EVIDENCE SUMMARY

Should D-dimer be used to guide anticoagulation among adult patients with COVID-19?

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RECOMMENDATION

We suggest the use of D-dimer to guide anticoagulation of adult patients with COVID-19, because of its significant association with mortality, thromboembolism, and worsening of disease *(Low quality of evidence; Conditional recommendation)*.

Consensus Issues

Due to the varied cut-off values used in the included studies for this review, the recommendation did not include a specific cut-off value of D-dimer to predict mortality, thromboembolism and worsening severity of disease. Further, the laboratories in the Philippines also make use of varying cut-offs due to the different assays and machines used, hence, it is difficult to define a specific cut-off value.

Key Findings

We found a total of 29 observational studies on the association between D-dimer and the outcomes of mortality, worsening severity, or thromboembolism. In general, the included studies showed increased odds of in-hospital mortality (OR 5.57 [95% CI 2.74, 11.31), worsening severity (critical illness (OR 1.91-2.58); disease progression (HR 2.84 [95% CI 2.10, 3.85]), or need for mechanical ventilation (HR 3.28 [95% CI 1.07, 10.10])), and thromboembolism (OR 5.61 [95% CI 3.97, 7.94]), with higher D-dimer levels across different COVID-19 severities. However, most studies yielded imprecise effect measures, due to the small number of event outcomes. Most of the studies were found to have serious risk of bias, with issues on data censoring, incomplete laboratory data, and unclear adequacy of follow-up rates. Differences in D-dimer cut-offs, definitions of critical illness and disease progression, and severities of COVID-19 in the study population contributed to the heterogeneity across studies. While the predictive ability of D-dimer for mortality appeared to be fair to good, prediction of worsening severity or progression of disease is inconsistent.

Introduction

Thromboembolic manifestations are reported in COVID-19 patients, resulting in increased morbidity and mortality. Mechanisms of coagulopathy in COVID-19 include endothelial dysfunction resulting in excessive thrombin formation and decreased fibrinolysis, hypoxemia, and hyperinflammatory state leading to increased blood viscosity and unstable hemostasis.

SARS-CoV-2 infection has been associated with an increase in coagulation markers such as fibrin, fibrin degradation products, fibrinogen, and D-dimer. Several studies have shown

association of D-dimer with thromboembolic events, severity of COVID-19, and mortality [1-3]. In a recent meta-analysis, D-dimer level higher than 500 or 1000 ng/mL was associated with higher risk of mortality [OR 4.81 (3.15-7.34)] and severe COVID-19 [OR 3.27 (2.46-4.36)] [4]. However, this systematic review did not apply restrictions in the selection of studies and included even those without multivariate analysis.

Review Methods

The MEDLINE, Cochrane Library, Cornell Open Access Publication (COAP), MedRxIV, and BioRxIV databases were searched for published articles and preprints using the search strategy for COVID-19, as well as the terms “D-dimer” or “D dimer”. Electronic search of the article references was also done. Inclusion criteria were as follows: (1) population: hospitalized adults with SARS-CoV-2 infection, (2) intervention: D-dimer level, (3) outcome: mortality, worsening severity (defined as progression from the current COVID-19 category to a more severe one), ICU admission, or need for mechanical ventilation), or thromboembolism; and (4) cohort studies, randomized controlled trials (RCT), and/or systematic reviews with or without meta-analyses of RCTs or observational studies. Studies without multivariate analysis and d-dimer cut-offs, as well as case reports, case series, and observational studies without control groups were excluded.

Results

We examined the utility of D-dimer for the three outcomes, namely mortality, worsening severity, and thromboembolism. Seven studies specified the assay method used for D-dimer measurement. Among these methods are immunoturbidimetric assay [12], high-sensitivity latex dimer assay using 3.2% citrated plasma [22,25], latex-enhanced photometrics immunoassay [24], and a quantitative D-dimer assay with a threshold of 500 ng/mL [7,8,15].

Mortality

We included ten studies: nine cohort studies [2,5-9,11,28,34] and one case-control study [12] reporting on the outcome of mortality (Table 1). Five were done in China, three in the USA, and two in Spain.

Eight studies looked at inpatients with COVID-19 in general [2,6-9,11-12,28,34]. One study included in patients with severe or critical COVID-19 who were admitted to the intensive care unit [5].

Table 1. Characteristics of included studies (n=10) with mortality outcomes.

Characteristic	Number of Studies	Studies
Study Design		
Prospective cohort	1	[11]
Retrospective cohort	8	[2,5-9,28,34]
Case-control study	1	[12]
Country		
China	5	[2,5,6,9,12]
USA	3	[7,28,34]
Spain	2	[8,11]
Number of Centers		
1	5	[2,5,8,12,28]
2	2	[6,9]
>2	3	[7,11,34]

Characteristic	Number of Studies	Studies
Study Population		
All admitted patients	9	[2,6-9,11-12,28,34]
Severe and/or critical patients only	1	[5]
D-dimer cutoffs for analysis (ng/mL)		
500	2	[6,11]
1000	3	[7,9,12]
1112	1	[2]
1500	1	[8]
2000	2	[5,34]
3000	2	[28,34]
Timing of D-dimer		
Admission	6	[2,6,8-9,12,34]
Initial clinical evaluation	1	[7]
Baseline	1	[11]
ICU admission	1	[5]
Peak	1	[28]
Outcome measure		
Adjusted OR	6	[6-7,9,11-12,34]
Adjusted HR	3	[2,5,8]
AUC	3	[2,8,12]

Pooled results from five studies that reported on in-hospital mortality among COVID-19 patients regardless of severity showed increased odds of in-hospital mortality with D-dimer levels above 500 ng/mL (OR 5.33 [95% CI 2.85, 9.97]) (Figure 1) [6,7,9,11,12]. The study by Alabyad et al. that found no significant association between D-dimer and mortality could not be included in the forest plot due to the unavailability of both the actual OR and raw data for OR computation [34].

Three retrospective cohort studies reporting hazard ratios showed increased risk of in-hospital mortality, 30-day all-cause mortality, and in-ICU mortality with admission D-dimer levels ranging from 1112 to 2000 ng/mL among patients with COVID-19, regardless of disease severity [2,5,8]. Two of these studies found that admission D-dimer levels above 1,500 ng/mL already conferred an almost fourfold increase in in-ICU death 14 days from admission (HR 3.600 [95% CI 1.46-8.91]), and that patients with levels above 2000 ng/mL had 22% higher risk of in-hospital death (HR 22.4 [95% CI 2.86, 175.7]). [5,31] In the study of Peiro et al., a slightly lower D-dimer cut-off of 1112 ng/mL had almost the same effect on 30-day in-hospital mortality (HR 3.35 [95% CI 1.58, 7.13]) [8]. Creel-Bulos and colleagues, who used peak D-dimer levels (the maximum level of D-dimer throughout hospitalization), also found that patients with values peaking at higher than 3000 ng/mL had almost five times greater risk of in-hospital death (OR 4.847 [95% CI 0.933, 25.167]) [28].

For the prediction of in-hospital mortality, a D-dimer cut-off level of 2000 ng/mL was shown to have good sensitivity (88.2%-92.3%) and specificity (71.3%-82.2%), with areas under the curve ranging from 0.85 to 0.89 indicating good discriminatory ability [2,12]. However, this cut-off has not been externally validated.

Worsening severity

All six studies on the association between baseline or admission levels of D-dimer and worsening severity were retrospective cohort studies [3,7,13-14,27,34] (Table 2). Four studies investigated

patients with COVID-19 in general [7,14,34,36], while the other two studies included patients with mild COVID-19 [13] and non-severe COVID-19 (defined as stable patients without dyspnea or desaturation, or those whose status improved) [3]. These studies used different outcome definitions and D-dimer cut-offs that ranged from 140 ng/mL [3] to ≥3000 ng/mL [34].

Disease progression

Regarding disease progression, which referred to the development of a more severe stage of COVID-19, Cen and co-authors found that patients with mild COVID-19 had a threefold higher risk of progression to severe illness, critical illness, or death if their D-dimer levels were at least 500 ng/mL (HR 2.85 [95% CI 2.10, 3.85]) [13].

Critical illness

Two studies had varying definitions of "critical illness" that included different combinations of respiratory distress or failure, need for mechanical ventilation, and ICU admission [7, 14]. The odds of critical illness was two to three times higher among patients with D-dimer levels above 660 ng/mL (OR 1.911 [95% CI 1.050, 3.478]) [14] or 1000 ng/mL (OR 2.58 [95% CI 1.57,4.24]) [7].

