International Journal of Advances in Medicine
Singhvi SD et al. Int J Adv Med. 2020 Sep;7(9):1451-1455
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20203614

Review Article

D-dimer, a biomarker for detecting severity of SARS-CoV2: a systematic review

Shreyans D. Singhvi[1]*, Preksha T. Singh[1], Gautam Bhandari[1], Rafe M. Khan[2]

[1]Department of Medicine, Manidhari Hospital, Jodhpur, Rajasthan, India
[2]Department of Medicine, Sardar Vallabhbhai Institute of Medical Sciences and Research, Gujarat, Ahmedabad, India

Received: 23 June 2020
Accepted: 30 July 2020

***Correspondence:**
Dr. Shreyans D. Singhvi,
E-mail: shreyanssinghvi4@gmail.com

ABSTRACT

A global pandemic of the novel corona virus has impacted the world on severe terms. Not only it has raised an impact on the health care systems as well as the economic and mental health of individuals. SARS-CoV-2 (severe acute respiratory virus- corona virus 2), the outbreak is associated to have likely started as a zoonotic transmission with a seafood market, it has now become clear of the person to person transmission of it. Currently, the virus has been called a global pandemic and has infected 8.72 million people worldwide (dated 21st June 2020). Since, the pandemic has affected multiple countries, our aim of the study is to study d-dimer a biomarker, that may reflect severity of the cases affected by the virus. The search was done based on preferred reporting system for meta-analysis and systemic review (PRISMA) guideline. All the scientific database like Pubmed central, NIH, NCBI, embrase, mediline, Cochrane and google scholar were used to research articles with keywords: 'd-dimer, 'SARS-CoV2', 'severe cases'. All the published peer reviewed articles till date 17th June 2020 were studied. 9 articles were selected in the review and they depicted a higher value of d-dimer can be related to severity of the case of SARS-CoV2. Our study concludes that, for early severe case detection, an early detection of d-dimer levels can be done and treatment to reduce the value in the early cases may provide intervention to the prognosis of the disease. As, the number of cases leading to a severe case and requiring an ICU facility will decline, the mortality rate might drastically decline as well as earlier screening of a severe case of SARS-CoV-2 would help in faster intervention for the same.

Keywords: D-dimer, SARS-CoV2, Biomarker

INTRODUCTION

A global pandemic of the novel corona virus has impacted the world on severe terms. Not only it has raised an impact on the health care systems as well as the economic and mental health of individuals. SARS-CoV-2 (severe acute respiratory virus- corona virus 2), the outbreak is associated to have likely started as a zoonotic transmission with a seafood market, it has now become clear of the person to person transmission of it.[1] On the molecular level, SARS-CoV2 has been reported to attach to the ACE2 receptors. ACE2 has been identified as a functional receptor for coronaviruses, 2 including SARS-CoV and SARS-CoV-2. SARS-CoV-2 infection is triggered by binding of the spike protein of the virus to ACE2, which is highly expressed in the heart and lungs.[2] Reports suggest that the Middle East respiratory syndrome-related coronavirus (MERS-CoV) can cause acute myocarditis and heart failure.[3] SARS-CoV-2 and MERS-CoV have similar pathogenicity, and the myocardial damage caused by infection with these viruses undoubtedly increases the difficulty and complexity of patient treatment.[4]

The clinical features of SARS-CoV-2 infection appears to be wide, even causing asymptomatic infection, mild upper respiratory tract illness and severe viral pneumonia in Wuhan where it first started.[5] Huang et al, first

reported 41 cases of SARS-CoV-2 in which most patients had a history of exposure to Huanan seafood whole- sale market.[5] Patients' clinical manifestations included fever, nonproductive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia. Organ dysfunction (e.g., shock, acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury and even death can occur in severe cases.[5]

Currently, the virus has been called a global pandemic and has infected 8.72 million people worldwide (21st June 2020). Since, the pandemic has affected multiple countries, the aim of the study was to study d-dimer a biomarker, that may reflect severity of the cases affected by the virus.

