D-dimer levels and COVID-19 severity: Systematic Review and Meta-Analysis

KLİNİK ÇALIŞMA
RESEARCH ARTICLE

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ABSTRACT

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Introduction: *Coronavirus disease 2019 (COVID-19) is a fatal and pandemic disease discovered in December 2019 in Wuhan, with lots of asymptomatic cases and a long incubation period. The researchers suggested that high d-dimer levels could predict disease severity, lung complications, and thromboembolic events before they occur.*

Materials and Methods: *We searched in PubMed, Scopus, and Web of Science using the keywords "D-dimer" and "coronavirus" or "D-dimer" and "COVID-19." We used Standardized Mean Differences (SMD) to build forest plots of continuous data and assess differences in serum D-dimer concentrations between severe and non-severe patients with COVID-19 disease. We evaluated p-value < 0.05 as statistically significant and preferred 95% confidence intervals (CIs).*

Results: *The pooled results of all studies revealed that the D-dimer concentrations were significantly higher in patients with more severe COVID-19 (SMD: 2.32 µg/mL; 95% CI, 0.72 3.92 µg/mL, p< 0.001). We evaluated severe patients with total D-dimer levels. D-dimer concentrations were significantly higher in severe patients against total COVID-19 patients (SMD: 2.01 µg/mL; 95% CI, 0.25 to 3.77 µg/mL, p= 0.08).*

Conclusion: *We do not know the D-dimer increment mechanism in severe patients yet, but we think that these findings will be useful in the early diagnosis of severe disease and the first treatment.*

Key words: *D-dimer; COVID-19; thrombus; fibrin*

ÖZ

D-dimer seviyeleri ve COVID-19 şiddeti: Sistematik Derleme ve Metaanaliz

Giriş: *Koronavirüs hastalığı 2019 (COVID-19), Aralık 2019'da Wuhan'da keşfedilen, çok sayıda asemptomatik vaka ve uzun bir kuluçka dönemi ile ölümcül ve pandemik bir hastalıktır. Araştırmacılar, yüksek D-dimer seviyelerinin hastalık şiddetini, akciğer komplikasyonlarını ve tromboembolik olayları ortaya çıkmadan önce tahmin edebileceğini öne sürdü.*

Materyal ve Metod: *PubMed, Scopus ve Web of Science'ta "D-dimer" ve "koronavirüs" veya "D-dimer" ve "COVID-19" anahtar kelimelerini kullanarak arama yaptık. Sürekli verilerin forest plot analizi ve COVID-19 enfeksiyonlu, şiddetli ve şiddetli olmayan hastalar arasındaki serum D-dimer konsantrasyonlarındaki farklılıkları değerlendirmek için Standart Ortalama Farklılıkları (SMD) kullandık. P değerini <0.05 istatistiksel olarak anlamlı olarak değerlendirdik ve %95 güven aralıklarını (CI) tercih ettik.*

Bulgular: *Tüm çalışmaların havuzlanmış sonuçları, daha şiddetli COVID-19 hastalarında D-dimer konsantrasyonlarının önemli ölçüde daha yüksek olduğunu ortaya çıkarmıştır (SMD: 2.32 µg/mL;%95 CI, 0.72 3.92 µg/mL, p< 0.001). D-dimer konsantrasyonları, şiddetli hastalarda tüm COVID-19 hastalarına göre anlamlı olarak daha yüksekti (SMD: 2.01 µg/mL; %95 CI, 0.25 ila 3.77 µg/mL, p= 0.08).*

Sonuç: *Şiddetli hastalarda D-dimer artış mekanizmasını henüz bilmiyoruz ancak bu bulguların ağır hastalığın erken teşhisinde ve ilk tedavide faydalı olacağını düşünüyoruz.*

Anahtar kelimeler: *D-dimer; COVID-19; trombüs; fibrin*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is the newest infectious disease generated from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Scientists discovered COVID-19 in December 2019 in Wuhan, Hubei, China, and now it became pandemic. As of September 27, 2020, we have more than 32.7 million cases across 188 countries, with more than 992.000 deaths (1,2). Common symptoms are fever, cough, fatigue, shortness of breath, and loss of smell and taste. Although most people have mild symptoms, some could develop acute respiratory distress syndrome (ARDS) caused by cytokine storms, multi-organ failure, septic shock, and blood clots. The known incubation period is two to fourteen days (3). Lots of asymptomatic cases and the long incubation period require us to understand more about the fatal disease. The growing incidence of COVID-19 has put a significant burden on health systems and countries' financial situation globally. Although we diagnose patients early, we find it difficult to get information about the prognosis at an early stage. Clinicians use numerous biochemical and radiological tests at this stage.

