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REVIEW

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COVID-19 (SARS-CoV-2) infection and thrombotic conditions: A systematic review and meta-analysis

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Abstract

Background: COVID-19 is an infectious disease caused by SARS-CoV-2 associated with haematological manifestations (thrombolytic events).

Aims: Considering the high prevalence of the thrombotic scenarios associated with COVID-19, the aim of this study was to perform a systematic review of the available literature, concerning the relation of COVID-19 and the thrombotic events, and identify prognostic factors for these events.

Materials & Methods: PubMed, Web of Science and Scopus databases were searched. Independent reviewers conducted all flow diagram steps. For qualitative analysis, Oxford level of evidence and Newcastle-Ottawa scale were used in the eligible articles. For the prognostic factors, a meta-analysis was conducted to age, number of neutrophils and platelets, and levels of ferritin, C-reactive protein, lactate dehydrogenase and D-dimer. Publication bias was accessed by funnel plot and by trim-and-fill test. Trim-and-fill test was also applied to evaluate meta-analysis bias.

Results: Twenty articles were included in the qualitative analysis, and 6 articles were included in the meta-analysis. Case-control studies showed bias related to exposure, and the main bias in cohort studies were related to selection and outcome. All articles received score 4 for the level of evidence. Hypertension and diabetes were the comorbidities more frequently associated with thrombolytic events. Significant results were found regarding D-dimer ($P < .0001$) and age ($P = .0202$) for thrombotic events in patients diagnosed with COVID-19.

Conclusion: Patients older than 60 years, with hypertension, diabetes and D-Dimer values above 3.17 μg/mL, can be considered prognostic factors for developing thrombotic events due to COVID-19.

KEYWORDS

COVID-19, D-dimer, meta-analysis, prognostic factors, SARS-CoV-2, systematic review, thrombosis

Paulo Roberto Gabbai-Armelin and Analú Barros de Oliveira contributed equally to this work.

Take-home message

- The review adds important information about COVID-19 and its influence on thrombotic conditions, regarding risk and prognostic factors.
- Patients older than 60 years, with comorbidity and D-dimer level above 3.17 μg/mL, are at increased risk of developing thrombotic events due to COVID-19.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an infectious disease that affects the human respiratory system, and it is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The first cases of this disease were reported in Wuhan, China, and it spread rapidly in more than 180 countries, threatening the health of millions of people. Based on that, the World Health Organization (WHO) has considered this disease an emergency global public health problem.[2,3] In this context, COVID-19 has been extensively studied, motivating the development of new researches, products and clinical approaches.

The clinical characteristics of COVID-19 may vary from asymptomatic infections to more severe conditions. The mild symptoms include fever, fatigue, cough, sore throat, nasal congestion and headache. In more complicated cases, manifestations of pneumonia can be observed based on imaging examinations. Subsequently, in more severe cases, the symptoms are shortness of breath, with lesions that can affect more than 50% of the lung. The clinical pattern with rapid progression found in some patients affected with COVID-19, if not quickly reversed, may lead to respiratory failure. In this case, mechanical ventilation is needed, and patients might perish.[3,4] Coagulation disorders and thrombotic events have been reported in patients that presented the severe pattern of COVID-19.[1]

SARS-CoV-2 may cause damage to the endothelial tissue, leading to coagulation alterations in patients affected by this disease.[5-7] SARS-CoV-2 accesses the endothelial cell through the binding, via spike protein envelope, with angiotensin-converting enzyme 2 (ACE-2) which is present on the cellular membrane of the endothelial cells.[8] It is suggested that the infection by SARS-CoV-2 promotes, via NADPH enzyme activation path, an increased expression of the platelet tissue factor. The tissue factor may interact with VII factor of the coagulation cascade, triggering the extrinsic via of coagulation and, finally, resulting in the thrombin and fibrin production.[8] Nevertheless, the exact mechanism that lead to the coagulation alterations was not totally clarified.[5]

Several studies[5-8] reported a strong relation between the occurrence of thrombotic events and SARS-CoV-2 infection. Helmes et al[5] and Fraissé et al[6] described, respectively, the prevalence of thrombotic events in 42.6% and 40% of the investigated patients. Considering the prevalence of the thrombotic events associated with COVID-19, the aim of this study was to perform a systematic review of the literature, concerning the relationship between COVID-19 and thrombotic events. Secondly, we evaluated possible prognostic factors (age, D-dimer, C-reactive protein, ferritin, lactate dehydrogenase, platelets and neutrophils numbers) for thrombotic events in patients affected by COVID-19.

2 | MATERIALS AND METHODS

2.1 | Eligibility parameters

The systematic review was performed conforming to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[9] and according to broad Enhancing the Quality and Transparency of Health Research (EQUATOR) guidelines,[10] and registered at PROSPERO (#CRD42020199814). The study intended at responding the query: What are the clinical implications of COVID-19 (SARS-CoV-2) regarding thrombotic conditions? This query was established based on the 'PECO' strategy for systematic review[11] in which P (patients affected with COVID-19), E (presence of thrombotic events in patients diagnosed with COVID-19), C (absence of thrombotic events in patients diagnosed with COVID-19) and O (clinical aspects and possible prognostic factors in patients affected with COVID-19 disease associated with thrombotic events).

The inclusion criteria for the systematic review were (a) observational human studies, such as case-control, cohort and cross-sectional studies; (b) studies associated explicitly to COVID-19 disease related to the presence of thrombotic events; and (c) scientific articles written in English language.

In contrast, the exclusion criteria were (a) review articles, letters, individual ideas, book sections or congress abstracts; (b) case series studies and case reports; (c) in vitro and animal studies; (d) non-English languages articles (or inappropriate English level) and (e) articles that did not have their full-text easily accessible.

2.2 | Search method

Two researchers (PRGA and ABO) completed the electronic examination on PubMed, Web of Science and Scopus. The following terms were utilized for searching: ((covid-19[Supplementary Concept] OR sars-cov-2[Supplementary Concept])) AND Thrombosis[MeSH]; TS = (thrombosis*) AND TS = (covid-19* OR sars-cov-2*); covid-19 OR sars-cov-2 AND thrombosis. By evaluating the titles and abstracts of the scientific articles, the papers were selected by the investigators. The EndNote X9® Reference Manager Software was used to eliminate duplicate manuscripts.

