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The association of D-dimers with mortality, intensive care unit admission or acute respiratory distress syndrome in patients hospitalized with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis

Agam Bansal, MD[a,*], Achintya D. Singh, MD[a], Vardhmaan Jain, MD[a], Manik Aggarwal, MD[a], Samiksha Gupta, MD[b], Rana Prathap Padappayil, MD[c], Mahum Nadeem, MD[b], Sonya Joshi, MD[a], Agrima Mian, MD[a], Tyler Greathouse, DO[a], David Wells, DO[a], Mohak Gupta, MD[d], Muhammad Zarrar Khan, MD[a]

[a] Internal Medicine, Cleveland Clinic Foundation, India
[b] Internal Medicine, University of Oklahoma, USA
[c] Internal Medicine, Brigham and Women's hospital, USA
[d] Internal Medicine, All India Institute of Medical Sciences (AIIMS) New Delhi, India

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ABSTRACT

Aim: To determine if D-dimers are elevated in individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who have adverse clinical outcomes including all-cause mortality, intensive care unit (ICU) admission or acute respiratory distress syndrome (ARDS).
Methods: We conducted a systematic review and meta-analysis of the published literature in PubMed, Embase and Cochrane databases through April 9, 2020 for studies evaluating D-dimer levels in SARS-COV-2 infected patients with and without a composite clinical endpoint, defined as the presence of all-cause of mortality, Intensive care unit (ICU) admission or acute respiratory distress syndrome (ARDS). A total of six studies were included in the meta-analysis.
Results: D-dimers were significantly increased in patients with the composite clinical end point than in those without (SMD, 1.67 ug/ml (95% CI, 0.72-2.62 ug/ml). The SMD of the studies (Tang et al, Zhou et al, Chen et al), which used only mortality as an outcome measure was 2.5 ug/mL (95% CI, 0.62-4.41 ug/ml).
Conclusion: We conclude that SARS-CoV-2 infected patients with elevated D-dimers have worse clinical outcomes (all-cause mortality, ICU admission or ARDS) and thus measurement of D-dimers can guide in clinical decision making.

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Introduction

The 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) first identified in Wuhan district in China has spread rapidly to more than 177 countries and was declared as a global pandemic on March 11th, 2020.[1] As of March 28th, there were 640,589 confirmed cases and 29,848 deaths globally.[2] In up to 5% of infected patients, the disease may manifest as hypoxic respiratory failure, multi organ dysfunction or shock and around 2.5% patients die from the infection.[3] Laboratory predictors of clinical deterioration can aid in escalating the care of the patients with this infection and assist in appropriate triaging and resource utilization. Studies have reported an association of D-dimer >1 ug/ml with increased mortality in patients with COVID 19 infection.[4] We systematically reviewed the current scientific literature to understand whether D-dimer is associated with an increased risk of all-cause mortality, Intensive care unit (ICU) admission or acute respiratory distress syndrome (ARDS) in patients hospitalized with SARS-CoV-2 infection.

Methods

Literature search

We carried out an electronic search in Medline (PubMed), Embase, and Cochrane database using the keywords "D-dimer" AND

* Corresponding author at: Internal Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave Cleveland Clinic, 44195, India
E-mail addresses: agambansal7@gmail.com (A. Bansal), aggarwm@ccf.org (M. Aggarwal), mnadeem@ouhsc.edu (M. Nadeem), joshis@ccf.org (S. Joshi), miana@ccf.org (A. Mian), Greatht3@ccf.org (T. Greathouse), weellsd@ccf.org (D. Wells).

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"Coronavirus 2019" OR "COVID 19" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" between 2019 and current date (9th April, 2020). Only the articles published in peer-reviewed journals were included in the analysis. Articles were limited to English language publications.

Selection of studies

We applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) to the methods for this study[5] (Fig. 1). After duplications were removed, the title and abstracts were independently screened by two reviewers (AB and VJ). The studies reporting the mean or the median D-dimer values in COVID 19 patients with and without a composite end point defined as all-cause mortality, ICU admission or ARDS were included in the study. All-cause mortality was analyzed as a separate outcome in addition to the composite end-point. We excluded case reports, studies involving pediatric patient population and those not reporting the above-mentioned composite end points. We cross-referenced the research papers to identify additional studies meeting the inclusion criteria. Full texts of the included studies were then reviewed by two independent reviewers (AB and VJ) and data was extracted. Any conflicts were settled by a third author (ADS).