COVID-19 causes serious thromboembolic complications in severe patients with the effect of the cytokine storm (4). Scientists found thrombi, endothelial damage, and fibrine in small pulmonary arteries in autopsies, and they discovered that disseminated intravascular coagulation (DIC) was the most critical coagulation abnormality (5). Nevertheless, we do not know if it is a direct effect of the SARS-CoV-2 virus or reflects the coagulation system's activation in response to the severity of the condition. D-dimer is a fibrin degradation product (FDP), releases into circulation when the blood clot dissolves via fibrinolysis (Figure 1). It has two D fragments of the fibrin protein attached by a cross-link (6). The researchers suggested that high D-dimer levels could predict disease severity, lung complications, and thromboembolic events before they even occur. In this way, they aimed to reduce the disease's morbidity and mortality with early diagnosis and treatment (7). However, there is no exact D-dimer value agreed to predict morbidity and mortality. Based on these studies, we conducted a review study on D-dimer levels suggested in the early recognition of patients whose clinical condition will deteriorate.

MATERIALS and METHODS

We searched in PubMed, Scopus, and Web of Science using the keywords "D-dimer" AND "coronavirus" or "D-dimer" and "COVID-19." The inclusion criteria were: (a) serum D-dimer concentrations in COVID-19 patients, (b) articles dividing COVID-19 patients into disease severeness, (c) studies approved by an ethical committee, and (d) articles published from January 1, 2020, to the date of the electronic search (September 27, 2020). (e) English written articles only. We excluded case reports and studies involving the pediatric patient population. Independent investigators evaluated titles, abstracts, and full texts. While patients hospitalized in the service or intensive care unit, those with oxygen saturation below 90%, those with lung involvement more than 50% in CT were included in the severe group; the patients who remained out of
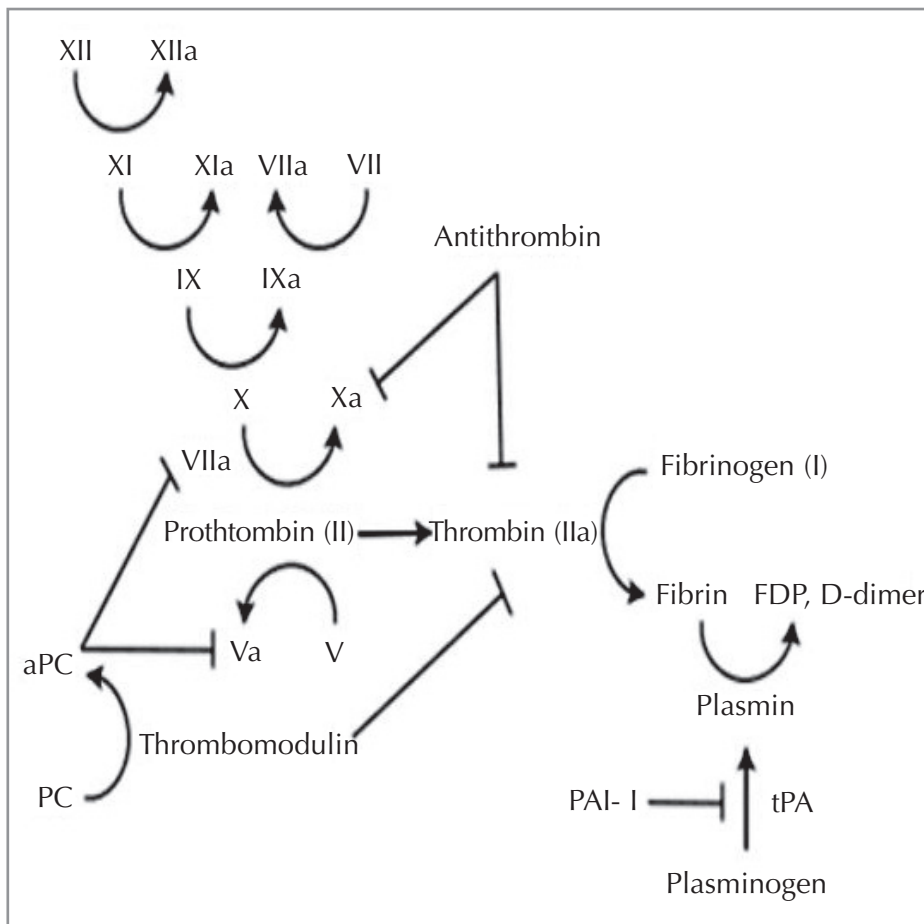
Figure 1. Coagulation and fibrinolysis cascade and D-dimer production. PC: Protein C, aPC: Activated protein C, FDP: Fibrin degradation products, PAI-1: Plasminogen activator inhibitor.