Need for mechanical ventilation

One study showed that adults with COVID-19 and d-dimer levels of more than 1500 ng/mL had a three-fold higher risk of needing mechanical ventilation (HR 3.28 [95% CI 1.07, 10.10]) [27]. The study by Alabyad et al. stated that D-dimer was not found to be associated with either ICU admission or intubation, but also did not report the ORs or the raw numbers [34].

Table 2. Characteristics of included studies (n=6) with disease progression outcomes.

Characteristic	Number of Studies	Studies
Study Design		
Retrospective cohort	6	[3,7,13-14,27,34]
Number of Centers		
1	1	[14]
2	1	[3]
>2	4	[7,13,27,34]
Country		
China	4	[3,13-14,27]
USA	2	[7,34]
Study Population		
All admitted patients	4	[7,14,27,34]
Mild/nonsevere only	2	[3,13]
D-dimer cutoffs for analysis (ng/ml)		
140	1	[14]
500	1	[13]
660	1	[3]
1000	1	[7]
1500	1	[27]
2000	1	[34]
3000	1	[34]
Timing of D-dimer		
Admission	4	[3,14,27,34]
Baseline	1	[13]

Characteristic	Number of Studies	Studies
Initial clinical evaluation	1	[7]
Outcome measure		
Adjusted OR	4	[7,14,27,34]
Adjusted HR	2	[13,27]
AUC	2	[3,14]

The discriminative ability of d-dimer to predict worsening severity was determined in two studies, but the results appear inconsistent [3,14]. In terms of progression from non-severe to severe COVID-19, a D-dimer cut-off of 140 ng/mL was shown to have poor discriminative ability (AUC 0.64, 95% CI 0.57-0.70), with good sensitivity (88%) but poor specificity (39%) [3]. For the development of critical illness (defined as a composite of acute respiratory distress syndrome, ICU admission, or death), a higher d-dimer cut-off of 660 ng/mL showed good ability to discriminate patients who will develop the outcome from those who will not (AUC 0.873 (95% CI 0.806, 0.923, p<0.0001), with a good balance of sensitivity (82.35%) and specificity (81.75%) [14].

Thromboembolism

We included 14 observational studies on the relationship between D-dimer and thrombosis in COVID-19 (Table 3). Most of the studies were single-center retrospective cohorts from Europe and the USA and included COVID-19 patients of varying severity. The subjects in all studies were given prophylactic and/or therapeutic anticoagulation even prior to diagnosis of thrombosis. Most studies had repeated determinations of D-dimer but the admission value was the basis of analysis in six of these studies [1,7,21, 23,24,25].

Table 3. Characteristics of included studies (n=14) with thromboembolic outcomes.

Characteristic	Number of Studies	Studies
Study Design		
Prospective cohort	3	[1,15,19]
Retrospective cohort	10	[7,16-17,18,20-23,25-26]
Cross-sectional study	1	[24]
Country		
China	1	[24]
USA	6	[7,18, 22-23,26-27]
Europe	7	[1,15-17,19,20-21]
Number of Centers		
1	11	[1,15-17,18-19,21-23,24,26]
>2	3	[7,20,25]
Study Population		
All admitted	11	[1,7,15-17,18,21,22,24,26]
Non-ICU only	1	[19]
Critically ill or mechanically ventilated only	1	[20]
Nonmechanically ventilated and non-expired	1	[23]
D-dimer cutoffs for analysis (ng/ml)		
500	1	[24]
956	1	[15]
1000	4	[1,20,23,24]
1500	1	[26]

Characteristic	Number of Studies	Studies
2000	3	[22,23,25]
2500	1	[7]
2590	1	[17]
3000	2	[22,25]
5000	2	[20,23]
6000	2	[1,16]
10,000	1	[20]
15,000	1	[20]
Timing of D-dimer		
Admission	6	[1,7,15,17,23,25]
Mixed (Admission and during hospitalization)	1	[21]
Not mentioned	6	[16,19,20,22,24,26]
Within 24-48hr of DVT imaging/nearest to the time DVT UTZ	1	[18]
Performance of Imaging Procedure		
With suspicion of thrombosis (at risk, symptomatic)	11	[1,7, 16-17, 18,20-23,25-26]
Routine/screening	3	[15,19,24]
Outcome		
Pulmonary thromboembolism	4	[1,15-17]
Deep vein thrombosis	3	[19,24,25]
Venous thromboembolism (pulmonary & deep vein)	5	[18,20-23,26]
Arterial and venous thrombosis	2	[7,25]
Outcome measure		
Adjusted OR	12	[1,7,16-19,21-24,25-26]
Adjusted HR	1	[15]

The presence of thrombosis was determined through imaging in 13 studies. Al-Samkari included patients with clinically diagnosed thrombotic events (as imaging was not possible) after adjudication by two independent reviewers [7]. Three studies [15,19,24] conducted screening imaging, while the rest proceeded with imaging because of clinical suspicion of thrombosis. Two studies reported arterial, venous, and clinically significant non-vessel thromboses; the rest only venous thromboembolism (VTE).

Incidence of Thromboembolism

The incidence of pulmonary thromboembolism ranged from 18.5-51%, DVT from 14.7-46%, and pulmonary and/or DVT from 9.3-41.7% among those who underwent an imaging procedure (n=13 studies). Two studies reported an overall incidence of pulmonary embolism in the hospitalized population of 2.6% (95% CI 1.7, 3.5) and 6.4% [1,16], and one study on VTE of 3.5% [26]. A study of arterial, venous, and clinically significant non-vessel thrombosis had an overall VTE incidence of 4.8% (95% CI 2.9, 7.3) and an overall thrombosis rate of 9.5% (95% CI, 6.8, 12.8) [7].

Association between D-dimer level and thromboembolism

All studies performed multivariate analysis and showed an association between elevated D-dimer and thrombosis at a cut-off of 1000 ng/mL (OR 5.61 [95% CI 3.97, 7.94]) (Figure 2).

Overall summary of methodological quality

Across the three outcomes, the risk of bias was judged to be serious due to the lack of accounting for censoring and other possible prognostic variables (e.g., the exclusion of certain variables without available data, such as IL-6 in some studies. Many studies had

small outcome events relative to the number of candidate predictors, resulting in very wide confidence intervals. In addition, not all of the included patients had complete laboratory measurements because of the retrospective nature of the studies; this may contribute to residual confounding effects.

For studies on thromboembolism, most studies had imprecision due to low event rates and a few studies had serious risk of bias due to incomplete prognostic factors or inadequate follow-up.

Recommendations from Other Groups

The US NIH COVID-19 Treatment Guidelines states that for hospitalized patients, data is insufficient to recommend either for or against the use of D-dimer in guiding management decisions [10].

Several US hospitals have included D-dimer measurement as a guide for monitoring and anticoagulant therapy. According to the guidance made by Massachusetts General Hospital for its medical professionals, D-dimer should be measured daily (or whenever labs are being drawn, if less frequent than this) if the baseline D-dimer obtained was above 1000 ng/mL and if subsequent levels remain above this value [28]. Meanwhile, the University Health System in Texas uses D-dimer levels as a dosing guide, with patients being escalated to therapeutic anticoagulation doses (enoxaparin 1 mg/kg subcutaneously twice a day) when D-dimer levels are above 5000 ng/mL and being given high-dose prophylactic doses (enoxaparin 0.5 mg/kg subcutaneously twice a day) either when baseline D-dimer at least 2000 to 3000 ng/mL, or when D-dimer has decreased to ≤2000 ng/mL [29].

The PSMID and other medical specialty societies in its interim guidance for adults with COVID-19 recommended D-dimer as one of the ancillary tests when COVID-19 is suspected, to prognosticate and guide management. Anticoagulation therapy in the form of heparin or low-molecular weight heparin is recommended for patients with a D-dimer level of > 1000 ng/ml [30].

Research Gaps

Prospective studies on the utility of d-dimer as a biomarker predictive of COVID-19 outcomes may help reduce the limitations inherent to retrospective studies, such as information bias (missing data due to reliance on existing records) and selection bias (due to inclusion of individuals after the outcome has occurred). Matching by age and/or sex in future studies are recommended. Efforts to set up standardized collection times, methods, and reference values for d-dimer are desired.

