Original Research Article

"D-Dimer: a primer biomarker in COVID-19"

Abstract

Aim & Objective: To explore risk factors associated with mortality in COVID-19 patients and assess the use of D-dimer as a first line biomarker for disease severity and clinical outcome.

Materials & Methods: We retrospectively analysed the pathological and radiological characteristics of 2087 consecutive cases of COVID-19 in PSH, Vadodara, Gujarat, from March 2021 to July 2022. Logistic regression methods were used. Correlations of D-dimer upon admission with disease severity and in-hospital mortality were analysed.

Results: 2087 patients of both gender (M-1373; F-714) having positive RTPCR were included. Mean age was 52 year. D-dimer > 250 ng/mL at admission was the only variable associated with increased mortality [(95% CI), $P = 0.025$]. D-dimer elevation (≥250 ng/mL) was seen in 81.31%. PE and DVT were ruled out in probability of thrombosis. D-dimer levels significantly increased with increasing severity of COVID-19 as determined by clinical improvement (within 5 days) and chest CT staging (Out of 25 score, $P = 0.000$). In-hospital mortality rate was 15.28%. Median D-dimer level in non-survivors 15.29%, was significantly higher than in survivors 84.71% ($n = 1768$, RR 24.69%). Median elevated D-dimer level was 600.5 ng/ml, of > 250 ng/mL predicted in-hospital mortality with a sensitivity of 81.31% (95% CI).

Conclusion: D-dimer is commonly elevated in patients with COVID-19. D-dimer levels correlate with disease severity and are a definitive prognostic marker for in-hospital mortality for COVID-19. Also a significant association between the high D-dimer level and severity of COVID-19 among comorbid patients.

Keywords: Biomarker, COVID-19, Mortality, Pandemics and Severity.

UNDER PEER REVIEW

INTRODUCTION

Coronavirus disease-19 (COVID-19) is the disease genesis by 2019-nCoV/SARS-CoV-2, a novel β coronavirus of group 2B. The affliction ranges from asymptomatic or mild infection to severe respiratory tract infections in humans such as those seen in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[3] Demonstrations of COVID-19 encompasses (but not limited to) fever, coughing, dyspnoea, watery diarrhoea, myalgia, severe lymphopenia, prolonged coagulation profiles, cardiac disease, and in some cases lead to sudden death.[4] Therefor the emergence in Wuhan, Hubei province of China in December 2019, COVID-19 has increased expeditiously in Wuhan as well other province in China and progressed worldwide. On January 30, 2020, WHO announced the outbreak as a Public Health Emergency. As of April 2022, approx. 50 Crore cases have been confirmed globally and approx. 60 Lacs deaths have been reported.[5]

Based on WHO epidemiology report, globally, nearly 2.9 million new cases and over 11000 deaths were reported in the week of 2 to 8 January 2023. This represents a reduction in weekly cases and deaths of 9% and 12%, respectively. In the last 28 days (12 December 2022 to 8 January 2023), over 13.9 million cases and over 49000 new deaths were reported globally- an increase of 10% and 22% respectively, compared to the previous 28 days. As of **8 January 2023, over 659 million confirmed cases and over 6.6 million deaths have been reported globally**.[6]

The more worrying omicron sub variant and one to watch closely is XBB1.5, which has rapidly spread in the USA, where it comprised 40·5% of cases at the end of December, 2022, and had a doubling time of 1 week, according to the Centers for Disease Control and Prevention.[7]

Considering a respiratory disease the coagulopathy was disclosed and D-dimer elevations were seen in 3.75 - 68.0% of the COVID-19 positive patients.[8] Due to lack of studies in COVID-19 few previous studies in Community-Acquired Pneumonia (CAP) and Chronic Obstructive Pulmonary Disease (COPD) patients have shown that D-dimer level is higher in severe cases and can be used as a prognostic biomarker, and D-dimer > 1 μg/ml is one of the risk factors for mortality in adult inpatients with COVID-19 positive. However, the characteristic role of D-dimer in COVID-19 patients has not been fully investigated and confirmed. In this study, we showed D-dimer levels in patient groups stratified by clinical severities, imaging staging, in-hospital death, and assessed the role of D-dimer as a primary biomarker for disease severity and clinical out-come**.**[9]