this and received outpatient diagnosis and treatment were included in the non-sever (milder) group. We used Standardized Mean Differences (SMD) to build forest plots of continuous data and assess differences in serum D-dimer concentrations between severe and non-severe patients with COVID-19 disease. We evaluated p-value < 0.05 as statistically significant and preferred 95% confidence intervals (CIs). We used Forest Plot analysis for D-dimer levels distribution of studies. As stated by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we prepared our meta-analysis. We evaluated the statistical analysis using Medcalc statistical software (MedCalc Software Ltd, Acacialaan 22, 8400 Ostend, Belgium).

RESULTS

We performed an electronic literature search, as shown in Figure 2. We conducted our search from 74 studies, chose the final 12, and included them in the meta-analysis (8-19); the total number of COVID-19 patients in these studies was 2801. Among them, 967 (34.5%) were affected by a severe form of COVID-19 (Table 1). The studies had no common point in determining the severity of the disease. Some studies focused on mortality, some clinical aggravation, other patients with complications.

The differences in serum D-dimer concentrations between COVID-19 patients with or without severe disease in the 12 studies are in Figure 3. In 11 studies, patients with severe COVID-19 displayed higher D-dimer serum concentrations than those with milder forms (mean difference range, 0.6-6.21 µg/mL) (8-19). However, there was no significant difference between D-dimer levels in other studies (9). The pooled results of all studies revealed that the D-dimer concentrations were significantly higher in patients
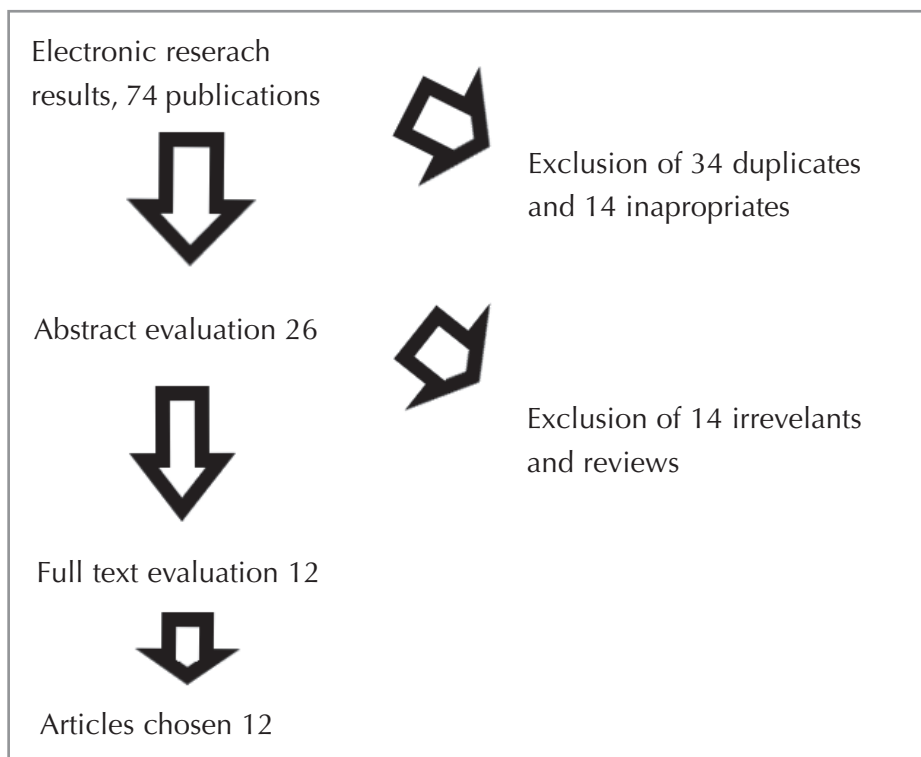
Figure 2. Electronic research diagram via Pubmed, Scopus, and Web of Science.

with more severe COVID-19 (SMD: 2.32 µg/mL; 95% CI, 0.72 to 3.92 µg/mL, p< 0.001). We evaluated severe patients with total D-dimer levels. D-dimer concentrations were significantly higher in severe patients against total COVID-19 patients (SMD: 2.01 µg/mL; 95% CI, 0.25 to 3.77 µg/mL, p= 0.08) (Figure 4). In meta-regression analysis, there was no correlation either between SMD and age (p= 0.61) or between SMD and gender (p= 0.39). Results from the forest-plot analysis in 7 studies, according to data, is in Figure 5.