2.3 | Data extraction and analysis

PRISMA statement was followed for data assessment and extraction.[9] Basically, the following data were extracted from the papers: (a) sort of study; (b) sample size; (c) control group; (d) influence of COVID-19 (SARS-CoV-2) on thrombosis (including venous and arterial thrombotic events, thrombotic complications, cerebral and pulmonary thrombosis, hypercoagulability, haemorrhagic events and D-dimer levels); (e) main conclusions and outcomes. The quality analysis of the case-control and cohort studies was done based on the Newcastle-Ottawa scale.[12] The Level of Evidence (LoE) for each one of the investigations was determined according to the guidelines of the Oxford University Center for Evidence-Based Medicine.[13]

2.4 | Statistical analysis

For quantitative analysis, R software, version 3.6.1, 'META' package and Rstudio platform were used. In the meta-analysis, the results were showed in forest plot. Mean difference and fixed effect model were the parameters used to interpret the results. The I^2 test measured the heterogeneity among the studies. In addition, to access the publication bias, the funnel plot (n = 2) and the trim-and-fill method (n > 2) were used. Moreover, the trim-and-fill method was also applied to evaluate the meta-analysis bias, utilizing mean difference and random effect model as parameters, such as a sensitivity test. The significance level of 5% and the reliability level of 95% were selected for the statistical analysis. In this step, only articles that investigated patients diagnosed with COVID-19 (presence and/or absence of thrombotic events) were eligible to statistical analysis. In this sense, the variables studied were age, number of neutrophils and platelets, and levels of ferritin, C-reactive protein, lactate dehydrogenase and D-dimer.

3 | RESULTS

3.1 | Search outcomes

The articles selection procedure is briefly presented in the flow diagram shown in Figure 1. The initial electronic examination generated 310 articles. In total, 76 duplicate articles were removed; therefore, 234 articles were maintained in the study.

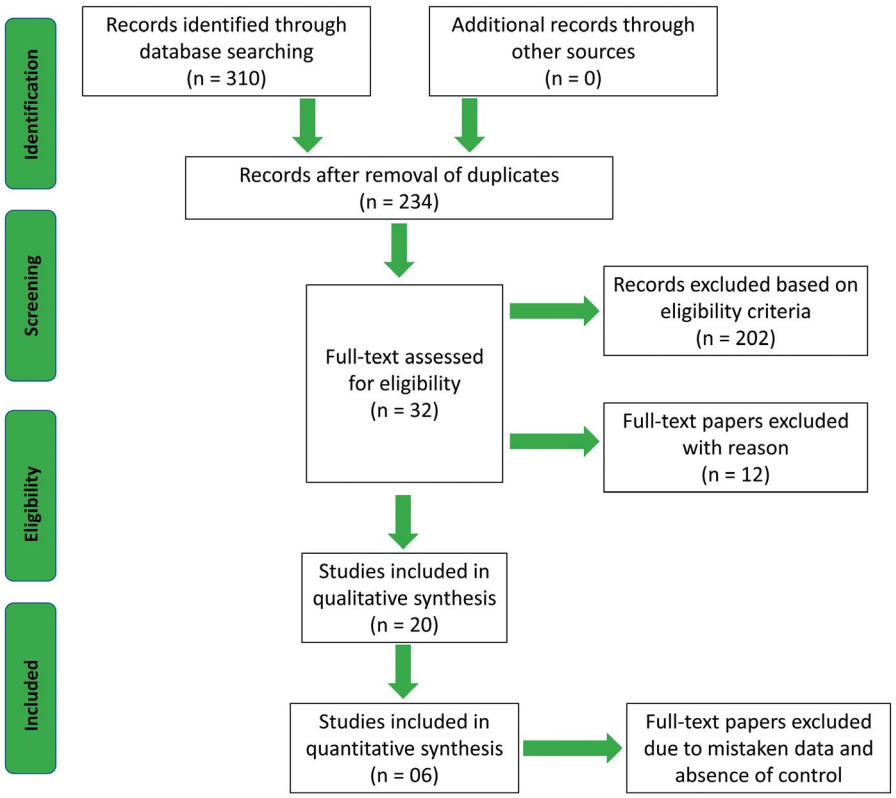

FIGURE 1 Flow diagram for the systematic review according to PRISMA Guidelines

TABLE 1 Summary of the main characteristics and outcomes of the included studies

	Author	Year	Type of study	LoE	Sample size (n)	Mean age	Most frequent comorbidities	Death toll	Control group
#1	Artifon et al	2020	Retrospective cohort study	IV	71 (64 patients with VTE and 7 patients without no VTE)	64	Hypertension (41%) and diabetes (20%)	1	Inpatients with no VTE.
#2	Ayerbeet al.	2020	Retrospective case-control study	IV	2075 (1734 Heparin treated patients and 341 Heparin non-treated patients)	67.57	-	301	Heparin non-treated patients.
#3	Cantador et al	2020	Retrospective cohort study	IV	1419	73.2	Multiple cardiovascular risk factors and diabetes	4	-
#4	Chen et al	2020	Retrospective case-control study	IV	88	63	-	-	-
#5	Cui et al	2020	Retrospective case-control study	IV	81 (20 patients with VTE and 61 patients without no VTE)	59.9	Hypertension, diabetes, and coronary heart disease and history of smoking	8	Non-VTE group.
#6	Demelo-Rodríguez et al	2020	Prospective case-control observational study	IV	156 (23 patients with DVT and 133 patients without no VTE)	68.1	Active cancer	-	Non-DVT group.

Exams performed	Medication	Prognostic factor	Influence of COVID-19 (SARS-CoV-2) on thrombosis	Main conclusions and outcomes
Duplex ultrasonography/ Angio-CT scan was performed in case of suspicion of PE	Enoxaparin thromboprophylaxis implemented within 24 h of hospital admission (40 mg/d for BMI < 30 kg/m^2, 60 mg/d for BMI 30 to 40 kg/m^2 and 40 mg twice daily for BMI > 40 kg/m^2)	D-dimer level	Coagulopathy (VTE and pulmonary embolism) due to COVID-19 infection.	VTE is an important concern in hospitalized patients with COVID-19 even under thromboprophylaxis. At admission, D-dimer <1.0 μg/mL had a negative predictive value for VTE whereas the risk of thromboembolic events was high in patients with D-dimer level ≥3.0 μg/mL.
-	Heparin (guidelines recommendations)	Temperature >37°C and saturation of oxygen <90% on admission	Findings support that there is a thrombotic constituent in the development of respiratory distress for patients admitted with COVID-19.	Heparin was associated with lower mortality when the model was adjusted for age and gender. The association between heparin and lower mortality may be recognized by clinicians.
-	Antiagreggation/Oral anticoagulation (dosage not described)	Levels of C-reactive protein/D-dimer/Creatine kinase/Lactate dehydrogenase/ Ferritin	Indications that thrombosis is a frequent finding in severe COVID-19 patients.	There is little data on incidence of coronary, cerebrovascular and peripheral vascular thrombotic events in COVID-19 infection. It was observed a 1% incidence of systemic arterial thrombotic events, with a death rate of 28.6%.
Lower limb compression ultrasonography	Heparin thromboprophylaxis (standard doses)	Sex, age, hypoalbuminemia, D-dimer, and Sequential Organ Failure Assessment (SOFA) score.	DVT in critically ill COVID-19 with thrombosis prophylaxis.	The incidence of DVT in patients with severely ill COVID-19 was 46% despite the use of guideline-recommended thromboprophylaxis. The occurrence of hypoalbuminemia, SOFA score, and elevated D-dimer were DVT predictors.
Chest computed tomography, lower limb venous Doppler ultrasound	-	D-dimer	Patients with severe new coronavirus pneumonia (NCP) COVID-19 may have a significant probability of VTE prevalence.	The incidence of VTE in patients with severe NCP was 25% (20/81). 1.5 μg/mL was utilized as the D-dimer cut-off for predicting VTE. Moreover, substantial increase in D-dimer in severe NCP patients is a good indicative for detecting high-risk groups of VTE.
Doppler ultrasound	Enoxaparin or bemiparin thromboprophylaxis (40 mg per day and 3500 UI per day, respectively)	D-dimer level	An increased risk of VTE in patients with COVID-19 admitted to ICU has been reported. On the other hand, COVID-19 may also increase the risk of VTE in non-ICU wards.	The study showed a significant incidence (14.7%) of asymptomatic DVT in a cohort of patients admitted in non-intensive care units with COVID-19 pneumonia. Patients with DVT had increased median D-dimer levels: 4527 ng/mL vs 2050 ng/mL; $P < .001$. D-dimer levels >1570 ng/mL were related to asymptomatic DVT. In patients with COVID-19 pneumonia and higher D-dimer levels, the incidence of asymptomatic DVT is comparable to that described in other series. Higher cut-off levels for D-dimer might be needed for the diagnosis of DVT in COVID-19 patients