References

[1] Benito N, Filella D, Mateo J, Fortuna AM, Gutierrez-Alliende JE, Hernandez N, Gimenez AM, Pomar V, Castellvi I, Corominas H, Casademont J and Domingo P (2020) Pulmonary Thrombosis or Embolism in a Large Cohort of Hospitalized Patients With Covid-19. Front. Med. 7:557. doi: 10.3389/fmed.2020.005574.

[2] Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020 Jun;18(6):1324-1329. doi: 10.1111/jth.14859.

[3] Duan J, Wang X, Chi J, Chen H, Bai L, Hu Q, Han X, Hu W, Zhu L, Wang X, Li Y, Zhou C, Mou H, Yan X, Guo S. Correlation between the variables collected at admission and progression to severe cases during hospitalization among patients with COVID-19 in Chongqing. J Med Virol. 2020 Nov;92(11):2616-2622. doi: 10.1002/jmv.26082. Epub 2020 Jun 9.

[4] Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, Ceirano A, Espinosa F, Saavedra E, Sanguine V, Tassara A, Cid C, Catalano HN, Agarwal A, Foroutan F, Rada G. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS One. 2020 Nov 17;15(11):e0241955. doi: 10.1371/journal.pone.0241955.

[5] Zhang W, Sang L, Shi J, Zhong M, Jiang L, Song B, Kang L, Zhang Y, Zhang D, Yu Y, Zheng X. Association of D-dimer elevation with inflammation and organ dysfunction in ICU patients with COVID-19 in Wuhan, China: a retrospective observational study. Aging (Albany NY). 2021 Feb 11;13(4):4794-4810. doi: 10.18632/aging.202496. Epub 2021 Feb 11.

[6] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-1062. doi: 10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11. Erratum in: Lancet. 2020 Mar 28;395(10229):1038. Erratum in: Lancet. 2020 Mar 28;395(10229):1038.

[7] Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020 Jul 23;136(4):489-500. doi: 10.1182/blood.2020006520.

[8] Peiró ÓM, Carrasquer A, Sánchez-Gimenez R, Lal-Trehan N, Del-Moral-Ronda V, Bonet G, Fort-Gallifa I, Picó-Plana E, Bastón-Paz N, Gutiérrez C, Bardaji A. Biomarkers and short-term prognosis in COVID-19. Biomarkers. 2021 Mar;26(2):119-126. doi: 10.1080/1354750X.2021.1874052. Epub 2021 Jan 18.

[9] Yang C, Liu F, Liu W, Cao G, Liu J, Huang S, Zhu M, Tu C, Wang J, Xiong B. Myocardial injury and risk factors for mortality in patients with COVID-19 pneumonia. Int J Cardiol. 2021 Mar 1;326:230-236. doi: 10.1016/j.ijcard.2020.09.048. Epub 2020 Sep 23.

[10] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 17 May 2021.

[11] Gil-Rodrigo A, Miró Ò, Piñera P, Burillo-Putze G, Jiménez S, Martín A, Martín-Sánchez FJ, Jacob J, Guardiola JM, García-Lamberechts EJ, Espinosa B, Martín Mojarro E, González Tejera M, Serrano L, Agüera C, Soy E, Llauger L, Juan MÁ, Palau A, Del Arco C, Rodríguez Miranda B, Maza Vera MT, Martín Quirós A, Tejada de Los Santos L, Ruiz de Lobera N, Iglesias Vela M, Torres Garate R, Alquézar-Arbé A, González Del Castillo J, Llorens P; en representación de la red de investigación SIESTA. Analysis of clinical characteristics and outcomes in patients with COVID-19 based on a series of 1000 patients treated in Spanish emergency departments. Emergencias. 2020 Ago;32(4):233-241.

[12] 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. J Intensive Care. 2020 Jul 10;8:49. doi: 10.1186/s40560-020-00466-z.

[13] Cen Y, Chen X, Shen Y, Zhang XH, Lei Y, Xu C, Jiang WR, Xu HT, Chen Y, Zhu J, Zhang LL, Liu YH. Risk factors for disease progression in patients with mild to moderate coronavirus disease 2019-a multi-centre observational study. Clin Microbiol Infect. 2020 Sep;26(9):1242-1247. doi: 10.1016/j.cmi.2020.05.041. Epub 2020 Jun 9.

[14] Yue T, Zhou W, He J, Wang H, Liu Y, Wang B, Zhu Q, Xia H, Hu H. Combined clinical and imaging features better predict the critical outcomes of patients with SARS-COV-2. Medicine (Baltimore). 2021 Mar 26;100(12):e25083. doi: 10.1097/MD.0000000000025083.

[15] García-Ortega A, Oscullo G, Calvillo P, López-Reyes R, Méndez R, Gómez-Olivas JD, Bekki A, Fonfría C, Trilles-Olaso L, Zaldívar E, Ferrando A, Anguera G, Briones-Gómez A, Reig-Mezquida JP, Feced L, González-Jiménez P, Reyes S, Muñoz-Núñez CF, Carreres A, Gil R, Morata C, Toledo-Pons N, Martí-Bonmati L, Menéndez R, Martínez-García MÁ. Incidence, risk factors, and thrombotic load of pulmonary embolism in patients hospitalized for COVID-19 infection. J Infect. 2021 Feb;82(2):261-269. doi: 10.1016/j.jinf.2021.01.003. Epub 2021 Jan 10.

[16] Mestre-Gómez B, Lorente-Ramos RM, Rogado J, Franco-Moreno A, Obispo B, Salazar-Chiriboga D, Saez-Vaquero T, Torres-Macho J, Abad-Motos A, Cortina-Camarero C, Such-Diaz A, Ruiz-Velasco E, Churruca-Sarasqueta J, Muñoz-Rivas N; Infanta Leonor Thrombosis Research Group. Incidence of pulmonary embolism in non-critically ill COVID-19 patients. Predicting factors for a challenging diagnosis. J Thromb Thrombolysis. 2021 Jan;51(1):40-46. doi: 10.1007/s11239-020-02190-9.

[17] Mouhat B, Besutti M, Bouiller K, Grillet F, Monnin C, Ecarnot F, Behr J, Capellier G, Soumagne T, Pili-Floury S, Besch G, Mourey G, Lepiller Q, Chirouze C, Schiele F, Chopard R, Meneveau N. Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients. Eur Respir J. 2020 Oct 22;56(4):2001811. doi: 10.1183/13993003.01811-2020.

[18] Cho ES, McClelland PH, Cheng O, Kim Y, Hu J, Zenilman M, D'Ayala M. Utility of D-dimer for diagnosis of deep vein thrombosis in coronavirus disease-19 infection. Journal of Vascular Surgery January 2021. https://doi.org/10.1016/j.jvsv.2020.07.009

[19] Demelo-Rodríguez P. Cervilla-Muñoz E, Ordieres-Ortega L, Parra-Virto A, Toledano-Macías M, Toledo-Samaniego N, García-García A et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. Thrombosis Research 2020: 192, 23-26. https://doi.org/10.1016/j.thromres.2020.05.018

[20] Dujardin RWG, Hilderink BN, Haksteen WE, Middeldorp S, Vlaar APJ, Thachil J et al. Biomarkers for the prediction of venous thromboembolism in critically ill COVID-19 patients. Thrombosis Research 2020. 196: 308-312. https://doi.org/10.1016/j.thromres.2020.09.017

[21] Kampouri E, Filippidis P, Viala B, Méan M, Pantet O, Desgranges F, Tschopp J, Regina J, Karachalias E, Bianchi C, Zermatten MG, Jaton K, Qanadli SD, Bart PA, Pagani JL, Guery B, Alberio L, Papadimitriou-Olivgeris M, RegCOVID Research Group. Predicting Venous Thromboembolic Events in Patients with Coronavirus Disease 2019 Requiring Hospitalization: an Observational Retrospective Study by the COVIDIC Initiative in a Swiss University Hospital. Biomed Res Int. 2020 Nov 6;2020:9126148. doi: 10.1155/2020/9126148.

[22] Creel-Bulos C, Liu M, Auld SC, Gaddh M, Kempton CL, Sharifpour M, Sniecinski RM, Maier CL, Nahab FB, Rangaraju S. Trends and diagnostic value of D-dimer levels in patients hospitalized with coronavirus disease 2019. Medicine 2020;99:46(e23186). http://dx.doi.org/10.1097/MD.0000000000023186

[23] Nauka PC, Baronb SW, Assab A, Mohrmannb L, Jindala S, Oranb E et al. Utility of D-dimer in predicting venous thromboembolism in non-mechanically ventilated COVID-19 survivors Thrombosis Research 199 (2021) 82–84. https://doi.org/10.1016/j.thromres.2020.12.023

[24] Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, Zhang C, Li H, Xia X, Kong S, Liao J, Jia H, Pang X, Song Y, Tian Y, Wang B, Wu C, Yuan H, Zhang Y, Li Y, Sun W, Zhang Y, Zhu S, Wang S, Xie Y, Ge S, Zhang L, Hu Y, Xie M. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. Circulation. 2020 Jul 14;142(2):114-128. doi: 10.1161/CIRCULATIONAHA.120.046702. Epub 2020 May 18. Erratum in: Circulation. 2020 Jul 14;142(2):e33.