UNDER PEER REVIEW

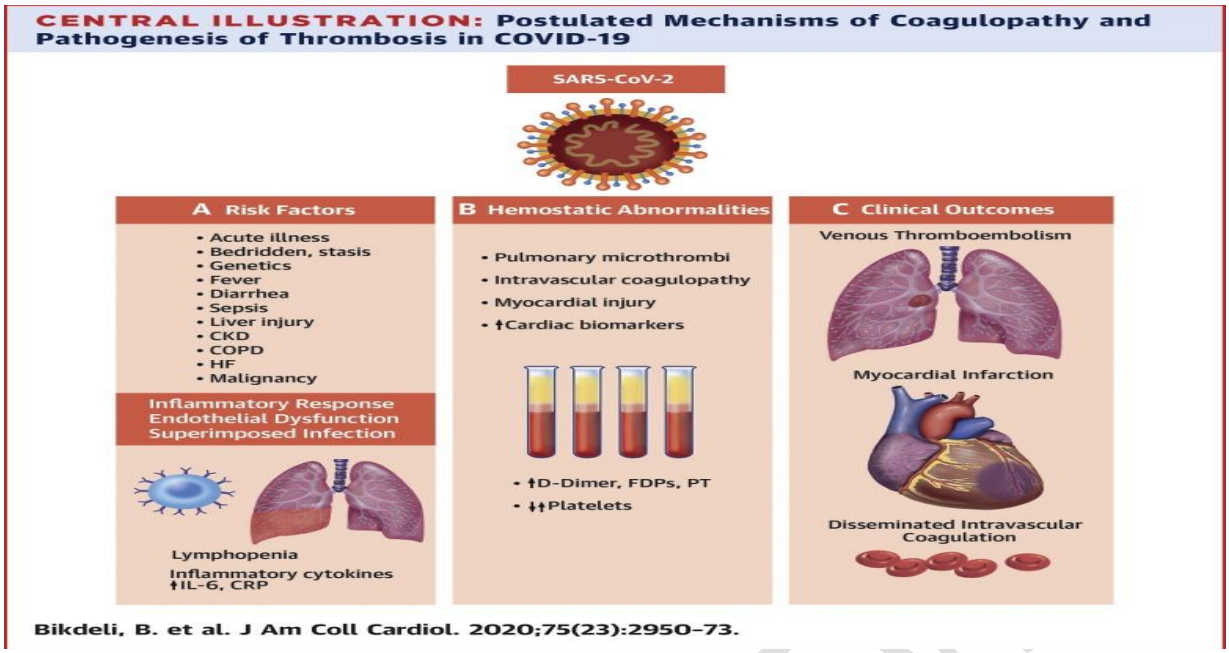

Figure 1: Postulated Mechanism of Coagulopathy and Pathogenesis of Thrombosis in COVID-19

The expansion in the value of D-dimer is the most companionate change in coagulation parameters in COVID-19 and preferably a greater risk for the evolution of thrombosis; nevertheless, D-dimer is a marker of fibrinolysis, and only a proxy for the ongoing thrombosis, and it is already known that its specificity for venous thromboembolism is low. Additionally, ago the D-dimer is well-known to be a mixture of fragments of different weight, and tests may report results in terms of weight for units of volume or as fibrinogen equivalent units (FEU). So, it may be not correct to compare results between different tests.[10]

Coagulation disorders and acute respiratory failure are the prevailing causes of death from COVID-19. Together with other parameters that compose the risk profile for severe COVID-19 evolution, the D-dimers dosing at admission proved to be extremely useful in the management of COVID-19.[11]

Management of Covid-19 is a challenging task although there is a different guidelines. In arterial thromboembolism D-dimer has a slight role, if any. Therefore, the basic use of heparin in the treatment of COVID-19 disease, should play an underlying role, and prophylactic doses of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) were accompanying with a reduced 28-day mortality in more severe COVID-19 patients.[12]

Additionally, in a retrospective cohort study conducted in 2 French centres[13], consecutive patients hospitalized in medical wards non-ICU with confirmed COVID-19 and adequate thromboprophylaxis were enrolled. D-dimers at baseline were crucially elevated in patients with deep venous thrombosis (DVT) ($P < 0.001$). The negative predictive value of a baseline D-dimer level <1.0 mg/ml was 90% for VTE and 98% for pulmonary embolism (PE). The positive predictive value for VTE was 44% and 67% for D-dimer level ≥1.0 mg/ml and ≥3 mg/ml, respectively. Expanded D-dimer concentrations of more than 1.0 mg/ml predict the risk of VTE. Furthermore, In another prospective study of 165 consecutive patients hospitalized in non-intensive care units with diagnosis of COVID- 19 pneumonia and D-dimer