(Continues)

TABLE 1 (Continued)

	Author	Year	Type of study	LoE	Sample size (n)	Mean age	Most frequent comorbidities	Death toll	Control group
#7	Fraissé et al	2020	Retrospective case-control study	IV	92 (37 patients with TE and 55 patients without TE)	62	Hypertension, Diabetes mellitus, Chronic respiratory diseases	-	Patients without thrombotic events
#8	Fu et al	2020	Retrospective case-control study	IV	75 (16 patients in severe and 59 patients in mild/moderate group)	46.6	Hypertension, Diabetes mellitus, Chronic respiratory diseases	0	Mild/moderate group (COVID-19 inpatients).
#9	Helms et al	2020	Prospective cohort study	IV	383 (150 patients with COVID-19 and 233 Non-COVID-19 ARDS	63	Cardiovascular diseases, Diabetes, Chronic renal disease, Respiratory disease	13 (8.7%) of COVID-19 patients	Non-COVID-19 ARDS
#10	Klok et al	2020	Cross-sectional observational clinical study	IV	184	64	Chronic renal disease, Active cancer	41 (22%)	-
#11	Klok et al	2020	Cross-sectional observational clinical study	IV	184	64	Chronic renal disease, Active cancer	23 (13%)	-

Exams performed	Medication	Prognostic factor	Influence of COVID-19 (SARS-CoV-2) on thrombosis	Main conclusions and outcomes
Laboratory tests (fibrinogen, prothrombin time, platelets)	All patients received usual (prophylactic) or full-dose (therapeutic) anticoagulation, as enoxaparin, tinzaparin, fondaparinux.	-	40% of patients experienced TE.	TE included 31 venous (79%) and 8 arterial (21%) thrombosis, and 19 of them (21%) experienced a total of 22 haemorrhagic events (HE) during their ICU stay. D-dimers (μg/mL) for patients without and with TE were 2.2 and 4.4, respectively. Moreover, full-dose anticoagulation did not prevent some patients from developing a TE.
Complete blood count (CBC), coagulation profile, arterial blood gas analysis, blood biochemistry, myocardial biomarker	Oxygenation therapy for hypoxemia, antivirus medications, corticosteroids	D-dimer level	The influence of COVID-19 on dynamic NLR and D-dimer was detected.	White blood cell (WBC), NLR, D-dimer, and fibrinogen levels of the severe group were significantly higher than the mild/moderate, and the lymphocyte was lower. The COVID-19 abnormal haematological indexes on admission included hyperfibrinogenemia, lymphopenia, the elevation of D-dimer, and leukopenia.
Angio-CT, fibrinogen level	Eighty-four COVID-19 patients (60%) received lopinavir + ritonavir, 8 (5.3%) remdesivir, 49 (32.7%) hydroxychloroquine, and 9 (7.5%) did not received any antiviral treatment	D-dimer level	Evidence of increased thrombotic risk in COVID-19 patients.	Sixty-four clinically relevant thrombotic problems were diagnosed in 150 patients, mainly PE. Most patients (>95%) had increased D-dimer and fibrinogen. level Comparison with non-COVID-19 ARDS patients confirmed that COVID-19 ARDS patients developed more thrombotic complications, mainly PE. Higher anticoagulation targets than in typical critically ill patients should, hence, be suggested.
CT pulmonary angiography/ ultrasonography	Thromboprophylaxis with nadroparin	-	High cumulative incidence of thrombotic complications in critically ill patients with COVID-19 admitted to the ICUs.	Most of the thrombotic events were PE. Chronic anticoagulation therapy at admission was associated with a lower risk of the composite outcome of VTE. It was confirmed the high cumulative incidence of thrombotic complications in critically ill patients with COVID-19 pneumonia.
CT pulmonary angiography/ ultrasonography	Thromboprophylaxis with nadroparin (2850 or 5700 IU sc per day, according to body weight and time onwards)	-	COVID-19 may predispose to both venous and arterial thromboembolism due to exacerbated inflammation, hypoxia, immobilization and diffuse intravascular coagulation.	The 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is remarkably high. This fact reinforces the recommendation to apply pharmacological thrombosis prophylaxis in all COVID-19 patients admitted to the ICU. It is suggested the increase in the prophylaxis towardss high-prophylactic doses.