Data extraction and study quality appraisal

The following data variables were collected: author name, year published, country where the study was performed, type of study, number of patients, composite end point definition, and mean D-dimer values in patients with and without outcome of interest (all-cause mortality, ICU admission and ARDS).

Two authors (AB and VJ) independently assessed the risk of bias in the included studies using the validated Newcastle-Ottawa Scale.

Statistical analysis

The meta-analysis was conducted with the calculation of standardized mean difference (SMD) and 95% confidence interval (95% CI) of D-dimers in coronavirus 2019 patients with and without a composite clinical end point. D-dimers were entered as a continuous variable. The mean and the standard deviation were extrapolated from the sample size, median and interquartile range (Q1-Q3) as per Hozo et al.[6] I^2 statistic was used to assess the heterogeneity between studies with values 0–30%, more than 30–60%, and more than 60% corresponding to low, moderate, and high degree of heterogeneity, respectively. DerSimonian and Laird random effects model was used for pooling the studies. The statistical analysis was performed using Stata 12 software (Stata Corp, College Station, Texas).

Results

Our systematic electronic search resulted in 21 publications after the initial screening of titles and abstracts. Subsequently, 16 studies were excluded, yielding 5 studies that met the inclusion criteria for systematic review. Cross-referencing of full-text articles resulted in 1 additional study. Therefore, 6 studies were included in the final meta-analysis for association of mean/median D-dimer values with all-cause mortality, ICU admission or ARDS. Table 1 elucidates the baseline characteristics and outcomes of the included studies.

There were a total of 1329 patients with 434 (32.65%) patients having a composite clinical end point. The composite end point was defined as defined as mortality in 3 studies,[4,8,10] ICU admission in 2