REVIEW OF LITERATURE

Step 1: Identification and literature search

The search was done based on preferred reporting system for meta-analysis and systemic review (PRISMA) guideline. All the scientific database like Pubmed central, NIH, NCBI, embrase, mediline, Cochrane and google scholar were used to research articles with keywords: 'd-dimer, 'SARS-CoV2', 'severe cases'. All the published peer reviewed articles till date 17th June 2020 were studied.

Step 2: Criteria for selection of studies

All studies which were peer reviewed, cohort studies and retrospective studies related to the topic were only included. Reviews of other studies or meta-analysis were not included in the study.

Step 3: Inclusion and exclusion criteria for the studies

Inclusion criteria

Studies which had both severe cases and mild cases of SARS-CoV2 were selected and studies which had included d-dimer values along their p values in their study were included

Exclusion criteria

Studies which did not differentiate between severe and mild cases were not included. Studies which did not report d-dimer values along their p values were not included in the study.

Step 4: Data extraction

Data was extracted and studied of the selected studies.

Authors included multiple studies in the systematic review. These studies included retrospective. Cohort as well as case series. Multiple studies depicted p values <0.01 and were associated with 99% confidence interval, while few had p values <0.05 and were associated with 95% confidence interval, while one study had a p value of 0.07 with no association found (Table 1).

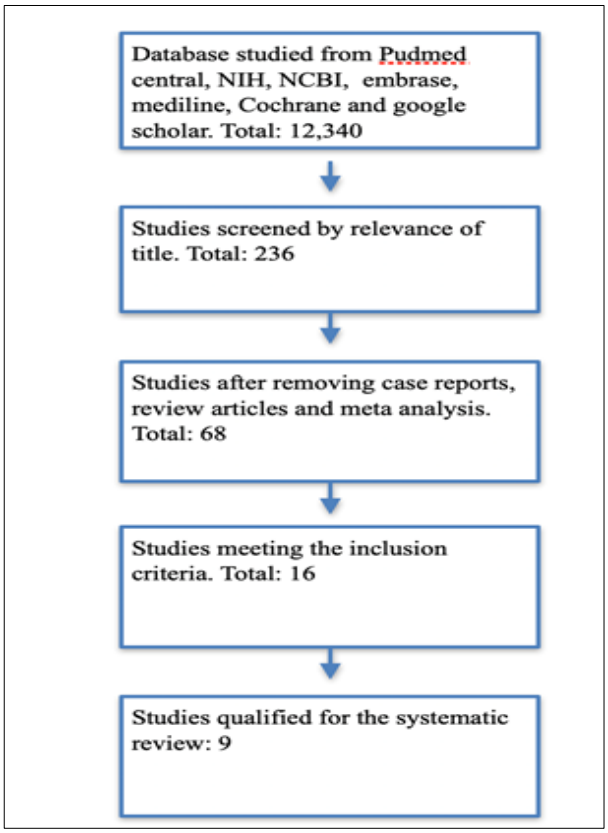

Figure 1: PRISMA flow diagram of included articles

DISCUSSION

Human SARS-CoV-2 is one of the main pathogens of respiratory infection.15 Most patients experience mild symptoms and a good prognosis but some patients with SARS-CoV-2 develop severe pneumonia, pulmonary edema, ARDS, or multiple organ failure and even die. Patients with severe illness developed ARDS and required ICU admission and oxygen therapy. So far, no specific treatment has been recommended for SARS-CoV-2 infection except for meticulous supportive care.[15]

In this study, authors did a systematic review of d-dimer a biomarker for detecting the severity of SARS-CoV-2 infection. Authors found 9 studies and in most of the studies, it was seen that severe cases of patients requiring ICU facilities and having increase risk of getting pulmonary emboli and even death had higher d-dimer values. In some studies, a threshold value of 2.0 g/ml, while some studies used a threshold of 0.5 μg/ml.

Table 1: Studies included in the review, their description, d-dimer values found in the study and their p values.