(Continues)

TABLE 1 (Continued)

	Author	Year	Type of study	LoE	Sample size (n)	Mean age	Most frequent comorbidities	Death toll	Control group
#12	Llitjos et al	2020	Retrospective case – control study	IV	26	68	Previous history of arterial hypertension	3 (12%)	-
#13	Lodigiani et al	2020	Retrospective cohort study	IV	388	66	Arterial hypertension on treatment, diabetes mellitus on treatment, chronic renal dysfunction	92 (23%)	-
#14	Middeldorp et al	2020	Retrospective Clinical cohort study	IV	198	61	Obesity	38 (19%)	-
#15	Panigada et al	2020	Prospective cohort study	IV	24 intubated COVID-19 patients	-	-	-	Healthy control (comparison purposes)

Exams performed	Medication	Prognostic factor	Influence of COVID-19 (SARS-CoV-2) on thrombosis	Main conclusions and outcomes
Complete duplex ultrasound	Low molecular weight heparin or unfractionated heparin with anti-Xa monitoring (therapeutic levels of 0.3-0.7 U/mL of anti-Xa activity)	-	Severe and anticoagulated COVID-19 patients with VTE.	The general rate of VTE in patients was 69%. The quantity of VTE was significantly higher in patients treated with prophylactic anticoagulation when compared to the group treated with therapeutic anticoagulation. Unexpectedly, it was found a high rate of thromboembolic events in COVID-19 patients treated with therapeutic anticoagulation. These results suggest taking to account both systematic screening of VTE and early therapeutic anticoagulation in severe ICU COVID-19 patients.
Two-point compression ultrasonography	Heparin with dosage weight-adjusted and therapeutic in two patients with direct oral anticoagulants.	D-dimer level	Thromboembolic complications in hospitalized patients with COVID-19.	Rapidly increasing D-dimer levels were observed in non-survivors, reflecting the inflammatory and pro-coagulant state of COVID-19. The high number of arterial and venous thromboembolic events were diagnosed within 24 h. There is an urgent need to improve specific VTE diagnostic strategies and investigate the efficacy and safety of thromboprophylaxis in ambulatory COVID-19 patients.
Blood tests on admission	Nadroparin (2850 IU once daily or 5700 IU)	D-dimer level/higher NLR	Coronavirus disease 2019 (COVID-19) may lead to systemic coagulation activation and thrombotic complications.	Median follow-up of 7 d, 39 patients (20%) were diagnosed with VTE of whom 25 (13%) had symptomatic VTE. VTE seemed to be related to death. The cumulative incidence of VTE was higher at 7, 14 and 21 d than on the wards. Optimal diagnostic and prophylactic strategies are needed to avoid VTE and possibly improve survival rate.
Thromboelastography, platelet count, prothrombin time, aPTT, fibrinogen levels	-	D-dimer level	COVID-19 leads to a severe imbalance of haemostasis that has been lately described as a state of disseminated intravascular coagulation (DIC) and consumption coagulopathy, defined as diminished platelet count, improved fibrinogen degradation products such as D-dimer, as well as low fibrinogen.	Thromboelastography by the TEG point-of-care device shows parameters consistent with a state of hypercoagulability. Platelet count was regular or increased, prothrombin time and aPTT were near normal. Fibrinogen was increased and D-dimer was dramatically increased. These findings may explicate the events of venous thromboembolism observed in some patients and support antithrombotic prophylaxis/ treatment.

(Continues)

TABLE 1 (Continued)

	Author	Year	Type of study	LoE	Sample size (n)	Mean age	Most frequent comorbidities	Death toll	Control group
#16	Ranucci et al	2020	Prospective case-control study	IV	16	61	Obesity	-	-
#17	van Dam et al	2020	Retrospective cohort study	IV	23	63	Previous VTE, active malignancy.	-	100 consecutive control patients diagnosed with acute PE before the COVID-19 outbreak.
#18	Yu et al	2020	Retrospective case-control study	IV	103 (57 = COVID/46 = bacterial pneumonia)	65	Arterial hypertension/ Diabetes mellitus	4	Patients with verified community-acquired bacterial pneumonia (CAP).
#19	Zhang et al	2020	Retrospective case-control study	IV	343	62	Diabetes, hypertension, coronary heart disease.	13 (3%)	Patients with negative D-dimer levels

Exams performed	Medication	Prognostic factor	Influence of COVID-19 (SARS-CoV-2) on thrombosis	Main conclusions and outcomes
The haemostasis and coagulation characterization included the measure of the aPTT International Normalized Ratio (INR), platelet count, fibrinogen, D-dimer, and antithrombin (AT) activity.	Heparin (4000 IU twice daily)	D-dimer level/ Fibrinogen levels and platelet count	A suggestion of thromboembolic complications with clinical relevance for COVID-19 ARDS.	Patients presented a pro-coagulant profile characterized by an increased clot strength (CS), platelet and fibrinogen contribution to CS, elevated D-dimer levels (5.5 μg/mL), and hyperfibrinogenemia (794 mg/dL). After increasing the thromboprophylaxis, there was a significant time-related decrease in fibrinogen levels, D-dimers, CS, PCS, and FCS. The pro-coagulant pattern of these patients may justify the clinical reports of thromboembolic complications during disease manifestation.
Image acquisition and analysis (CT scanner)	Supplemental oxygen therapy	Gender, D-dimer.	COVID-19 infections are related to a high occurrence of venous thromboembolism, particularly PE.	All thrombotic lesions in COVID-19 patients were found to be in lung parenchyma. The thrombus load was lower in COVID-19 patients as was the prevalence of the most proximal PE in the main/lobar pulmonary artery. Additionally, the mean right to left ventricular diameter (RV/LV) ratio and the prevalence of RV/LV ratio >1.0 were lower in COVID-19 patients. It is suggested that the phenotype of COVID-19 associated PE differs from PE in patients without COVID-19.
Numbers of leukocytes, lymphocytes, and eosinophils; high sensitivity C-reactive protein (hsCRP), procalcitonin, and serum creatine kinase	Heparin (dosage was not described)	D-dimer level	After COVID-19 outbreaks, the risk of thrombosis and bleeding has concerned much consideration.	On admission, both in COVID-19 patients and CAP patients, D-dimer levels were significantly higher. Compared with CAP patients, D-dimer levels were increased in COVID-19 patients. D-dimer values were associated with inflammation markers, especially with hsCRP. However, there was low correlation between VTE score and D-dimer levels, weakening the role of D-dimer in the prediction of thrombosis. Summarily, elevated baseline D-dimer levels are related to inflammation, but not with VTE score in COVID-19 patients. Abnormal changes in the D-dimer and inflammatory factors suggest that anticoagulant therapy may be needed.
Blood count, coagulation profile, serum biochemical tests (including renal and liver function)	-	D-dimer level	Early and effective predictors of clinical outcomes is crucial needed to advance management of COVID-19 patients. This may be the case of D-dimer level on admission.	The optimal cut-off value of D-dimer to predict in-hospital mortality was 2.0 μg/mL. D-dimer on admission higher than 2.0 μg/mL may predict in-hospital mortality in patients with COVID-19.

(Continues)

TABLE 1 (Continued)

	Author	Year	Type of study	LoE	Sample size (n)	Mean age	Most frequent comorbidities	Death toll	Control group
#20	Zuo et al	2020	Prospective case-control study	IV	80 (50 = COVID/30 = Healthy)	61	Hypertension, diabetes, heart disease, history of smoke, renal disease, lung disease, obesity	-	Serum of healthy volunteers.

Note: Data not described or approach not performed.