UNDER PEER REV

>1000 ng/ml were screened for asymptomatic DVT with complete compression Doppler ultrasound and suggested D-dimer association as a marker of disease severity.[14]

Clinical studies found correlations between the severity of COVID-19 and its unfavourable evolution and the degree of liver damage.[15-16] Coagulation disorders and microthrombus formation are also responsible for some of the dermatological lesions in the COVID-19.[17-18] Another study of critically ill patients with COVID-19 showed dermatological manifestations of hypercoagulability such as significant ischemia of the limbs with plantar plaques and acral cyanosis.[19]

Coagulation disorders along with inflammatory mechanisms have also been implicated in the onset of neurological manifestations in COVID-19, such as cerebral haemorrhage or ischemia, cerebral venous thrombosis, demyelinating and neurodegenerative lesions, taste, smell and visual dysfunctioning and consciousness disorders.[20]

However, there are some early indications that hospital admissions are increasing in the northeast of the USA and China, where it is most prevalent. Rather than hoping for the end, letting our guard down, and thinking that the problem is somewhere else, everyone needs to remain alert; encourage maximum transparency in reporting cases, hospital admissions, and deaths; and accelerate collaborative surveillance of variant testing and vaccinations. The pandemic is far from over

MATERIAL AND METHODS

An retrospectively study was carried out in **2087 patients** of Parul Sevashram hospital during the period from March 2021 to July 2022 after obtaining an approval from Institutional Ethics Committee. The data's were collected in the Patient Profile Form (PPF) for complete duration of therapy, the analysis made from the data was reported in predesigned forms which includes information such as patient demographic details (BP, all vitals, weight, medical & medication history, physical examination etc.) and required laboratory information were performed and documented.
Univariable and multivariable logistic regression methods were used to explore risk factors associated with in-hospital mortality. Correlations of D-dimer upon admission with disease severity and in-hospital mortality were analyzed. Excel curve was used to determine the optimal cut off level for D-dimer that discriminated those survivors versus non-survivors during hospitalization.

- Observation was carried out to find out the scope of the study in the Parul Sevashram hospital
- Relevant literatures were reviewed.
- Data collection form was designed.
- Data of the patients was recorded in Patient Profile Form and analysed for the role of (Study title After Confirmation)

❖ **Study Criteria**

- **Inclusion criteria**
  1. Age about ≥16 years
  2. Subjects having confirm diagnosis of Covid-19 along with comorbid condition.
  3. Patients without microangioma
  4. Absence of ocular disease.

UNDER PEER REVIEW

- **Exclusion criteria**
  1. Pregnant, lactating women
  2. Mentally ill or other psychological subjects
  3. Subject who are on antineoplastic medication
  4. Other comorbid disease or condition which can interfere with study as per investigators discretion.
- **Biochemical estimations**

  Physical examination, all vitals, RBS, HbA1c, Hematology, D-dimer, CRP, Trop-I, Serum electrolyte, IL6 and lipid profile and echocardiography. Coagulation profile, renal and liver function, creatinine kinase, myocardial enzymes, C-reactive protein, and procalcitonin were collected routinely on admission.
- **Radiological estimation**

  HRCT and X-ray chest. Doppler ultrasound and CT pulmonary angiography were done for any patients with high clinical suspicion of pulmonary embolism/deep vein thrombosis (PE/ DVT). Chest CT scan was done for all inpatients.
- **Statistical analysis**

  The data was represented graphically in MS-Excel with median values.

RESULT

A total of 2087 patients of both gender were randomly selected after having positive RTPCR result. Our study result reveals that 65.78% (n= 1373/2087) were male and 34.21% (n= 714) were female. Median age was 52 years. D-dimer > 250 ng/mL at admission was the only variable associated with increased mortality [(95% CI), P = 0.025].