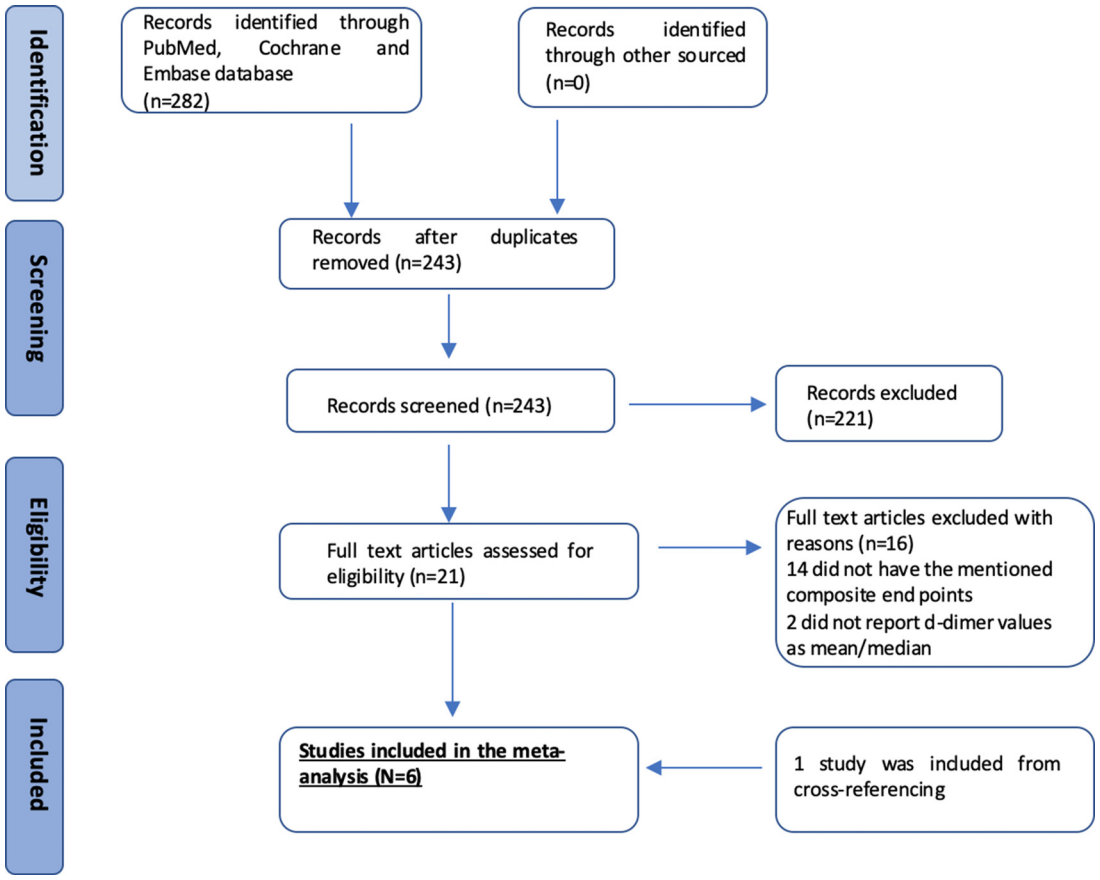

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses statement (PRISMA) flow chart for this study

Table 1
Characteristics of the studies (n=6) included in the meta-analysis

Study	Zhou et al	Chen et al	Tang et al	Wang et al	Huang et al	Wu et al
Study year	2020	2020	2020	2020	2020	2020
Study location	Wuhan, China	Wuhan, China	Wuhan, China	Wuhan, China	Wuhan, China	Wuhan, China
Study type	Retrospective cohort	Retrospective cohort	Cross-sectional study	Retrospective cohort	Prospective Cohort	Retrospective Cohort
Sample size	191 (Cases 54, Controls 137)	274 (Cases 113, Controls 161)	183 (Cases 21, Controls 162)	138 (Cases 36, controls 102)	41 (Cases 13, Controls 28)	201 (Cases 84, Controls 117)
Median age	56 (46-67)	62 (44-70)	54 (44-62)	56 (42-68)	49 (41-58)	51 (43-60)
Female	72 (38%)	103(38%)	85 (46.44%)	63 (45.7%)	11 (27%)	73 (36.3%)
Composite end point	All-cause mortality (in-hospital)	All-cause mortality (in-hospital)	All-cause mortality (in-hospital)	ICU admission	ICU admission	ARDS (WHO definition)
Median D-dimer level, case and control	Cases- 5.2 (1.5-21.1) Controls- 0.6 (0.3-1.0)	Cases- 4.6 (1.3-21.0) Controls- 0.6 (0.3-1.3)	Cases- 2.12 (0.77-5.27) Controls- 0.61 (0.35-1.29)	Cases- 4.14 (1.91-13.24) Controls- 1.66 (1.01-2.85)	Cases- 2.4 (0.6-14.4) Controls- 0.5 (0.3-0.8)	Cases- 1.16 (0.46-5.37) Controls- 0.52 (0.21-0.94)

studies[7,11] and onset of ARDS in another study.[9] Zhou et al[4] showed the clinical and laboratory data of 191 hospitalized patients and observed that D-dimer levels were about 8-9 times higher in patients who died (median D-dimer 5.2 ug/ml, IQR:1.5-21.1 ug/ml) than those who survived (median D-dimer 0.6 ug/ml, IQR 0.3-1.0 ug/ml). Similarly, Chen et al[10] also observed an approximate seven-fold increase in D-dimer values in patients who had in-hospital all-cause mortality (median 4.6 ug/ml, IQR: 1.3-21.0 ug/ml) compared to patients who did not have the outcome (median 0.6 ug/ml, IQR: 0.3-1.3 ug/ml). Tang et al[8] showed a 3-4 times greater levels of D-dimer levels in patients who had in-hospital mortality compared to those who did not. Wang et al and Huang et al[7,11] showed that D-dimers were significantly elevated in patients who required ICU admission. Furthermore, D-dimers were also significantly higher in patients having ARDS during the admission than those not having the outcome.[9]

The standardized mean difference (SMD) for the six studies is summarized in Fig. 2. The values of D-dimer were found to be significantly increased in patients with the composite clinical end point than in those without (SMD, 1.67 ug/ml (95% CI, 0.72-2.62 ug/ml). The SMD of the studies (Tang et al,[8] Zhou et al,[4] Chen et al[10]), which used only mortality as an outcome measure was 2.5 ug/mL (95% CI, 0.62-4.41). The heterogeneity of the studies was found to be relatively high (i.e. I^2 statistic 98%).