Study	Study description	d-dimer values	P value
Huang et al[5]	In the study, all patients with suspected 2019-nCoV(n=41) were admitted to a designated hospital in Wuhan. We prospectively collected and analysed data on patients with laboratory-confirmed 2019-nCoV infection by real-time RT-PCR and next-generation sequencing. Data were obtained with standardised data collection forms shared by the International Severe Acute Respiratory and Emerging Infection Consortium from electronic medical records. Researchers also directly communicated with patients or their families to ascertain epidemiological and symptom data. Outcomes were also compared between patients who had been admitted to the intensive care unit (ICU) and those who had not. [5]	In the patients admitted to the ICU, the d-dimer values were- 2.4 (0.6-14.4) mg/l and in patients not admitted in ICU were 0.5 (0.3-0.8) mg/l	0·0042
Giamarellos-Bourboulis et al[6]	The researchers studied the baseline clinical and laboratory characteristics of the cohorts of bacterial community acquired pneumonia (CAP) and of pneumonia caused by SARS-CoV-2. The study assessed the differences of immune activation and dysregulation between SARS-CoV-2 and other known severe infections in three patient cohorts: 104 patients with sepsis caused by bacterial CAP; 21 historical patients with 2009 H1N1 influenza; and 54 patients with community acquired pneumonia (CAP) caused by SARS-CoV-2. [6]	In patients of SARS-CoV 2, patients who had respiratory failure (n=26), had d-dimer values of 2.76±2.02 g/dl and patients who did not have respiratory failure had d-dimer values of 5.43±6.41 g/dl	<0.0001
Leonard-lorant et al[7]	The third study selected was by Leonard-lorant et al, [7] The study demonstrated 106 pulmonary CT angiograms of COVID-19 patients over a one-month period in a tertiary care centre. They reported higher d-dimer values in patients with pulmonary embolism. In these patients with COVID-19 infection, D-dimer greater than 2660 µg/L had a sensitivity of 32/32 (100%, 95%CI 88-100) and a specificity of 49/74 (67%, 95% CI 52-79) for pulmonary embolism on CT angiography[7]	In patients with pulmonary emboli present(n=32) the d-dimer values were- 15385±14410 µg/l and in patients with absent pulmonary emboli, the d-dimer values were- 1940±30160 µg/l	0.001
Zhang et al[8]	The study included a total of 343 eligible patients in the study. The optimum cutoff value of D-dimer to predict in-hospital mortality was 2.0 µg/ml with a sensitivity of 92.3% and a specificity of 83.3%. According to the study, among routine laboratory tests, D-dimer has the highest C-index to predict in-hospital mortality in Covid-19 patients[8]	In patients with d-dimer values <2.0 µg/ml (n=276) there was 1 non survivor with d-dimer values as 0.41 (0.15, 0.69) µg/ml while in patients with d-dimer values (n=67), there were 12 non survivors with d-dimer values as 4.76 (2.99, 11.9) µg/ml	<0.001
Gao et al[9]	The study investigated 43 adult patients with COVID-19. The patients were classified into mild group (28 patients) and severe group (15 patients). A comparison of the hematological parameters between the mild and severe groups showed significant differences in interleukin-6 (IL-6), d -dimer (d -D), glucose, thrombin time, fibrinogen, and C-reactive protein (P<0.05). The optimal threshold and area under the receiver operator characteristic curve (ROC) of d -D were 0.28 and 0.750 µg/L, respectively[9]	The d-dimer values for patients in the severe group (n=15) were 0.49 (0.29,0.91) µg/l and for patients in the mild group (n=28) were 0.21(0.91,0.27) µg/l	0.07
Tang et al[10]	Consecutive patients with confirmed SARS-CoV-2 admitted to Tongji Hospital of Huazhong University of Science and Technology in Wuhan from January 1 to February 3, 2020, were enrolled (n=183). Complete clinical information and the laboratory data required for this study. All patients received antiviral and supportive therapies after diagnosis. By the end of February 13, 78 (42.6%) patients had been discharged and 21 (11.5%) patients had died, the rest 84 (45.9%) patients remains hospitalized in stable condition. The coagulation parameters on admission between survivors and non-survivors were compared[10]	In survivor patients (n=162) the d-dimer values were- 0.61 (0.35, 1.29) µg/mL. In non-survivor patients (n=21), the d-dimer values were- 2.12 (0.77-5.27) µg/ml	<0.001

Continued.

