we observed a notable correlation. Specifically, a significant number of non-survivors were found to have either diabetes mellitus or hypertension, indicating the significant impact of these two co-morbidities on patient outcomes. Additionally, the study identified a range of other co-morbidities among the participants, such as hypothyroidism, chronic kidney Disease (CKD), Ischemic heart disease (IHD), asthma, stroke, myocardial infarction (MI), convulsion, cirrhosis, coronary artery disease (CAD), atrial fibrillation (AF), hyperthyroidism, migraine, ischemic heart disease (IHD), acute coronary syndrome (ACS), alcoholic liver disease (ALD), anemia, percutaneous transluminal coronary angioplasty (PTCA), tuberculosis (TB), and chronic obstructive pulmonary disease (COPD) some of the co-morbidities were also consistent with Chaomin Wu et al. [29] (as shown in Table 1).

Conclusion

In conclusion, we found that many factors must be considered while treating COVID-19 patients from the beginning to the end of management. An exact portrayal must be regarded as disease progression using prognostic parameters. We further conclude that demographic factors like age and gender might link to the disease's severity. Viewing the coagulation profile, we found that properly using an antithrombotic agent can significantly reduce disease outcomes. We further believe that commodities are the most critical factor that will be crucial yet difficult to manage with an ongoing COVID-19 infection. As COVID-19 is a systemic inflammatory disease, our study found potential risk factors for disease outcome are diabetes mellitus and hypertension, which are present in most non-surviving patients. It shows a better relation between factors that played an important role and where it changed the disease outcome.

Limitations

This retrospective observational study has obvious limitations. As it was a retrospective study, we have no access to real-time patient observation, which might not be so clearly expressed through the files. During data collection, we noticed that not all patient files included the same pattern of laboratory assessment data which might be due to clinical relevancy and patient severity depending on the clinical features. Some were missing critical COIVD-19 reports, making the person-specific evaluation less reliable. In several cases, the patient's medical and prescription histories were unavailable. Yet, we recommend that to discover the best dose and course of thromboprophylaxis for COVID-19 patients, randomized clinical studies are required.

Future scope

As this study was conducted on a large cohort it will definitely provide a strong portrait of evidence related to the prognostic factors throughout the progression of COVID-19 management and impact of anti-thrombotic agent use with respect to survival and non-survival.

Abbreviations

COVID-19	Coronavirus disease of 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV	Severe acute respiratory syndrome coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
HCoV-229E	Human coronavirus 229E
HCoV-NL63	Human coronavirus NL63
HCoV-OC43	Human coronavirus OC43
HCoV-HKU1	Human coronavirus Hong Kong University 1
ACE2	Angiotensin-converting enzyme 2
ARDS	Acute respiratory distress syndrome
RNA	Ribonucleic acid
PT	Prothrombin time
aPTT	Activated partial thromboplastin time
CRP	C-reactive protein
LDH	Lactate dehydrogenase
RT-PCR	Real-time reverse transcription–polymerase chain
CT scan	Computed tomography scan
SD	Standard deviation
DM	Diabetes mellitus

HTN Hypertension

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Not applicable.

Authors' contributions
All authors have made substantial contributions to the conception of the study, MP, MO, and MB have performed acquisition analysis and interpretation of data. MR and MM have substantively revised the final draft. All the authors had read and approved the submitted version.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval was taken from the Parul University-Institutional Ethics Committee on Human Research (PU-IECHR). Approval Number: PUIECHR/PIMSR/00/081734/3908. Consent for participation is not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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