Abbreviations: aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; CT, computed tomography; DVT, deep vein thrombosis; ICU, intensive care unit; LoE, Level of evidence according to Oxford Center for Evidence-Based Medicine; NLR, neutrophil to lymphocyte ratio; PE, pulmonary embolism; TE, thrombotic events; VTE, venous thromboembolism.

After the title and abstract screening, 202 articles were excluded, resulting in 32 articles which were selected for full-text evaluation. Then, 20 articles were eligible to qualitative analysis and 6 articles were included in the meta-analysis (quantitative synthesis). Amongst the 20 eligible articles in the present systematic review, 7 of all of them were cohort studies (25% retrospective and 10% prospective), 11 case-control studies (40% retrospective and 15% prospective) and 2 investigations were cross-sectional studies (10%). Table 1 summarizes the characteristics and key results of the included articles.

3.2 | Synthesis of results

Eighteen studies (86%) evaluated patients in the age group from 59.9 to 73.2 years.[5,6,14-29] Fu et al[30] investigated 75 patients within the mean age of 46.6 years and Panigada et al[31] did not present the age of patients. Among these studies, the mean age of patients affected by COVID-19 and without thrombotic events was 62.40 and the mean age of patients diagnosed with COVID-19 associated with thrombotic events was 63.78.[6,14,17-19,24]

Seventeen articles (85%) described comorbidities that were frequently associated with the inpatient care, such as hypertension[6,14,18,22,23,27-30]; diabetes[5,6,14,16,18,23,27-30]; respiratory diseases[5,6,29,30]; chronic kidney disease[5,20,21,23,29]; cardiovascular diseases[5,16,18,28,29]; cancer[19-21,26] and obesity.[24,25,29] The frequency of these comorbidities was the same for patients affected by COVID-19 with and without thrombotic events.

Thirteen studies (65%) reported death tools. The fatality rate varied from 0% to 23.7%. Moreover, different therapeutic approaches were described. Anticoagulants were used in 13 studies (65%).[6,14-17,19-25,27] Antiviral or corticosteroids were used in two studies (10%).[5,29] Three studies did not mention any type of therapy.[18,28,31] Among these studies, only one evaluated the death tools in patients affected by COVID-19 associated with thrombotic events, being this rate of 40%.[18]

Examinations that evaluated prognostic factors for thrombosis were used in some of the included studies. A total of 16 articles (80%) requested complementary examinations and 14 (70%) of them included D-dimer level for evaluating the thrombosis risk.[5,14,16-19,23-28,30,31]

Zhang et al[28] established that D-dimer levels higher than 2.0 μg/mL may correlate with hospital mortality in patients affected by COVID-19. In addition, Artifoni et al[14] suggested that D-dimer values ≥3.0 μg/mL could act as a prognostic factor for the development of thromboembolic events. Demelo-Rodríguez et al[19] and Ranucci et al[25] showed that patients with deep vein thrombosis (DVT) and thromboembolic complications have increased D-dimer levels (4.5 μg/mL and 5.5 μg/mL, respectively). Still to demonstrate the importance of D-dimer as a prognostic factor, Helms et al[5] observed that the majority of patients (>95%; n = 150) have increased D-dimer and fibrinogen levels.

Besides D-dimer level, other factors, such as oxygen saturation[15]; levels of C-reactive protein, creatine kinase, lactate dehydrogenase and ferritin[16]; Sequential Organ Failure Assessment (SOFA) score[17]; neutrophil-to-lymphocyte ratio[24]; fibrinogen levels and platelet count[25] and evaluation

Exams performed	Medication	Prognostic factor	Influence of COVID-19 (SARS-CoV-2) on thrombosis	Main conclusions and outcomes
Laboratory tests/ Quantification of cell-free DNA/ Quantification of Cit-H3/ Quantification of MPO-DNA complexes	Hydroxychloroquine	Neutrophil extracellular traps (NETs)	Unregulated NETs have the potential to propagate inflammation and microvascular thrombosis; including in the lungs of patients with COVID-19 acute respiratory distress syndrome.	Elevated levels (in the serum from COVID-19 patients) of cell-free DNA, myeloperoxidase-DNA (MPO-DNA), and citrullinated histone H3 (Cit-H3) were found. The latter 2 are specific markers of NETs. Cell-free DNA strongly correlated with C-reactive protein, D-dimer, and lactate dehydrogenase, as well as absolute neutrophil count. MPO-DNA associated with both cell-free DNA and absolute neutrophil count, while Cit-H3 correlated with platelet levels. These findings may indicate NETs as novel therapeutic targets in COVID-19.

of neutrophil extracellular traps (NETs),[29] have been studied as prognostic factors for thromboembolic events.

Imaging examinations, such as duplex ultrasonography, angiotomography[5,14,20,21,23]; lower limb compression ultrasonography[17]; chest computed tomography (CT), Doppler ultrasound[18,19,26]; complete duplex ultrasound[22]; and thromboelastography,[31] have been also performed for the evaluation of thrombotic conditions associated with COVID-19. Moreover, other types of evaluation were also utilized, such as haematology laboratory tests[6,24,25,27-30] and quantification of cell-free DNA/ quantification of Cit-H3/ quantification of MPO-DNA complexes.[29]

3.3 | Quality analysis of studies and level of evidence

Table 2 shows the outcomes of the quality analysis of the case-control and cohort studies based on the Newcastle-Ottawa scale. Additionally, all included scientific articles presented level of evidence 4, according to Oxford University Center for Evidence-Based Medicine criteria (Table 1).

In the case-control studies included in the present systematic review, the main bias was related to the exposure. The studies have failed in the sample size formation (very divergent) and details about the formation of the control and case groups. In addition, cohort studies presented bias associated with selection and outcome. Selection bias was associated with the lack of representativeness of the exposed cohort and with the lack of drawing the non-exposed cohort from a different source. Outcome bias was associated with the absence of the following information: follow-up and lost rates.

3.4 | Meta-analysis

Articles that investigated possible prognostic factors of thrombotic events in COVID-19 patients were included. Almost all data collected in the eligible articles showed non-parametric data. Therefore, the mean was estimated according to Luo et al[32] and the standard deviation was estimated according to Wan et al.[33]

COVID-19 patients with thrombotic events were 2.23 years older than COVID-19 patients without thrombotic events ($P = .0493$). The high level of heterogeneity ($I^2 = 66\%$) made the data unreliable (Figure 2A). Additionally, the trim-and-fill test identified two articles with possible publication bias,[14,19] but no significant results were found ($P = .1038$) and the high level of heterogeneity ($I^2 = 69\%$) remained (Figure 2B). After excluding the articles responsible for the high level of heterogeneity, an additional meta-analysis was conducted and showed significant results (2.83 years) ($P = .0202$). However, high level of heterogeneity was still found ($I^2 = 77\%$) (Figure 2C).