DISCUSSION

The pathogenesis of COVID-19 is understood more and more over time, and the authors determined that the frequency of thrombotic attacks and the use of heparin to reduce mortality. The researchers reported various thromboembolic events in autopsy reports, histopathology series, and clinical cases. Based on these and coagulation markers, we can say that COVID-19 is a prothrombotic disease. According to Virchow's triad, scientists found vascular endothelium abnormalities, altered blood flow, and platelet dysfunction that lead to multiple various thromboses in COVID-19. Scientists thought that activation of the Renin-angiotensin-aldosterone system (RAAS), the increase of plasminogen activator inhibitor (PAI-1), and systematic immune response from activated platelets causes thrombogenesis in COVID-19 (20).

D-dimer and fibrinogen levels are higher in hospitalized COVID-19 patients. Contrasting classical DIC (Dissemine intravascular coagulation), prolongation of the aPTT, and or PT is minimal, the platelet count is low (platelet count ~100 x10^9/L), and lab results supporting microangiopathy are rare. Infrequently patients with severe COVID-19 infection and multiorgan failure progress to a coagulopathy meeting criteria for overt DIC per ISTH (The ISTH DIC score is calculated using platelet count (≥100.000 = 0; 50.000-99.999 =1; <50.000 =2), fibrinogen level (≥100 mg/dL =0; <100 mg/dL =1), prothrombin time prolongation above upper limit of normal (ULN) (<3 seconds =0, 3-6 seconds =1, >6 seconds =2), and D-dimer (<2 times ULN =0, 2-4 times ULN =2, >4 times ULN =3) criteria. ThromboElastoGraphy (TEG) and ROtational ThromboElastoMetry (ROTEM) is under investigation for COVID-19 associated coagulopathy/DIC but should not be used routinely for patient management (21).

Table 1. Studies, severe cases and mean D-dimer levels according to groups

References	Total Cases	Severe Cases	Non COVID-19	Mean Age	Males, n	D-dimer non-severe (ug/mL)	D-dimer severe (ug/mL)	p	Cut-off D-dimer value (ug/mL)	COVID-19 Mean	Non COVID-19 Mean
Mouhat et al. (8)	349	162	N/A	65.6	109	1.31	5.36	< 0.01	2.59	N/A	N/A
Pizzi et al. (9)	324	162	162	71.6	190	≤ 0.5	≥ 0.5	> 0.5	N/A	2.185	2.814
Santotoribio et al. (10)	203	94	109	61.3	102	≤ 0.5	1.2	< 0.01	1.2	N/A	N/A
Cheng et al. (11)	305	85	220	65	184	0.6	5.3	< 0.01	2.56	1.85	N/A
Zhang et al. (12)	343	67	N/A	62	169	0.41	4.76	< 0.01	2	0.54	N/A
Jianhong Fu et al. (13)	75	16	N/A	46.6	45	0.19	0.31	< 0.01	N/A	0.21	N/A
Bikdeli et al. (14)	71	23	62	64	43	0.67	1.63	< 0.01	1	0.79	N/A
Wenjing Ye et al. (15)	349	52	N/A	62	173	0.35	1.81	< 0.01	0.73	0.39	N/A
Bilian Yu et al. (16)	103	57	46	65	52	0.4	1.8	< 0.01	N/A	0.8	0.4
Chenghong Li et al. (17)	749	78	N/A	N/A	N/A	≤ 1	≥ 1	< 0.01	1	N/A	N/A
Yong Li et al. (18)	279	120	N/A	55	149	0.2	0.6	< 0.01	1	0.3	N/A
Yumeng Yao et al. (19)	248	51	N/A	63	75	1.02	6.21	< 0.01	2.14	N/A	N/A

NA: Not available.