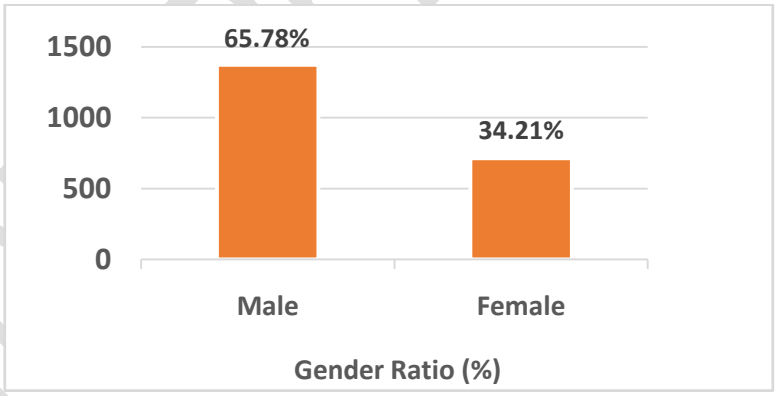

Figure 2: Gender Ratio Presentation

D-dimer elevation (≥250 ng/mL) was seen in 81.31% (n= 1697/2087) of the patients. Pulmonary embolism and deep vein thrombosis were ruled out in patients with higher probability of thrombosis. D-dimer levels significantly increased with increasing severity of COVID-19 as determined by clinical improvement (within 5 days) and chest CT staging (Out of 25 score, P = 0.000). In-hospital mortality rate was 15.28% (n= 319/2087). Median D-dimer level in non-survivors 15.29 % (n = 319) was significantly higher than in survivors 84.71% (n = 1768, RR 24.69%). Median elevated D-dimer level was 600.5 ng/ml, of > 250 ng/mL predicted in-hospital mortality with a sensitivity of 81.31% (95% CI).

UNDER PEER REVIEW

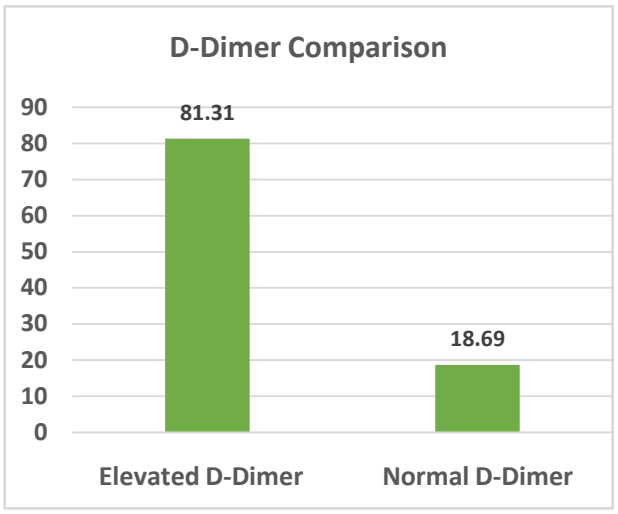

Figure 3: Comparison of D-Dimer

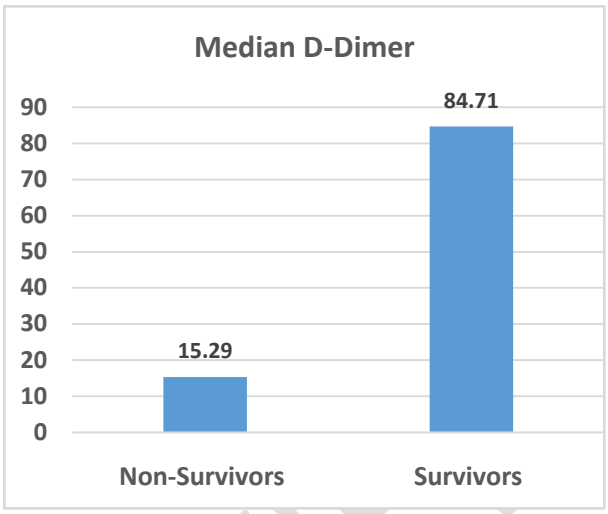

Figure 4: Survivor Vs Non- Survivors

DISCUSSION

D-dimer level is one of the measures used in patients to detect thrombosis. **Rostami M et al.** [1] reported an increase in D-dimer and fibrinogen concentrations in the early stages of COVID-19 disease a 3 to 4-fold rise in D-dimer levels is linked to poor prognosis. Similarly, **Yao Y et al.**[2] also concluded that D-dimer is commonly elevated in patients with COVID-19. D-dimer levels correlate with disease severity and are a reliable prognostic marker.