[25] Alabyad D, Rangaraju S, Liu M, Imran R,Kempton CL, Sharifpour M, et al. (2021) Validation of an admission coagulation panel for risk stratification of COVID-19 patients. PLoS ONE 16(3): e0248230. https://doi.org/10.1371/journal.pone.0248230

[26] Rali P, O'Corragain O, Oresanya L, Yu D, Sheriff O, Weiss R, Myers C, Desai P, Ali N, Stack A, Bromberg M, Lubitz AL, Panaro J, Bashir R, Lakhter V, Caricchio R, Gupta R, Dass C, Maruti K, Lu X, Rao AK, Cohen G, Criner GJ, Choi ET; Temple University COVID-19 Research Group. Incidence of venous thromboembolism in coronavirus disease 2019: An experience from a single large academic center. J Vasc Surg Venous Lymphat Disord. 2021 May;9(3):585-591.e2. doi: 10.1016/j.jvsv.2020.09.006. Epub 2020 Oct 5.

[27] Wang T, Tang C, Chen R, et al. Clinical Features of Coronavirus Disease 2019 Patients With Mechanical Ventilation: A Nationwide Study in China. *Crit Care Med*. 2020;48(9):e809-e812. doi:10.1097/CCM.0000000000004473

[28] Hematology recommendations and dosing guidelines during COVID-19, version 9.0. In: Boston (MA): Massachusetts General Hospital; 2020: https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/guidance-from-mass-general-hematology.pdf. Accessed 2021 May 23.

[29] Guidelines for Anticoagulation in Hospitalized COVID-19 Patients ≥18 years of Age. In: Texas: University Health System; 2020: https://www.universityhealthsystem.com/~/media/files/pdf/covid-19/guidelines-for-anticoagulation-in-hospitalized-covid-19-patients.pdf?la=en. Accessed 2021 May 23.

[30] Interim Guidance on the Clinical management of Adult Patients with Suspected or Confirmed COVID-19 Infection. In: Manila: Philippine Society for Microbiology and Infectious Diseases, Philippine College of Chest Physicians, Philipiine College of Physicians, Philippine Rheumatology Association, Philippine College of Hematology and Tranfusion Medicine; 2020: https://www.psmid.org/interim-management-guidelines-for-covid-19-version-3-1/. Accessed 2021 May 23.

Appendix 1. Characteristics of Included Studies

Mortality (n=10 studies)

Author (Year) Study design	Population and number of outcome events	Outcome	D-dimer timing	D-dimer association with outcome	Prediction of outcome
Zhou (2020) China Retro cohort Multicenter	Hospitalized adults with confirmed COVID-19 (191) Deaths (54) D-dimer ≤500 ng/mL (55) D-dimer >500 ng/mL (117)	In-hospital death	Admission	Reference for multivariate analysis: ≤0.5 D-dimer >1000 ng/mL: OR 18.42 (2.64, 128.55, p=0.0033) >500 ng/mL: OR 2.14 (0.21, 21.39, p=0.52)	None
Yao (2020) China Case control Single-center	Hospitalized adults with confirmed COVID-19 (248) Deaths (17)	Mortality	Admission	D-dimer measured using Sysmex, CS5100 Reference for multivariate analysis: <1000 ng/mL 1000-2000 ng/mL: OR 2.21 (0.12, 38.61) p=0.612 >2000 ng/L: OR 10.17 (1.10, 94.38) p = 0.041	For prediction of in-hospital mortality: D-dimer > 2140 ng/mL Sn 88.2% Sp 71.3% (AUC 0.85; 95% CI = 0.77– 0.92)

Author (Year) Study design	Population and number of outcome events	Outcome	D-dimer timing	D-dimer association with outcome	Prediction of outcome
Zhang L (2020) China Retrospective cohort single-center	Hospitalized adults with confirmed COVID-19 (248) Deaths (13)	In-hospital mortality	Admission (within 24h)	D-dimer measured using CS5100 automatic coagulation analyzer (Sysmex, Japan) Kaplan-Meier cut-off: D-dimer ≥2000 ng/mL as predictor of in-hosp mortality Adjusted HR 22.4 (2.86, 175.7) on Cox proportional hazard analysis p=0.003 after adjusting for sex, age, underlying disease	For prediction of in-hospital mortality: D-dimer ≥2000 ng/mL Sn 92.3% Sp 83.3% (AUC 0.89; No CI reported)
Al-Samkari (2020) USA Retrospective cohort Multicenter	Adults with confirmed covid from the Research Patient Data Registry at Partners Healthcare (400) - mortality models included only patients reaching completion of hospitalization (discharge or death) Deaths (29) Critically ill (144) D-dimer ≤1000 (148) 1001-2500 (78) >2500 (26)	In-hospital mortality	Initial clinical evaluation	D-dimer measured in FEU using Vidas (bioMerieux) in 2 laboratories, Sta-Liatest (Stago) in 2 laboratories, and HS 500 (Instrumentation Laboratory) in 1 laboratory Reference for multivariate analysis: D-dimer ≤1000 ng/mL D-dimer 1001-2500 ng/mL: Adjusted OR 6.26 (1.53, 25.58) >2500 ng/mL: Adjusted OR 15.14 (2.19, 104.53)	None
Gil-Rodrigo (2020) Spain Prospective nested cohort study Multicenter March 1- Apr 30, 2020	Hospitalized adults with covid, either RT-PCR-confirmed or clinically diagnosed (1000) Deaths (119) ICU (62) Invasive mechanical ventilation (IMV) (46) Patients with D-dimer measurement (759; 443 of them have D-dimer >500 mg/mL)	In-hospital mortality Composite of in-hosp mortality/ICU admission/ need for IMV	Baseline	Reference for multivariate analysis: D-dimer >500 ng/mL In-hospital mortality: Adjusted OR 2.96 (1.58, 5.54) Composite of in-hosp mortality/ICU admission/need for MV: Adjusted OR 2.42 (1.44, 4.06)	None

Author (Year) Study design	Population and number of outcome events	Outcome	D-dimer timing	D-dimer association with outcome	Prediction of outcome
Peiro (2021) Spain Retrospective cohort study Single-center Mar 16-May 15, 2020	Hospitalized adults with covid, either RT-PCR-confirmed or clinically diagnosed, with biomarker information (196) Deaths (37; 10 in low d-dimer; 27 in high d-dimer) D-dimer <1112 ng/mL (119) D-dimer ≥1112 ng/mL (77)	30-day all-cause mortality	Admission	D-dimer measured using ACL TOP 500 CTSVR using HemosIL D-Dimer HS- 500 (HemosIL, Instrumentation Laboratory, Bedford, MA) Reference for multivariate analysis: D-dimer ≥1112 ng/mL Adjusted HR 3.35; 95% CI 1.58–7.13; p<0.002	None
Yang (2020) China Retrospective cohort study Multicenter (2 hospitals) Jan 10-Feb 29, 2020; pts followed from admission to Mar 20, 2020/ discharge/death	Hospitalized adults with covid, either RT-PCR-confirmed or clinically diagnosed, with biomarker information (196) Deaths (58)	In-hospital mortality	dmission	Reference for multivariate analysis: D-dimer >1000 ng/mL In-hospital mortality: OR 9.51 (3.61, 25) p<0.001 Other findings (serial biomarker measurements of each patient for dynamic change analysis): D-dimer raised rapidly from day 12 in non-survivors and its level was significantly higher than in survivors	None
Zhang W (2021) China Retrospective cohort study Single-center Admitted bet Jan 20-Feb 26, 2020; outcome monitored until Mar 4, 2020	Hospitalized adults with confirmed covid (203) Deaths (58; 51.7% severe, 43.1% critical) Hospitalized adults with confirmed severe or critical COVID-19 and admitted to ICU (158) Deaths (77) Patients into 4 groups based on their D-dimer level at the time of ICU admission: D0 (normal DD): DD <1.5 ug/mL (57) D1-D3 (abnormal DD): D1:1.5≤DD<10 ug/mL (38) D2: 10≤DD<40 ug/mL (31) D3: ≥40 ug/mL (32)	In-ICU death	ICU admission	Reference for multivariate analysis: D-dimer <1500 ng/mL for in-ICU-death: D-dimer 1500-10,000 ng/mL: HR 3.600 (1.455, 8.911) p=0.006 10000-40000 ng/mL: HR 4.160 (1.727, 10.022) p=0.001 >40000 ng/mL: HR 2.732 (1.077, 6.927) p=0.034 7-day mortality: no significant diff among D1, D2, and D3 groups 14-day mortality rate: significantly lower in D0 vs D1-D3 (all p<0.01); also significantly lower in D1 vs D2-D3 (p<0.05); but no diff between D2 and D3	None