No statistically significant results were found for platelet ($P = .6904$) and neutrophils ($P = .2353$) count and for levels of C-reactive protein (0.9838), lactate dehydrogenase ($P = .4243$) and ferritin ($P = .2538$) (Figure 3A-F and Figure 4C-F). A high level of heterogeneity ($I^2 > 50\%$) was observed for platelet count, lactate dehydrogenase and ferritin. In contrast, the neutrophils count, and C-reactive protein level demonstrated low level of heterogeneity ($I^2 < 50\%$). In addition, there were publication biases for lactate dehydrogenase levels (Figure 3D) and platelet count (Figure 3B). For platelet count, after the removal of one article,[19] an additional meta-analysis was performed, showing no significant results ($P = .6594$).

TABLE 2 Quality analysis of the case-control and cohort studies based on the Newcastle-Ottawa scale

Study	Study design	Selection (maximum 4 stars)	Comparability (maximum 2 stars)	Outcome/Exposure (maximum 3 stars)
Artifoni et al	Retrospective cohort	★★	★★	★
Ayerb et al	Case-control	★★★	★★	★★
Cantador et al	Prospective cohort	★★	★★	★★★
Chen et.	Case-control	★★★	★★	★★
Cui et al	Case-control	★★★	★★	★★
Demelo-Rodrígues et al	Prospective Case-control	★★★	★★	★
Fraissé et al	Case-control	★★★	★★	★★
Fu et al	Case-control	★★★	★★	★
Helms et al	Prospective cohort	★★	★★	★★★
Llitjos et al	Case-control	★★★	★★	★★
Lodigiani et al	Retrospective cohort	★★	★★	★★★
Middeldorp et al	Retrospective cohort	★★	★★	★★★
Panigada et al	Prospective cohort	★★	★★	★
Ranucci et al	Prospective Case-control	★★★	★★	★
van Dam et al	Retrospective cohort	★★	★★	★
Yu et al	Case-control	★★★	★★	★★
Zhang et al	Case-control	★★★	★★	★★
Zuo et al	Prospective Case-Control	★★★★	★★	★★

D-dimer showed significant results in the meta-analysis ($P < .0001$). Patients with COVID-19 reached D-dimer levels up to 3.17 μg/mL, even with the absence of any thrombotic events. Low level of heterogeneity ($I^2 = 48\%$) and inexistence of publication and meta-analysis biases were also observed (Figure 4A,B).

4 | DISCUSSION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new type of respiratory transmitted virus. The coronavirus disease 2019 (COVID-19) pandemic is responsible for highly intensive care unit (ICU) admission rates and high fatality rate.[6,18,22,28]

Besides respiratory failure, coagulopathy and thrombosis are abnormalities that can occur in patients affected by COVID-19.[22] Previous works highlighted that the new coronavirus can activate inflammatory and thrombotic processes. In this scenario, mononuclear cells interact with activated platelets and with the coagulation cascade, which triggers inflammatory cells. The exacerbated inflammatory process due to COVID-19 infection, accompanied by the release of pro-inflammatory cytokines, lead to the impairment of the natural coagulation pathways.

In other words, this disease can be related with increased inflammatory cytokines and coagulation disorders, predisposing to the development of thrombus.[34,35] Up to now, there is no correlation between the clinical behaviour of COVID-19 and the presence of thrombotic events.[36,37] However, patients that presented coagulation abnormalities have a poor prognosis in COVID-19.[37] This fact expresses the need to establish reliable prognostic factors related to thrombotic events.

Among the findings in qualitative synthesis in the present systematic review, diverse clinical conditions—such as coagulopathy (as disseminated intravascular coagulation—DIC), thrombosis (including deep vein thrombosis (DVT)), venous thromboembolism (VTE), arterial TE (thrombotic events), pulmonary embolism (PE), as well changes in D-dimer level, fibrinogen and platelet count—were frequently associated to severe COVID-19 cases.[5,6,14-31,38]

Moreover, comorbidities are factors associated with COVID-19 disease exacerbation. Gold et al[39] centrally considered a relationship between COVID-19 and comorbidities showed that hypertension, diabetes and respiratory diseases were prevalent in severe and fatal cases. In the present study, the most prevalent comorbidities found in patients with COVID-19 were cardiovascular diseases,[5,16,18,28,29] diabetes,[5,6,14,16,18,23,27-30] respiratory diseases[5,6,29,30] and cancer.[19-21,26] Thus, patients diagnosed with these comorbidities should have a closer medical follow-up.

The risk of thromboembolic events in oncologic patients affected by COVID-19 seems to be considerably increased, especially in older patients and those with other important