There were two additional studies which reported higher d-dimer levels in patients with worse outcomes. However, they were not included in our meta-analysis as they did not report the median/mean D-dimer levels. Zhang et al[12] described the characteristics of 95 patients and found that out of the 25 patients having an outcome (ICU admission, mechanical ventilation or death), 23 (92%) had D-dimer values $\geq$ 1 ug/ml. Similarly, another study[13] showed around 70% of the patients with worse outcome (death, mechanical ventilation or ICU admission) having D-dimers $\geq$ 0.5 ug/ml.

Discussion

We performed a systematic review and meta-analysis of studies to assess whether the D-dimer levels were associated with a composite end point defined as the presence of all-cause mortality, ICU admission or ARDS in patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We found that 1) D-dimers were significantly elevated in patients having a composite end point compared to those not having the outcome, 2) the level of D-dimers was higher in studies having mortality as an outcome in comparison to other end-points.

There are several plausible reasons for elevated D-dimer over the normal value of $<$ 0.5 ug/ml in patients hospitalized with SARS-CoV-

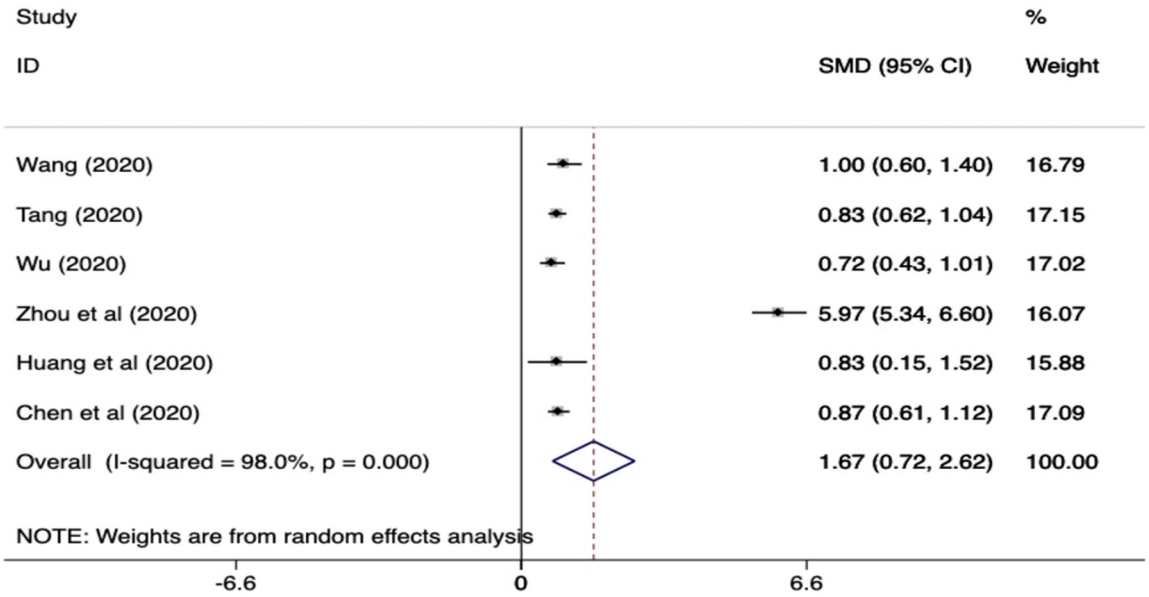

Fig. 2. Standardized mean difference (SMD) and 95% confidence interval (CI) for predicting composite clinical end point (ARDS, ICU admission and mortality) in patients with COVID 19 infection

2 infection having worse clinical outcomes. First, patients with severe SARS-CoV-2 infection can have disseminated intravascular coagulation (DIC) secondary to sepsis. Severe acute lung injury or ARDS by itself has also been associated with increased incidence of DIC. Tang et al[8] mentioned in their study that the vast majority of patients who died during admission fulfilled the criteria for DIC (71.6% vs 0.6% in survivors). Second, prior studies have shown that severe acute respiratory infection can cause injury to the endothelial cells and increase the levels of hemostatic factors such as d-dimers and vWF.[14] Third, respiratory infections have been associated with deep vein thrombosis and pulmonary embolism. Wang et al[15] postulated about the possible formation of pulmonary microthrombus in patients infected with H1N1 infection and a consequent elevation in D-dimer. There have been 2 cases reported of pulmonary embolism in SARS-CoV-2 infected patients.[16] Fourth, the SARS-CoV-2 infected patients with critical form of the disease are more likely to have additional complications including acute kidney injury, acute cardiac injury, congestive heart failure, all of which can cause increase the levels of D-dimers. Finally, the elderly patients are at an increased risk of having worse clinical outcomes from SARS-CoV-2 infection and D-dimer levels are higher in elderly patient population.[17]