Author (Year) Study design	Population and number of outcome events	Outcome	D-dimer timing	D-dimer association with outcome	Prediction of outcome
Creel-Bulos (2020) USA Retrospective cohort study Single-center Mar 12-Apr 6, 2020, Reviewed from admission through discharge or until the censor date of April 30, 2020	Hospitalized adults with confirmed COVID-19 with D-dimer measurements (115) Deaths (21) Peak D-dimer >2000 ng/mL (83) Peak D-dimer >3000 ng/mL (74) (Patients with overlapping D-dimer values not reported)	In-hospital mortality	Peak (maximum) D-dimer throughout hospitalization	high sensitivity latex dimer assay (Instrumentation Laboratories, Bedford, MA) *Most patients had a single D-dimer level on a given day Mean value was used if >1 d-dimer measurement was made in one day Peak d-dimer of >3000 ng/mL: OR 4.847 (0.933, 25.167) p=0.060 on multivariate analysis Peak d-dimer of >2000 ng/mL was not found to be predictive of mortality even on univariate analysis	Death was not predicted by pre-VTE ceiling D-dimer, change (absolute increase) in D-dimer, rate of D-dimer rise, or peak D-dimer (maximum level from hospital days 1-7) >2500 ng/mL
Alabyad (2020) USA Retrospective cohort study multi-center April 3-July 31, 2020 Reviewed from admission through discharge or until the censor date of September 14, 2020	Hospitalized adults with confirmed COVID-19 who had markers of coagulation and hemostatic activation (MOCHA) measurements that included D-dimer (276) Deaths (31) Admission D-dimer >2000 ng/mL (51) Admission D-dimer >3000 ng/mL (40) (Patients with overlapping D-dimer values not reported)	In-hospital mortality	Admission	ORs and raw numbers for mortality not reported	Not reported

Worsening severity (n=6 studies)

Author (Year) Study design	Population	Outcome	D-dimer timing	D-dimer association with outcome	Prediction of outcome
Yue (2020) China Retrospective cohort study Single-center Jan 18-Feb 16, 2020	Hospitalized adults with confirmed covid (180) Divided into critical and noncritical according to presence of absence of end-point events: Critical (20; no deaths) Noncritical (160; 14 deaths)	Critical illness (defined as composite endpoint of ICU admission, ARDS, or death)	Admission	Reference for multivariate analysis: D-dimer >660 ng/mL Critical illness OR 1.911 (1.050, 3.478) p=0.034	AUC 0.873 (0.806, 0.923) p <0.0001 Sn 82.35% Sp 81.75 AUC improved if DD is combined with CRP and CT scan score to 0.921 (0.863, 0.960) p <0.0001 Sn 82.35% Sp 89.43%
Cen (2020) China Retrospective cohort Single-center	Hospitalized adults with confirmed MILD COVID-19 (1007) 1007 broken down into stable (720) and progression (severe = 222, critical = 22, deceased =43)	Disease progression (patients who recovered OR became symptomatically stable, vs those who developed severe* disease, critical illness**, or died) *Severe defined as either: (a) respiratory rate >30 breaths/min, or (b) oxygen saturation ≤93%, (c) PF ratio ≤300 mmHg **Critical defined as any of the following: (a) shock, (b) respiratory failure requiring mechanical ventilation, or (c) organ failure requiring ICU admission	"Baseline" (unknown if on admission, but probably)	Reference for multivariate analysis: D-dimer ≥500 ng/mL Disease progression HR 2.846 (2.103, 3.851)	None
Duan (2020) China Retrospective cohort study Multicenter (2 hospitals) Data collection from Jan 1 to Feb 29, 2020	Hospitalized adults with confirmed nonsevere* COVID-19 (348) Stable/improved (328); progression to severe (20)	Progression to severe* case *Severe defined as those meeting ANY the ff: 1) dyspnea, RR >30 breaths/min; 2) O2 sat <93% in ambient air; 3) PFratio <300	Admission	Reference value and machine for D-dimer unspecified	DD cutoff >140 ng/mL by Youden index AUC* 0.64 (0.57, 0.70) Sn 88% Sp 39%

Author (Year) Study design	Population	Outcome	D-dimer timing	D-dimer association with outcome	Prediction of outcome
Al-Samkari (2020) USA Retrospective cohort Multicenter	Adults with confirmed covid from the Research Patient Data Registry at Partners Healthcare (400) - mortality models included only patients reaching completion of hospitalization (discharge or death) Deaths (29) Critically ill (144)	Critical illness (defined as requirement for endotracheal intubation and mechanical ventilation, including patients for whom intubation was clinically indicated but who chose to forego it)	Initial clinical evaluation	D-dimer measured in FEU using Vidas (bioMerieux) in 2 laboratories, Sta-Liatest (Stago) in 2 laboratories, and HS 500 (Instrumentation Laboratory) in 1 laboratory Reference for multivariate analysis: D-dimer ≤1000 ng/mL D-dimer 1001-2500 ng/mL: Adjusted OR 2.58 (1.57, 4.24) >2500 ng/mL: Adjusted OR 2.05 (1.03, 4.07)	None
Wang (2020) China Retrospective cohort study Multicenter Until January 31, 2020 (unknown study start date)	Hospitalized adults with confirmed COVID-19 and were mechanically ventilated (141) Non-invasive ventilation (91); invasive mechanical ventilation (50)	Need for invasive mechanical ventilation	Admission	Reference for multivariate analysis: D-dimer >1500 ng/mL HR 3.05 (1.07, 8.69) *p* = 0.037 OR 3.28 (1.07, 10.10) p = 0.039	None
Alabyad (2020) USA Retrospective cohort study multi-center April 3-July 31, 2020 Reviewed from admission through discharge or until the censor date of September 14, 2020	Hospitalized adults with confirmed COVID-19 who had markers of coagulation and hemostatic activation (MOCHA) measurements that included D-dimer (276) ICU admission (159) Intubation (90)	ICU admission Intubation	Admission	ORs and raw numbers for ICU admission and intubation not reported	Not reported

Author (Year) Study design	Population	Outcome	D-dimer timing	D-dimer association with outcome	Prediction of outcome
	Admission D-dimer >2000 ng/mL (51) Admission D-dimer >3000 ng/mL (40) (Patients with overlapping D-dimer values not reported)				

Thromboembolism (n=14 studies)

Study	Population	Site of Thrombosis and Proportion details	D-dimer (ng/ml) median (IQR) (unless specified)	Association of D-dimer with thrombosis (effect size (95% CI))	Prediction of thrombosis
Al-Samkari (2020) USA Retrospective cohort Multicenter	Adults with confirmed covid from the Research Patient Data Registry at Partners Healthcare (400) - mortality models included only patients reaching completion of hospitalization (discharge or death) Deaths (29) Critically ill (144) D-dimer ≤1000 (148) 1001-2500 (78) >2500 (26)	Thrombotic complications	Initial clinical evaluation	D-dimer measured in FEU using Vidas (bioMerieux) in 2 laboratories, Sta-Liatest (Stago) in 2 laboratories, and HS 500 (Instrumentation Laboratory) in 1 laboratory Reference for multivariate analysis: D-dimer ≤1000 ng/mL D-dimer 1001-2500 ng/mL: Adjusted OR 3.04 (1.26-7.31) >2500 ng/mL: Adjusted OR 6.79 (2.39-19.30) Combined OR (1001-2500 and >2500): OR 3.530 (1.6677-7.4930)	None