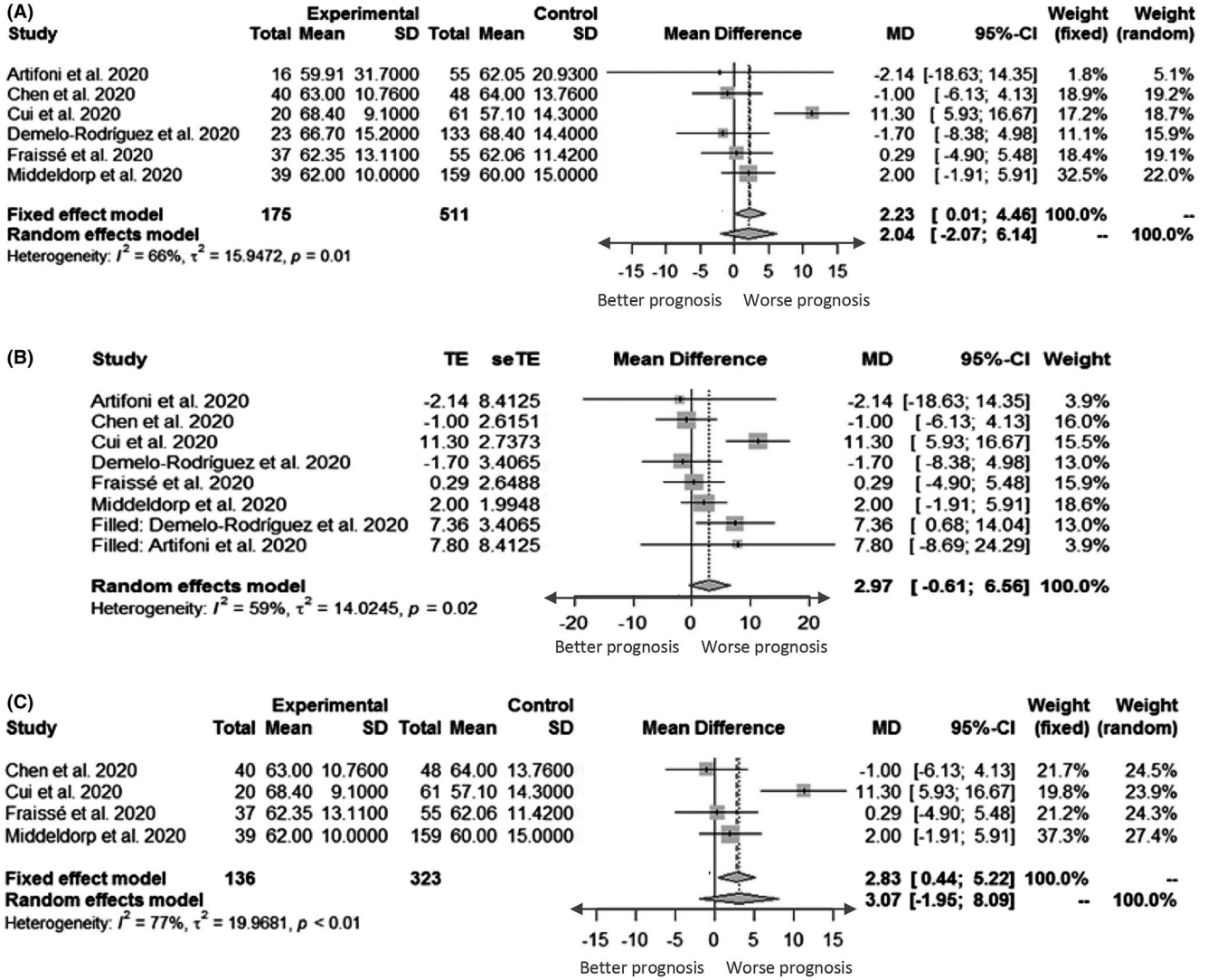

FIGURE 2 Meta-analysis illustrated in a forest plot showing significant results related to age in fixed effect model (A). Trim-and-fill test illustrated in a forest plot showing that Demelo-Rodrígues et al 2020 and Artifoni et al 2020 are responsible for publication and meta-analysis biases. There was no significant result for random effect model (B). Meta-analysis illustrated in a forest plot performed after the exclusion of the articles responsible for biases. Significant results can be observed for fixed effect model (C). Experimental group was formed by patients tested positive for COVID-19 with thrombolytic event. Control group was formed by patients tested positive for COVID-19 without thrombolytic event. CI, confidence interval; MD, mean difference; SD, standard deviation; SeTE, standard error of treatment estimate; TE, estimate of treatment effect. Arrows indicate the direction of the effect

comorbidities (including pulmonary illness).[40,41] That is partly due to the cancer itself, once cancer can directly influence the presence of hypercoagulability that is responsible for the clinical events of vascular occlusion.[42] Furthermore, the effects of antineoplastic therapy, supportive drugs, such as steroids, and the immunosuppressive properties of cancer itself might be responsible for this higher thromboembolic risk.[42,43]

The treatment of cancer patients with COVID-19 is quite challenging, due to their vulnerable status and the aggressive nature of their underlying disease.[44] Considering that, the European Society for Medical Oncology states that prophylaxis of thromboembolic events should be continued in accordance with existing guidelines.[40] Moreover, proper and preventive measures must be taken to reduce the risk of COVID-19 in patients with cancer, and to effectively manage those who are infected by the virus. These actions are pivotal, since inpatients with cancer infected by SARS-CoV-2 have high chance of mortality.[45]

There are many types of thrombotic diseases found in patients affected by COVID-19; however, the most prevalent are VTE,[22] PE,[5,20,21] and arterial and venous thromboembolism.[6,16] This prevalence can vary according to the type of tissue that the SARS-CoV-2 infect, presence of systematic diseases of COVID-19 patients, and genetic and epigenetic factors inherent to the host.[46] In this regards, a recent study reported that lung parenchyma was the most usual site for

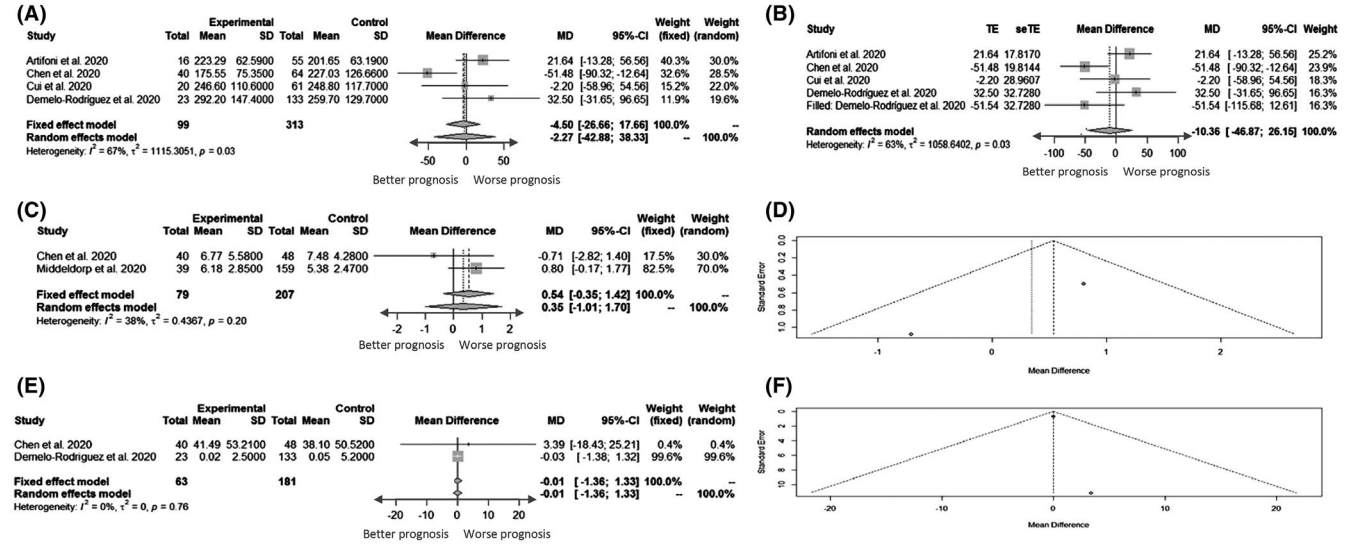

FIGURE 3 Meta-analysis illustrated in a forest plot showing no significant results related to platelet count in fixed effect model (A). Trim-and-fill test illustrated in a forest plot showing that Demelo-Rodrígues et al 2020 are responsible for publication and meta-analysis biases related to platelet count in a random effect model (B). Meta-analysis illustrated in a forest plot showing no significant results related to neutrophil count in fixed effect model (C). Funnel plot showing no publication bias for neutrophil count (D). Meta-analysis illustrated in a forest plot showing no significant results related to C-reactive protein in fixed effect model (E). Funnel plot showing no publication bias for C-reactive protein (F). Experimental group was formed by patients tested positive for COVID-19 with thrombolytic event. Control group was formed by patients tested positive for COVID-19 without thrombolytic event. CI, confidence interval; MD, mean difference; SD, standard deviation; SeTE, standard error of treatment estimate; TE, estimate of treatment effect. Arrows indicate the direction of the effect