Few investigators, **I Martinelli et al., J S Barger et al** [21-22] have also concluded that the upregulated levels of D-dimer in individuals with severe novel coronavirus infection might be associated with severe illness, higher rates of thrombotic activity, and higher mortality rates of such patients and in hospital mortality

The novel coronavirus infection leads to helicases of the inflammatory pathways. According to the results of several previous studies, the abnormal enhancement in the levels of D-dimer under inflammatory conditions indicates that the helicases of inflammatory reactions and proinflammatory agents might be accompanying with the Anemia induction of the coagulatory pathways[23]. Hence, it follows that the coagulatory events in the COVID-19 patients might be activated by the helicases inflammatory reactions. Furthermore. The predicate was further strengthened by the findings of **Bilian Y et al.2020**[24] who delineate a significant correlation of the levels of D-dimer with the levels of hsCRP, a marker of inflammation, in COVID-19 patients. In another study, **Chen N et al 2020**[25] concluded that how the levels of D-dimer could imaginably be used as a marker to predict the in hospital mortality rate of COVID-19 patients. Based on their research & results, they were able to establish a cut-off D-dimer value of more than 2.14 mg/L to predict the outcome of COVID-19 patients at the time of admission to the hospital which was very similar to our study.

Currently, the COVID-19 patients are managed using pharmacological DVT prophylaxis treatment protocol. However, this management approach is not specified to COVID-19 patients.[26] Acutely ill or hospitalized COVID-19 patients, including those receiving critical care, were found to have peak rates of venous thromboembolism (VTE). In these patients, the best thromboprophylaxis strategy is still uncertain.[27]. Recently, the American Society of Hematology (ASH) guideline panel suggests using

UNDER PEER REVIEW

prophylactic-intensity over interpose vehemence or therapeutic intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE.[28]

As stated above, the levels of D-dimer straight correlate with the rate of formation and degradation of plasmin in the blood. Hence, any pathological condition that helicases the rate of plasmin generation and degradation would also expand the levels of D-dimer. Also few pathologies that promote chronic inflammation, such as rheumatoid arthritis, asthma, and cancer, also lead to an expansion in the levels of D-dimer. It follows that infection of a novel coronavirus, which leads to helicases inflammatory reactions among individuals, would also increase the levels of D-dimer. [29-30] It is perceptible by the findings of several previous studies that showed that levels of D-dimer were crucially higher in COVID-19 patients, especially those who were either severely ill or had deceased.

CONCLUSION

Our study concluded that D-dimer is commonly elevated in patients with COVID-19. D-dimer levels correlate with disease severity and are a definitive prognostic marker for in-hospital mortality in patients admitted for COVID-19 and accelerate more personalized and coherent clinical management that could significantly reduce the mortality rate of such patients and allow more rapid recovery with in minimum time period. D-dimer-based anticoagulant escalation may be associated with a lower risk of death in patients with severe SARS-CoV-2 infection. This study also concluded that there is a significant association between the high D-dimer level and severity of COVID-19 among comorbid patients.

LIMITATION

The only limitation of this study was a single centre study Indeed it needs multicentre study to evaluate the same. Our study used comorbid subject along with Covid-19 Infected patients that was probably interfere with D-dimer level reveals long standing inflammatory status, comorbid disease condition and other medical conditions in the human body which might interfere with the study result.

ABBREVIATION

CAP	Community-Acquired Pneumonia
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Corona Virus Disease-19
CRP	C-Reactive Protein
CT	Computerized Tomography
DVT	Deep Venous Thrombosis
FEU	Fibrinogen Equivalent Units
HbA1c	Haemoglobin A1c
HRCT	High Resolution Chest Tomography
ICU	Intensive Care Unit
LMWH	Low Molecular Weight Heparin
MERS	Middle East Respiratory Syndrome

UNDER PEER REVIEW

nCOV	Novel Corona Virus
PE	Pulmonary Embolism
PPF	Patient Profile Form
RBS	Random Blood Sugar
RTPCR	Real-Time Reverse Transcription – Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
UFH	Unfractionated Heparin
VTE	Venous Thromboembolism
WHO	Word Health Organization

DECLARATIONS

Ethical approval: Yes (Institutional Ethics Committee)