Study	Study description	d-dimer values	P value
Wang et al[11]	This study represented case series, (n=138) the data was extracted as medical records of patients and was analyzed by the research team of the Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University. Epidemiological, clinical, laboratory, and radiological characteristics and treatment and outcomes data were obtained with data collection forms from electronic medical records. The data were reviewed by a trained team of physicians. Information recorded included demographic data, medical history, exposure history, under- lying comorbidities, symptoms, signs, laboratory findings, chest computed tomographic (CT) scans, and treatment measures[11]	In patients admitted to the ICU (n=36), the d-dimer values were 414(191-1324 mg/l and in patients not admitted in ICU were 166(101-285) mg/l.	<0.01
Chaomin et al[12]	This is a retrospective cohort study of 201 patients aged 21 to 83 years with confirmed COVID-19 pneumonia hospitalized at Jinyintan Hospital in Wuhan, China. All patients were diagnosed with COVID-19 pneumonia according to World Health Organization interim guidance.6 According to hospital data, patients were admitted from December 25, 2019, to January 26, 2020. The majority of the clinical data used in this study was collected from the first day of hospital admission unless indicated otherwise.[12]	In patients with Acute respiratory distress syndrome(ARDS)(n=84) the d-dimer values were-0.52(0.33-0.93), in these patients the surviving patients (n=40) had-0.49(0.31,1.18) and non surviving (n=44) the values were- 3.95 (1.15,10.96), while those without ARDS- the values were - 1.16 (0.46, 5.73).	<0.01
Zhou et al[13]	In this retrospective, multicentre cohort study, we included all adult inpatients (≥18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or had died by Jan 31, 2020. Demographic, clinical, treatment, and laboratory data, including serial samples for viral RNA detection, were extracted from electronic medical records and compared between survivors and non-survivors. The researchers used univariable and multivariable logistic regression methods to explore the risk factors associated with in-hospital death[13]	In the non-survivor group of patients (n=54), the values were 5·2 (1.5-21.1) µg/ml, while in surviving group of patients the values were- 0.6 (0.3-1.0) µg/ml.	<0.0001

This study concludes that, for early severe case detection, an early detection of d-dimer levels can be done and treatment to reduce the value in the early cases may provide intervention to the prognosis of the disease. As, the number of cases leading to a severe case and requiring an ICU facility will decline, the mortality rate might drastically decline as well as earlier screening of a severe case of SARS-CoV-2 would help in faster intervention for the same.

This study did not show any results of interventions for the same biomarker, there is still paucity of data in that field and further extensive research may help in forming a basis for the same.

ACKNOWLEDGEMENTS

Authors would like to thank all the researchers in the review and the active work that has been going on for SARS-CoV2.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382:1199-207.
2. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci. 2004;25:291-4.
3. Alhogbani T. Acute myocarditis associated with novel middle east respiratory syndrome coronavirus. Ann. Saudi Med. 2016;36:78-80.
4. Zheng Y, Ma Y, Zhang J, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020;17:259-60.
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
6. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020;27:1-9.

7. Leonard-Lorant I, Delabranche X, Severac F, Helms J, Pauzet C, Collange O, et al. Acute pulmonary embolism in COVID-19 patients on CT angiography and relationship to D-dimer levels. Radiol. 2020:201561.
8. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thrombo Haemo. 2020;18(6):1324-9.
9. Gao, Y, Li, T, Han, M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020;92:791-6.
10. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thrombo Haemos. 2020;18(4):844-7.
11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
12. Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;1:E1-E10.
13. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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(0229):1054-62.
14. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.
15. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523-34.

Cite this article as: Singhvi SD, Singh PT, Bhandari G, Khan RM. D-dimer, a biomarker for detecting severity of SARS-CoV2: a systematic review. Int J Adv Med 2020;7:1451-5.