Study	Population	Site of Thrombosis and Proportion details	D-dimer (ng/ml) median (IQR) (unless specified)	Association of D-dimer with thrombosis (effect size (95% CI))	Prediction of thrombosis
Benito 2020 Prospective Spain Mar-Apr 2020	Hospitalized, n=1,275 Suspected thrombosis with CTPA, n=76 March- standard prophylactic anticoagulation April- standard therapeutic anticoagulation	Pulmonary: 32/76 (42.1%) Cumulative incidence 2.6% (95 CI 1.7–3.5%) None: 44/76 (57.9%)	Admission 5,274.5 (16,419) Peak 22,791 (42,552) Admission 1,045.5 (6,287.8) Peak 6039.5 (15,982.3)	Admission 1,000 ng/mL OR 4.5 (1.2–17.2) Peak 6,000 ng/mL OR 5.6 (1.3–24.5)	No data
Garcia-Ortega 2021 Prospective Spain Mar 8-Apr 25, 2020	Hospitalized 119 randomly selected from 272 admitted patients Routine CTPA Prophylactic anticoagulation	Pulmonary: 26/73 (35.6%) None: 47/73 (64.4%)	Admission, mean (SD) 6270 (13,814) 2384 (6134)	Admission HR 1.02 (1.01–1.04)	No data
Mestre-Gomez 2020 Retrospective Spain Mar 30-Apr 12, 2020	Hospitalized Not critically ill Prophylactic anticoagulation	Pulmonary: 29/91 (31.9%) Cumulative incidence 29/452 (6.4%) None: 62/91 (68.1%)	Peak median (Q1-Q3) 7230 ng/mL (2105–16,415) 14,480 ng/mL (5540–33,170)	With dyslipidemia, OR 3.77; CI 95% (1.18–12.16) Without dyslipidemia, (OR 9.06; CI 95% (1.88, 43.60).	Peak D-dimer cut-off of > 5000 ng/mLl and history of Dyslipidemia AUC-ROC 0.755
Mouhat 2020 Retrospective France April-May 2020	349 hospitalized Severe COVID-19 Suspected PE in 162 Prophylactic or therapeutic anticoagulation at discretion of AP	Pulmonary: 44/162 (27.2%) None: 118/162 (72.8%)	5364 ng/mL (2928–12 275) 1310 ng/mL (800–2335)	D-dimer on day of CTPA OR 4.0 (95% CI 2.4–6.7) per quartile increase in D-dimer on day of CTPA For D-dimer >2590 ng/mL: OR 16.9 (95% CI 6.3-45)	Cut-off value of 2590 ng/mL AUC 0.88

Study	Population	Site of Thrombosis and Proportion details	D-dimer (ng/ml) median (IQR) (unless specified)	Association of D-dimer with thrombosis (effect size (95% CI))	Prediction of thrombosis
Cho 2021 Retrospective Mar1-May 13, 2020, USA	Hospitalized 1170 screened Imaging at AP discretion N=158 included 90% on prophylactic anticoagulation	DVT 52/158 (32.9%) None 106/158	Highest level prior to US median, 13,602 ng/mL [IQR, 6616-36,543 ng/mL] 2880 ng/mL [IQR, 1030-9126 ng/mL]	D-dimer >6494 ng/mL: OR 6.12; (95% CI 2.79-13.39)	6494 ng/mL for DVT SN 80.8% SP 68.9% NPV 88.0% The C statistic (AUC) was 0.802
Demelo-Rodriguez 2020 Prospective Spain April 1-15, 2020	Non-ICU All screened for asymptomatic DVT if with D-dimer>1000 ng/ml and hospitalized for ≥48 hours, all on prophylactic anticoagulation	DVT: 23/156 (14.7%) None: 133/156	4527 ng/mL (IQR 1925–9144) ng/mL 2050 ng/mL (IQR 1428–3235 ng/mL)	Adjusted OR 9.8; CI 95% 2.9–33.7	To rule out asymptomatic DVT, D-dimer cutoff 1570 ng/mL SN 95.7%, SP 29.3%, PPV 19% NPV 97.5%
Zhang 2020 Cross-sectional survey China Jan 29-Feb 29, 2020; followed up until Mar 24, 2020	Hospitalized ≥3 days adult pts with COVID-19, critical; all with DVT screening (N = 159 screened, 143 with imaging) 37% on prophylactic anticoagulation	DVT: 66/143 (46.15) None: 77/143	6600 ng/mL (2500, 8000) 0.9 (0.4, 3.5)	Admission D-dimer >1000 ng/mL (OR 5.818 (1.422–23.809] odds of DVT OR 13.506 [95% CI, 1.334–136.741] odds of PROXIMAL DVT OR, 3.564 [95% CI, 1.122–11.323] odds of DISTAL DVT	AUC 0.708 (0.622, 0.784) Sn 88.52% Sp 52.86%
Dujardin 2020 Retrospective Amsterdam Mar13-Apr9, 2020	ICU patients Observation (data extracted) till death/discharge Weekly screening US, suspected PE had CTPA, D-dimer done 2x a week All with prophylactic anticoagulation	VTE: 53/127 (41.7%) None: 64/127 (58.3)		Multivariate analysis D-dimer not associated with VTE. Only CRP was associated with VTE.	D-dimer cut-off >2000 ng/mL SN 80 (61–92) SP 29 (15–49) PPV 53 (46–61) NPV 60 (38–79) D-dimer AUC 0.64

Study	Population	Site of Thrombosis and Proportion details	D-dimer (ng/ml) median (IQR) (unless specified)	Association of D-dimer with thrombosis (effect size (95% CI))	Prediction of thrombosis
Kampouri 2020 Retrospective Switzerland Feb 28-Apr 30, 2020, follow-up till May 5.	All documented COVID-19 with consent for data review, n=443 Documented VTE (imaging) on admission or during hospitalization Crea-clearance adjusted thromboprophylaxis for all in the ICU.	VTE: 41/443 (9.3%) 14/41 On admission 27/41 during hospital stay None: 402/443	D-dimer (ng/ml) (among 363 patients) 3610.0 (1934.0-7093.8) 1039.0 (549.0-2020.0)	VTE on admission >3120 ng/ml- OR 15.8, 95% CI 4.7-52.9 VTE during hospitalization > 5611 ng/ml OR 6.3, 95% CI 2.4-16.2	To predict VTE on admission D-dimer value ≥ 3000 ng/ml SN 71.4 SP 87.9 PPV 99. NPV 87.4 Diagnostic Accuracy 0.797 Wells score for PE ≥ 2 points or D-dimer value ≥1000 ng/ml SN 92.9 SP 46.9 PPV 5.4 NPV 99.5 DA 0.483
Creel-Bulos 2020 Retrospective USA Mar 12-Apr 6, 2020, Reviewed from admission through discharge or until the censor date of April 30, 2020	All severity of COVID Criteria for imaging not mentioned Therapeutic anticoagulation in 59 patients (51%)	VTE: 27/115 (23%) None: 88/115 (76.6)	Median D-dimer within the first 7 days of hospitalization 6450 ng/mL 1596 ng/mL	2000 ng/mL: OR 9.592 (95% CI 1.110-82.866) 3000 ng/mL: OR 15.595 (95% CI 1.902-127.848) Combined OR (2000 and 3000): OR 14.1404 (1.83-109.26)	Prediction of future VTE Within first 7 HD peak level >2500 ng/mL, AUC 0.72 Only change (absolute increase) in D-dimer level (AUC=0.72 P=.004) and rate of D-dimer rise (AUC=0.75 P=.001) were also predictive of VTE Diagnosis of VTE- rise of >150ng/mL/d or >2000ng/mL within any 24 hour period through HD10 Sensitivity 75% Specificity 74%

Study	Population	Site of Thrombosis and Proportion details	D-dimer (ng/ml) median (IQR) (unless specified)	Association of D-dimer with thrombosis (effect size (95% CI))	Prediction of thrombosis
Nauka 2020 Retrospective USA Mar11-May2, 2020	Hospitalized & discharged, not critical, had imaging during hospitalization or within 14 days post-discharge (performed at provider's discretion) D-dimer within 48h of admission 3855 screened, 306 had imaging 193 had prophylactic or therapeutic anticoagulation	VTE: 67/306 (21.9%) 67/2630 (2.5%) estimated population prevalence None: 239/306	5200 ng/mL [1900–20000] 1700 ng/mL [900–3500]	≥2000 ng/mL OR 3.9 (1.1,14.6) ≥5000 ng/mL OR 10.8 (3, 39.2)	None
Rali 2020 Retrospective USA Apr1-27, 2020	147/703 (20.9% of admissions to COVID unit) had imaging for high clinical suspicion of VTE, CTPA and/or extremity venous duplex US (proximal DVT only) VTE prophylaxis at admission or sequential compression devices	VTE:25/147 None: 122/147		admission D-dimer level 1500 ng/mL: adjusted OR 3.55; 1.29-9.78	None