UNDER PEER REVIEW

REFERENCES

1. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert review of hematology. 2020 Nov 1;13(11):1265-75.
2. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, Chen X, Chen S, Yu K, Huang Z, Hu B. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. Journal of intensive care. 2020 Dec;8 (1):1-1.
3. Zhou P, Yang X, Wang X, Hu B, Zhang L, Zhang W, Si H, Zhu Y, Li B, Huang C, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579 (7798):270–3.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395 (10223):497–506.
5. Coronavirus disease (COVID-19) Situation Report-89 edition. who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---27-april-2022.
6. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---11-january-2023
7. Lancet 2022; 400: 1967–2006 and https://www.thelancet.com/ commission/healthy-ageing-inChina
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229):1054-62.
9. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, Chen X, Chen S, Yu K, Huang Z, Hu B. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. Journal of intensive care. 2020 Dec;8(1):1-1.
10. Righini M, Perrier A, De Moerloose P, Bounameaux H. D-dimer for venous thromboembolism diagnosis: 20 years later. J Thromb Haemost. 2008;6(7):1059-1071. doi:10.1111/j.1538-7836.2008. 02981.x.
11. Baroiu L, Lese AC, Stefanopol IA, Iancu A, Dumitru C, Ciubara AB, Bujoreanu FC, Baroiu N, Ciubara A, Nechifor A, Anghel L. The role of D-Dimers in the initial evaluation of COVID-19. Therapeutics and Clinical Risk Management. 2022;18:323.
12. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost.2020;18(5):1094-1099.
13. Artifoni M, Danic G, Gautier G, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. J Thromb Thrombolysis. 2020;50(1):211-216.
14. Demelo-Rodr´ıguez P, Cervilla-Mun˜oz E, Ordieres-Ortega L, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. Thromb Res. 2020;192:23-26.
15. Baroiu L, Dumitru C, Iancu A, et al. COVID-19 impact on the liver. World J Clin Cases. 2021;9(16):3814–3825. oi:10.12998/wjcc.v9.i16.3814

UNDER PEER REVIEW

16. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. 2020 Preprint. bioRxiv. 2020. doi:10.1101/2020.02.03.931766
17. Manalo IF, Smith MK, Cheeley J, Jacobs R. A dermatologic manifestation of COVID-19: transient livedo reticularis. J Am Acad Dermatol. 2020;83 (2):700. doi:10.1016/j.jaad.2020.04.018
18. Tatu AL, Nadasdy T, Bujoreanu FC. Inflammation and vascular injury as the basis of COVID-19 skin changes: preliminary analysis of 23 patients from the literature [Letter]. Clin Cosmet Investig Dermatol. 2021;14:185–186.
19. Al Samman M, Caggiula A, Ganguli S, Misak M, Pourmand A. Non-respiratory presentations of COVID-19, a clinical review. Am J Emerg Med. 2020;38(11):2444–2454. doi:10.1016/j.ajem.2020.09.054.
20. Singh V, Allawadhi P, Khurana A, Banothu AK, Bharani KK. Critical neurological features of COVID-19: role of imaging methods and biosensors for effective diagnosis. Sens Int. 2021;2:100098. doi:10.1016/j.sintl.2021.100098.
21. I. Martinelli, E. Ferrazzi, and A. Ciavarella, "Pulmonary embolism in a young pregnant woman with COVID-19," -rombosis Research, vol. 191, pp. 36-37, 2020.
22. J. S. Berger, D. Kunichoff, and S. Adhikari, "Prevalence and outcomes of D-dimer elevation in hospitalized patients with COVID-19," Arteriosclerosis, -rombosis, and Vascular Biology, vol. 40, pp. 2539–2547, 2020.
23. A. F. Shorr, S. J. ,omas, and S. A. Alkins, "D-dimer correlates with proinflammatory cytokine levels and outcomes in critically ill patients," Chest, vol. 121, pp. 1262–1268, 2002.
24. Y. Bilian, X. Li, and J. Chen, "Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis," Journal of -rombosis and -rombolysis, vol. 50, pp. 548–557, 2020.
25. N. Chen, M. Zhou, and X. Dong, "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study," Lancet, vol. 395, pp. 507–513, 2020.
26. Thrombosis UK, Practical Guidance for the Prevention of thrombosis and Management of Coagulopathy and Disseminated Intravascular Coagulation of Patients Infected with COVID-19, ,thrombosis UK, Llanwrda, UK, 2020.
27. J. F. Llitjos, M. Leclerc, and C. Chochois, "High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients," Journal of thrombosis and Haemostasis, vol. 18, no. 7, pp. 1743–1746, 2020.
28. A. Cuker, E. K. Tseng, and R. Nieuwlaat, "American society of hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19," Blood Advances, vol. 5, no. 3, pp. 872–888, 2021.
29. D. Wang, B. Hu, and C. Hu, "Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China," JAMA, vol. 323, pp. 1061–1069, 2020.
30. C. Huang, Y. Wang, and X. Li, "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China," Lancet, vol. 395, pp. 497–506, 2020.

UNDER PEER REVIEW