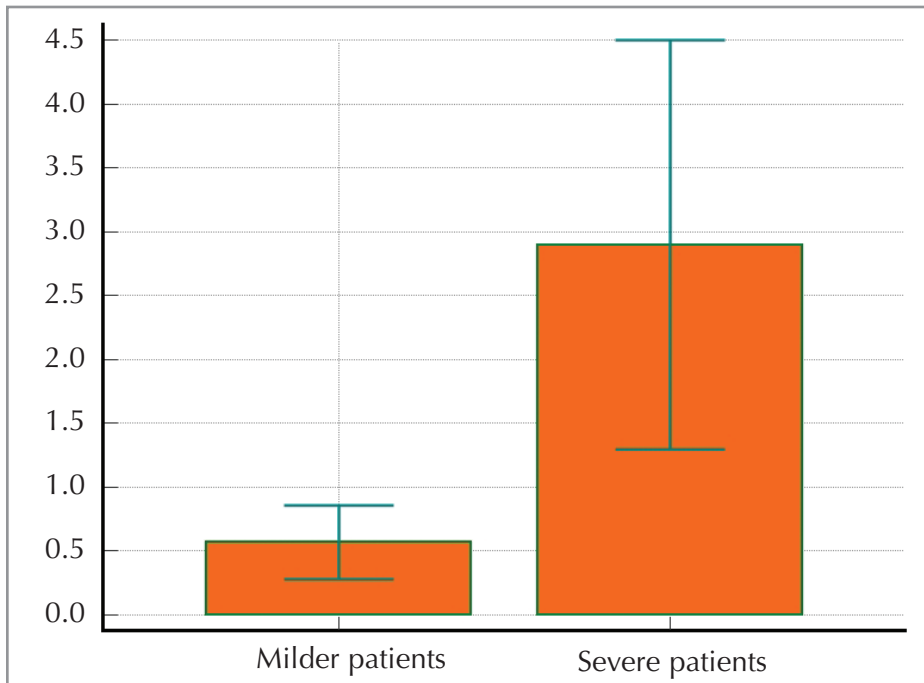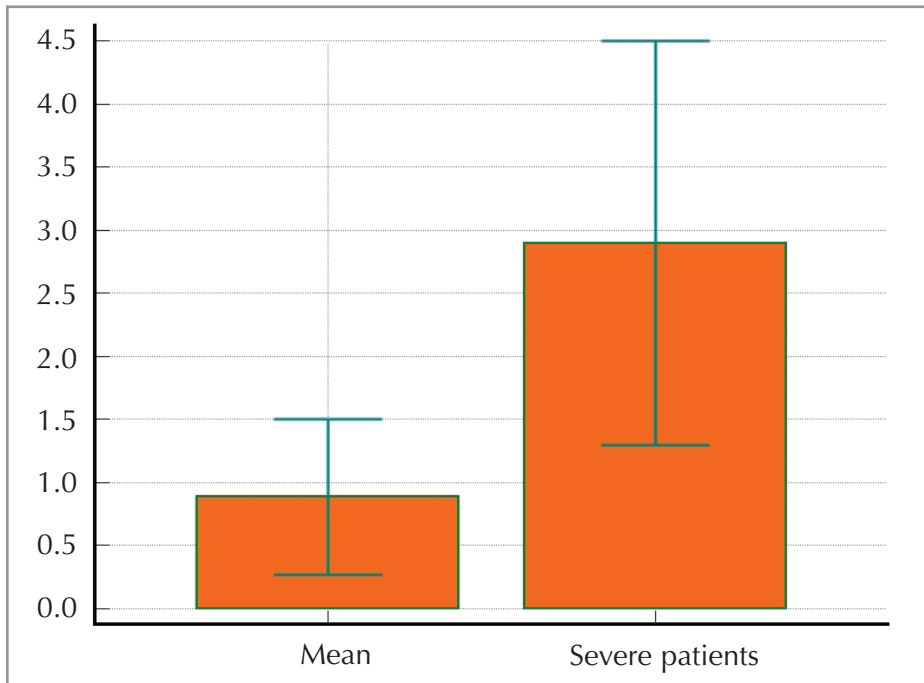**Figure 3.** Comparison of D-dimer levels (µg/mL) between milder and severe patients.

Figure 4. Comparison of D-dimer levels (µg/mL) between all patients (mean) and severe patients.