Study	Population	Site of Thrombosis and Proportion details	D-dimer (ng/ml) median (IQR) (unless specified)	Association of D-dimer with thrombosis (effect size (95% CI))	Prediction of thrombosis
Alabyad 2020 Retrospective cohort USA Multicenter Apr 3-Jul 31, 2021 (censored till Sep 14, 2020)	Hospitalized On prophylactic anticoagulation Outcomes of DVT, pulmonary embolus, MI, ischemic stroke, dialysis or central line clots (with imaging & adjudication), plasma D-dimer within 72 hours of admission (reference value <574 ng/mL) N=276, 58% in ICU (159)	45 patients (16%) with thrombosis DVT 24 (8.7%) PE in 8 (2.9%), MI in 4 (1.5%), ischemic stroke in 5 (1.8%) central or dialysis line thrombosis in 7 (2.5%), 6 (2.2%) RRT thrombosis 1 (0.4%) patient ECMO circuit thrombosis		D-dimer ≥2000 ng/mL (OR 3.1, 95% CI 1.5–6.6; p = .003) D-dimer ≥ 3000 ng/mL (OR 3.6, 95% CI 1.6–7.9; p = .002) Associated with thrombosis within 14 days of admission D-dimer ≥2000 ng/mL (OR 2.5, 95% CI 1.1–5.9	Cut-off ≥ 2000 Total thrombotic endpoints Sensitivity 33% Specificity 84% PPV 29% NPV 87% Thrombotic endpoints within 14 days from admission Sensitivity 31% Specificity 83% PPV 20% NPV 90% Total VTE Sensitivity 39% Specificity 84% PPV 24% NPV 92% VTE <14 days from admission Sensitivity 44% Specificity 84% PPV 20% NPV 94%

Appendix 2. GRADE Evidence Profile

Question: D-dimer levels for mortality, worsening severity, and thromboembolism among COVID-19 patients?

Setting: COVID-19 patients

Author(s): Patricia Pauline M. Remalante-Rayco, Evelyn O. Salido, Joey A. Tabula

No. of studies	Certainty assessment						Certainty
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Mortality							
5	observational studies	serious [a,b,c,d]	not serious	not serious	not serious	strong association dose response gradient	⨁⨁⨁⨁ HIGH
Worsening Severity							
6	observational studies	serious [a,b,d]	serious [e,f]	not serious	not serious	none	⨁⨁◯◯ LOW
Thromboembolism							
12	observational studies	serious [c,e]	not serious	not serious	not serious	strong association dose response gradient	⨁⨁⨁⨁ HIGH

Explanations

a. Did not account for censoring
b. Patients with incomplete laboratory data were included
c. Not all prognostic variables were considered
d. Small number of events relative to number of predictors
e. Different d-dimer cut-off values were used
f. Different effect measures used for the outcome

Appendix 3. Forest Plots

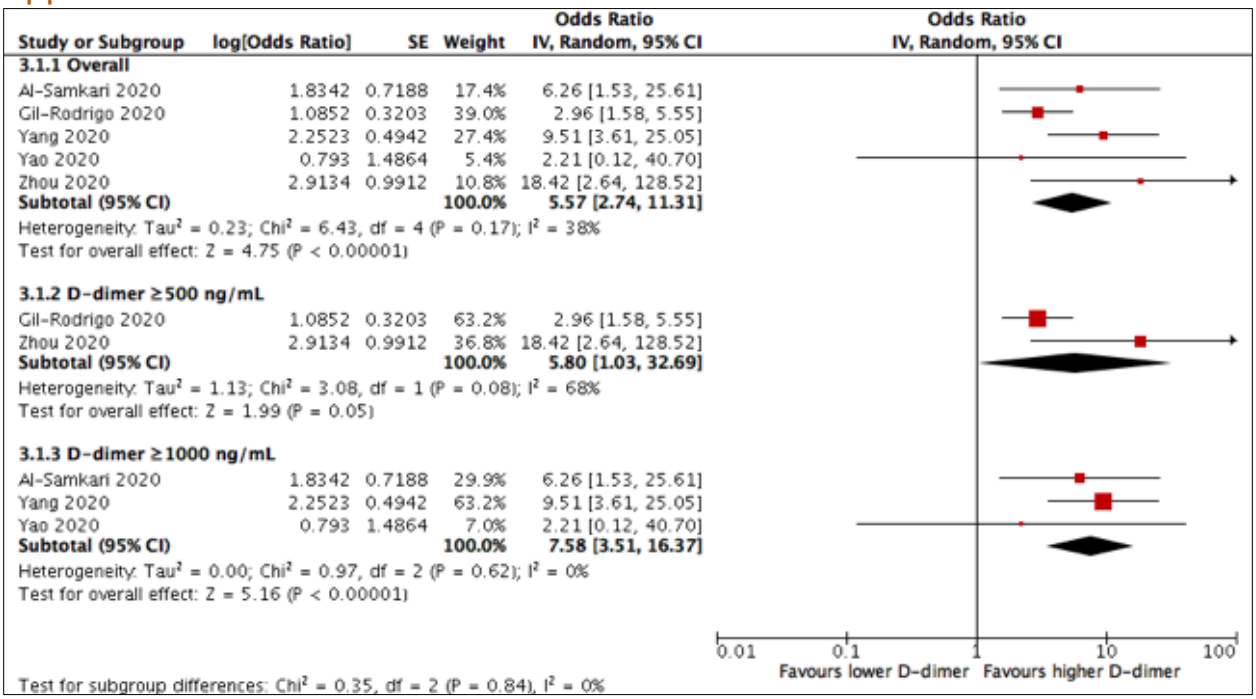

Figure 1. Comparison of mortality between patients with low D-dimer <500 ng/mL versus D-dimer ≥500 ng/mL among adults with confirmed COVID-19, with subgroup analyses at cut-off values of 500 ng/mL and 1000 ng/mL