In severe cases of SARS-CoV-2 infection, there is an uncontrolled release of pro-inflammatory cytokines (IL-2, IL-6, IL-8, IL-17, and TNF-a) which lead to upregulation of tissue factor expression on the endothelial cells, resulting in an increased pro-coagulant state. There is increasing evidence that SARS-CoV-2 infection is associated with increased risk of venous thromboembolism (VTE) and in-situ microvascular thrombosis which has been linked to worse clinical outcomes.[18]

The major limitation of the studies included was lack of information on the timing of the D-dimer measurements relative to admission. In addition, there was a significant heterogeneity in the reported results. This was likely due to differences in study size, selection bias, and different stages at which the D-dimer values were measured. Also, since all the studies included have been performed in China, the external validity is lacking.

The results of this concise meta-analysis suggest that D-dimer is significantly increased in patients having a worse clinical outcome (all-cause mortality, ICU admission or ARDS). Further studies are required to assess if the serial measurement of D-dimer plays any role in predicting evolution towards a more critical form of disease. Finding a threshold D-dimer level, above which SARS-CoV-2 infected patients are at an increased risk of having worse clinical outcomes can assist in following a proactive approach and aid in clinical decision making. Also, it will be imperative to know if anticoagulation therapies are of use in patients with severe SARS-CoV-2 infection.

Declaration of Competing Interest

There were NO conflicts of interest

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None

References

1. World Health Organization. *The Coronavirus Disease 2019 (COVID-19):Situation report-36*. WHO; 2020.
2. Johns Hopkins University & Medicine. Coronavirus resource center. Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU).
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA*. 2020 Feb 24.
4. 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(28 (10229)):1054–1062.
5. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, Atkins D, Barbour V, Barrowman N, Berlin JA, Clark J, Clarke M, Cook D, D'Amico R, Deeks JJ, Devereaux PJ, Dickersin K, Egger M, Ernst E, Gøtzsche PC, Grimshaw J, Guyatt G, Higgins J, Ioannidis JPA, Kleijnen J, Lang T, Magrini N, McNamee D, Moja L, Mulrow C, Napoli M, Oxman A, Pham B, Rennie D, Sampson M, Schulz KF, Shekelle PG, Tovey D, Tugwell P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009.
6. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5(Apr 20):13.
7. 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(Mar 17 (11)):1061.
8. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(Apr (4)):844–847.
9. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, 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(Mar 13).
10. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020 (Mar 26). m1091.
11. 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. *The Lancet*. 2020;395(Feb (10223)):497–506.
12. Zhang G, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. *Respir Res*. 2020;21(Mar 26(1)):74.
13. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020(Feb 28).
14. van Wissen M, Keller TT, van Gorp ECM, Gerdes VEA, Meijers JCM, van Doornum GJJ, et al. Acute respiratory tract infection leads to procoagulant changes in human subjects. *J Thromb Haemost*. 2011;9(Jul (7)):1432–1434.
15. Wang ZF, Su F, Lin XJ, Dai B, Kong LF, Zhao HW, et al. Serum D-dimer changes and prognostic implication in 2009 novel influenza A(H1N1). *Thromb Res*. 2011;127 (Mar (3)):198–201.
16. Xie Y, Wang X, Yang P, Zhang S. COVID-19 complicated by acute pulmonary embolism. *Radiol: Cardiothorac Image*. 2020;2:(Apr 1(2)) e200067.
17. Tita-Nwa F, Bos A, Adjei A, Ershler WB, Longo DL, Ferrucci L. Correlates of D-dimer in older persons. *Age Clin Exp Res*. 2010;22(Feb (1)):20–23.
18. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020;135(23):2033–2040. 04.