The Fibrinolytic system activates when the coagulation cascade initiates and works to limit the clot. Fibrinolysis is an enzymatic procedure that breaks down the fibrin clot into D-dimer. D-dimer emerges with the dissolution of cross-linked fibrin and is one of the specific indicators of fibrinolysis used to estimate and diagnose pulmonary embolism, DIC, or deep vein thrombosis (22). Apart from venous and
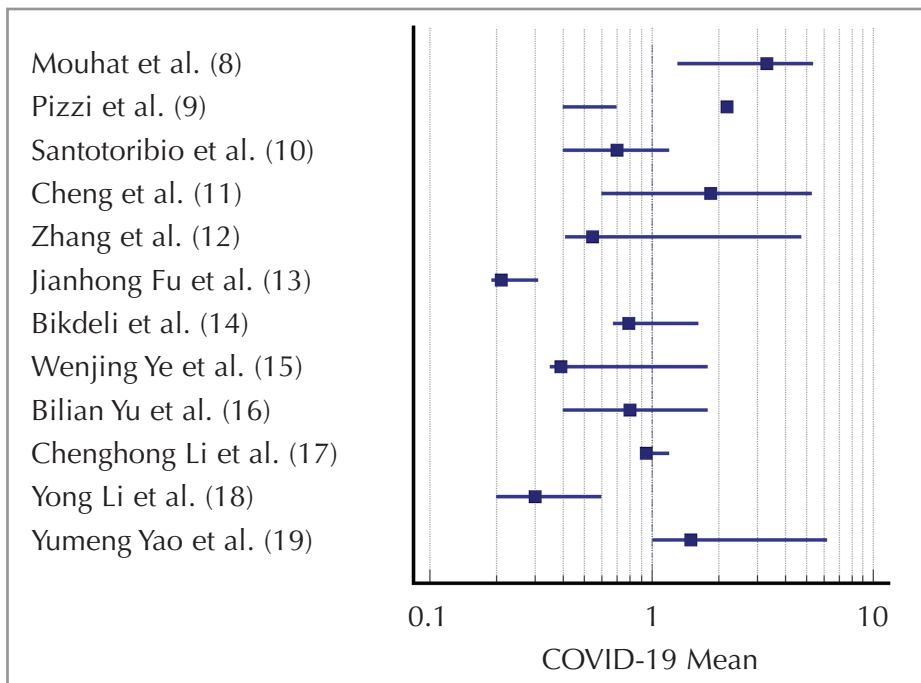
Figure 5. Forest plot analysis of D-dimer levels for analyzed studies. One study had no precise data for the upper limit (9).

arterial thromboembolic events, D-dimer may also elevate due to infections, pregnancy, inflammation, cancer, etc. Also, D-dimer levels correlate with pneumonia. However, D-dimer is not a biomarker for viral pneumonia yet (19).

We performed our study of meta-analysis to determine if the D-dimer levels associate with disease severity. We included 3343 people from 12 publications in our meta-analysis study. Of all that, 2801 were COVID-19 patients, 967 were severe patients. As a result of our meta-analysis study, we determined that D-dimer levels were significantly higher in severe patients compared to mild patients. We also discovered higher D-dimer levels when compared to mean D-dimer levels. We think that these findings will be useful in the early diagnosis of severe disease and the first treatment. The patient's first D-dimer level may associate with an intense course of the disease. In this way, doctors can prevent patients from mortality and morbidity.

One of our review's shortcomings was that D-dimer levels were not available in people who did not have COVID-19. Also, in some of the studies, the cut-off value for D-dimer was unavailable. Studies with cut-off values had different criteria for evaluating the disease's severity, which prevented us from performing pooled analysis for cut-off D-dimer levels.

The pandemic has led the D-dimer studies far above the usual numbers worldwide. Companies faced with D-dimer demand over routine numbers caused severe difficulties in the test kits supply, especially in developing countries. Also, D-dimer kits are expensive than regular biochemical tests and have placed health systems at an unexpected financial burden. Because of all this, although its significance in determining the severity of the disease, we find it appropriate to evaluate D-dimer analyzes according to countries' hospital and health systems. More distant studies are needed to understand how D-dimer levels determine the disease's severity and reach the separator data.

Ethical Committee Approval: Since the study is a meta-analysis, there was no need to receive ethics committee approval.

CONFLICT of INTEREST

The authors of this meta-analysis declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: MED

Analysis/Interpretation: MED, AB

Data Acqusition: EM

Writing: MED, EM

Clinical Revision: AB

Final Approval: AB, EM

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