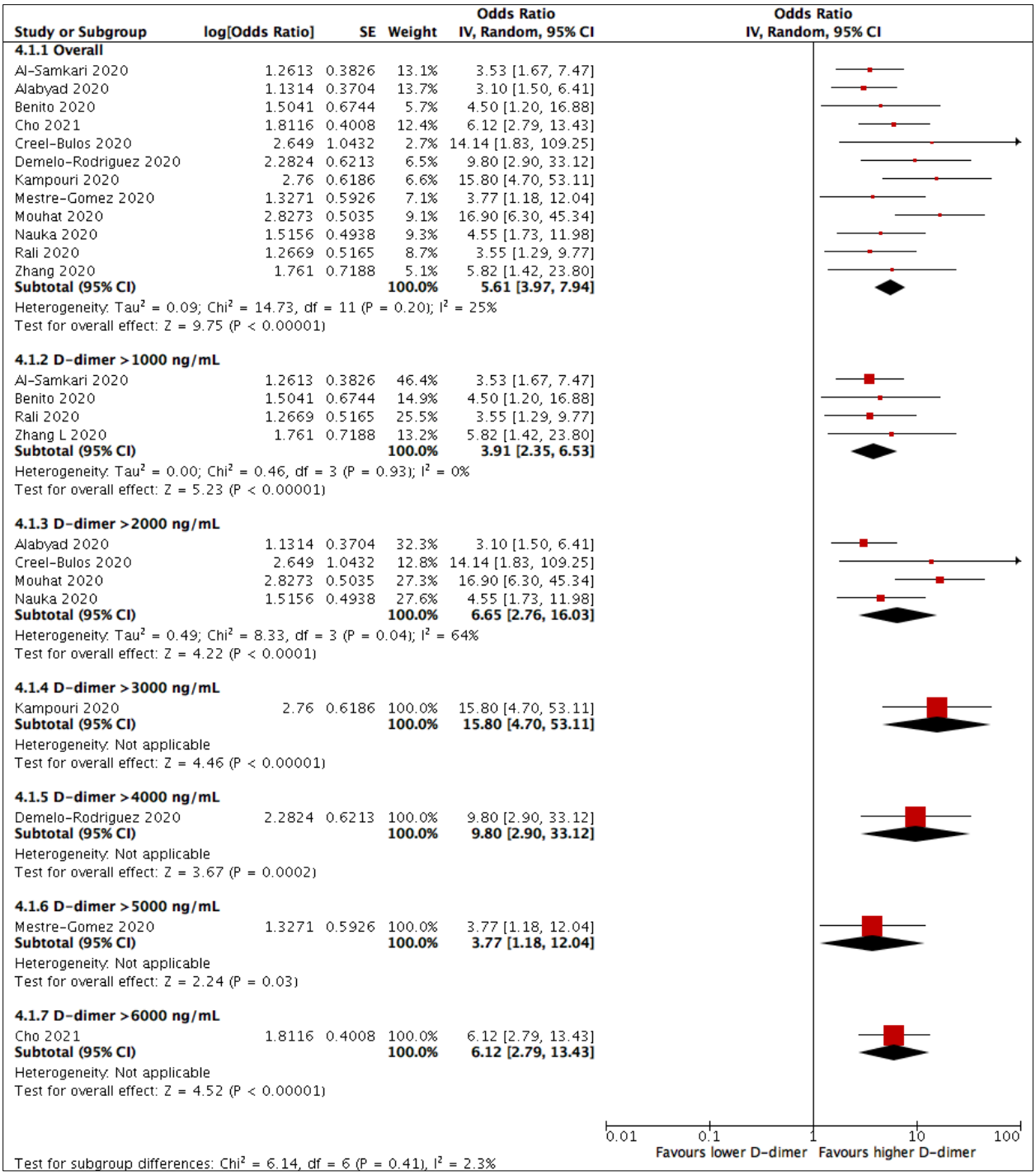

Figure 2. Comparison of thromboembolism between patients with low D-dimer <1000 ng/mL versus D-dimer ≥1000 ng/mL among adults with confirmed COVID-19, with subgroup analyses at cut-off values of 1000, 2000, 3000, 4000, 5000, and 6000 ng/mL

Appendix 4. Detailed Study Appraisal

Articles on Mortality

Author and Year	Direct?	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Risk of Bias
Zhou (2020)	Yes (35 % severe, 28% critical)	Yes (Nonsurvivor group was older, had more comorbidities, more tachypneic/tachycardic, higher risk scores)	Yes	Yes	n/a	Very Serious limitation Selection bias: patients still admitted are excluded and may underestimate mortality
Yao (2020)	Yes	Yes Pts with high d-dimer were older, more had HPN, more had severe and critical covid, higher severity scores, higher mortality	Yes	Yes	n/a	Serious limitation Imprecision: Wide CI due to low number of events (n=17)
Zhang L (2020)	Yes (severe 44%, critical 20%)	Yes Pts with D-dimer ≥2.0 ug/mL were older, more comorbids, more deaths	Yes	Yes	n/a	Serious limitation Imprecision: Wide CI due to low number of events (n=13)
Al-Samkari (2020)	Yes (critical 36%)	Yes Pts who are critically ill have more diabetes, CKD on dialysis and less chronic lung disease	Yes	Yes	n/a	Serious limitation Imprecision: Wide CI due to low number of events (n=29)
Gil-Rodrigo (2020)	Yes	Yes Nonsurvivors and patients with composite events were older and had higher prevalence of obesity	Yes	Yes	n/a	Serious limitation: Imprecision from the small number of events per predictor Impact on effect size from

Author and Year	Direct?	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Risk of Bias
						incomplete laboratory data leading to exclusion of potentially important prognostic variables and the obviation of collinearity
Peiro (2021)	Yes	No Limited number of variables in Cox regression analyses More nonsurvivors were older, smokers, had hypertension, had myocardial infarction, chronic kidney disease, and chronic pulmonary disease	Yes	Yes	n/a	Serious limitation: impact on effect size Number of variables included was limited (to avoid overfitting); hence multivariable Cox regression analyses were adjusted only by age, hypertension, history of chronic pulmonary disease, renal impairment at admission, and d-dimer level
Yang (2020)	Yes	Yes More nonsurvivors were older, had COPD, had hypertension, had severe or critical COVID-19, and had higher levels of cardiac biomarkers, inflammatory indicators and coagulation function	Yes	Yes	n/a	Serious limitation: Impact on effect size/estimation of OR -data censoring -exclusion of variables like SaO2 and IL-6 from the final logistic model due to absence of events (possibly overestimating the effect of d-dimer)

Author and Year	Direct?	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Risk of Bias
Zhang W (2021)	No Only ICU patients were included	Yes	Yes	Unclear (not mentioned if all patients had known outcomes)	n/a	Serious limitation: Imprecision Small number of events per predictor (3.66 events per candidate predictor)
Creel-Bulos (2020)	Yes	Yes	Yes	Yes	n/a	Serious limitation: Impact on effect size/estimation of OR due to: -lack of imputation for missing data -Inconsistency in daily D-dimer testing in all patients due to lack of a universal policy for D-dimer testing -Data censoring
Alabyad (2020)	Yes	Yes	Yes	Yes	n/a	No ORs reported

Articles on Worsening Severity

Author and Year	Direct?	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Limitations
Yue (2020)	Yes	Yes	Yes	Yes	n/a	Serious limitation: Impact on effect size from incomplete laboratory

Author and Year	Direct?	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Limitations
						data leading to exclusion of potentially important prognostic variables and the obviation of collinearity
Cen (2020)	No (mild COVID-19 only)	Yes Patients in the progressive group were older, mostly males, had more comorbidities	Yes	Yes	n/a	Serious limitation: Impact on effect size from incomplete laboratory data leading to exclusion of potentially important prognostic variables and the obviation of collinearity -data censoring (28-day follow-up only)
Duan (2020)	No (nonsevere COVID-19 only)	Yes Patients in the progressive group were older, with higher body temperature, heart rate, and laboratory parameters	Yes	Yes	n/a	Serious limitation: Impact on effect size from incomplete laboratory data leading to exclusion of potentially important prognostic variables and the obviation of collinearity -data censoring (28-day follow-up only)
Al-Samkari (2020)	Yes (critical 36%)	Yes Pts who are critically ill have more diabetes, CKD on dialysis	Yes	Yes	n/a	Serious limitation: Impact on effect size from incomplete

Author and Year	Direct?	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Limitations
		and less chronic lung disease				laboratory data leading to exclusion of potentially important prognostic variables and the obviation of collinearity
Wang (2020)	Yes	Yes	Yes	Yes	n/a	Serious limitation: Impact on effect size from data censoring
Alabyad (2020)	Yes	Yes	Yes	Yes	n/a	No ORs reported

Articles on Thromboembolism

Author (Year)	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Overall Risk of Bias (Not serious, Serious, Very Serious)	Any imprecision?
Al-Samkari (2020)	Yes	Yes	Yes	n/a	Serious	Likely yes
Benito (2020)	Yes	Yes	Probably yes	n/a	Not serious	Likely yes
Garcia-Ortega (2021)	Yes	Yes	Probably yes	n/a	Not serious	Likely yes
Mestre-Gomez (2020)	Yes	Yes	Yes	n/a	Not serious	Likely yes
Mouhat (2020)	Yes	Yes	Yes	n/a	Not serious	Likely yes

Author (Year)	Included all important factors?*	Unbiased criteria for outcome?**	Adequate follow-up rate?***	Separate validation study for prediction rule done?	Overall Risk of Bias (Not serious, Serious, Very Serious)	Any imprecision?
Cho (2021)	Yes	Yes	Unclear	n/a	Serious	Likely yes
Demelo-Rodriguez (2020)	Yes	Probably yes	Probably yes	n/a	Not serious	Likely yes
Dujardin (2020)	Maybe not	Yes	Yes	n/a	Serious	Likely yes
Kampouri (2020)	Yes	Yes	Probably yes	n/a	Not serious	Likely yes
Creel-Bulos (2020)	Yes	Yes	Unclear	n/a	Serious	Likely yes
Nauka (2020)	Maybe not	Yes	Yes	n/a	Serious	Likely yes
Zhang (2020)	Yes	Yes	Yes	n/a	Not serious	Likely yes
Alabyad (2020)	Yes	Yes	Yes	n/a	Not serious	Likely yes
Rali (2020)	Yes	Probably not	Yes	n/a	Serious	Likely yes

*All prognostic factors are said to be considered if either of the following is done:
1. Homogeneous subgroup of individuals with specific combination of prognostic factors
2. Clinical prediction rule used

**Outcomes are said to be unbiased if hard outcomes are used (e.g, mortality). For soft outcomes, bases or criteria need to be defined

***Follow-up is said to be adequate if the conclusions are similar between best-case and worst-case scenarios; worst outcomes are assumed for drop-outs