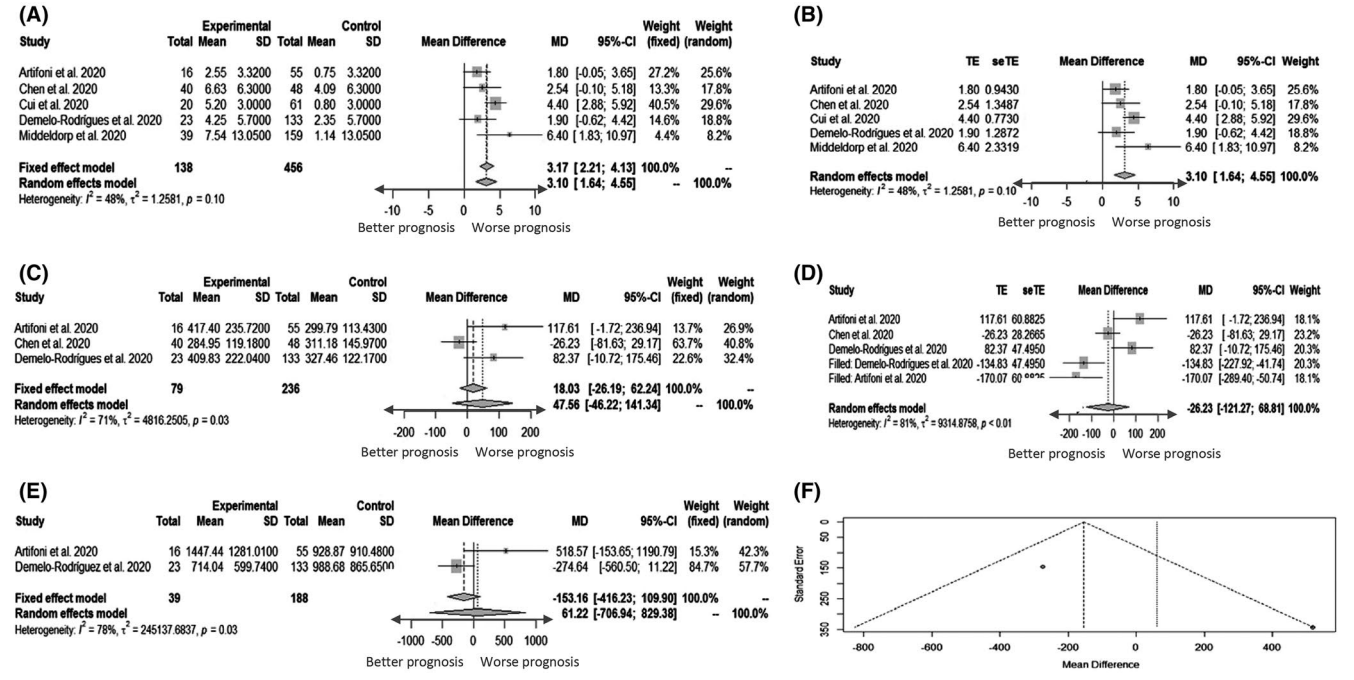

FIGURE 4 Meta-analysis illustrated in a forest plot showing significant results for D-dimer in fixed effect model (A). Trim-and-fill test illustrated in a forest plot showing significant results in a random effect model and no publication and meta-analysis biases for D-dimer (B). Meta-analysis illustrated in a forest plot showing no significant results for lactate dehydrogenase in fixed effect model (C). Trim-and-fill test illustrated in a forest plot showing that Demelo-Rodrígues et al 2020 and Artifoni et al 2020 are responsible for publication and meta-analysis biases related to lactate dehydrogenase (D). Meta-analysis illustrated in a forest plot showing no significant results for ferritin in fixed effect model (E). Funnel plot showing no publication bias for ferritin (F). Experimental group was formed by patients tested positive for COVID-19 with thrombolytic event. Control group was formed by patients tested positive for COVID-19 without thrombolytic event. CI, confidence interval; MD, mean difference; SD, standard deviation; SeTE, standard error of treatment estimate; TE, estimate of treatment effect. Arrows indicate the direction of the effect

thrombotic events found in patients with COVID-19, using computed tomography (CT) scanner for diagnostics.[26]

Though the precise mechanisms of COVID-19-associated pulmonary emboli and lung microcirculatory thrombotic disease have not been clarified, some mechanisms related to infection, inflammation and coagulation are probably involved. When SARS-CoV-2 infects cells expressing the surface receptors ACE-2, the virus is released inside the host cells, promoting pro-inflammatory apoptosis, triggering oxidative stress and producing pro-inflammatory cytokine and chemokine which are also released from neighbouring cells. The tissue factor, generally hidden in the subendothelium, is upregulated on endothelial cells, leukocytes and platelets, leading to activation of the extrinsic and intrinsic coagulation paths for thrombin production. Subsequently, thrombin binds to protease-activated receptors to promote fibrin formation, activating platelets and allowing clot stabilization. Additionally, blocked small lung blood vessels are expected to contain fibrin, platelets and coagulation factors.[47]

The most frequently investigated prognostic factor for thrombotic events in COVID-19 patients was D-dimer levels, which was evaluated in 70% of the studies.[5,14,17-19,23-26,28,30,31] Based on these results of the present review, D-dimer levels can be considered a central prognostic factor for thrombosis and inflammatory conditions in patients with COVID-19. However, D-dimer precise values are different and varied among the studies included in this work. Thus, more randomized studies, notably observational studies with bigger sample sizes and adequate control groups, are essential to clarify the role of this factor on predicting thrombotic complications in COVID-19 patients.

Classic anticoagulants from heparin family were the main medication used for thrombotic events complications due to COVID-19 disease.[48] Averbe et al[15] showed that heparin was associated with lower mortality. In addition, there are scientific evidences that chronic anticoagulation therapy at admission was associated with a lower risk of VTE.[20,21] Moreover, after increasing the thromboprophylaxis, patients with COVID-19 showed a significant time-related decrease in fibrinogen and D-dimers levels.[25]

On the other hand, there are also scientific evidences that the use of thromboprophylaxis cannot significantly reduce the risk of TE and DVT.[6,17] Still, taken all these findings together, it is suggested considering both systematic screening of TE and early therapeutic anticoagulation in severe ICU COVID-19 patients with the urgent need to improve specific VTE diagnostics, and investigate the efficacy and safety of thromboprophylaxis in COVID-19 patients.[22-24,27]

Concerning the quality analysis, observational investigations present different study designs, which is associated with different research purposes. The bias related to case-control and cohort studies brings great difficulty for inferencing the results to other population and groups.[49,50] The requirement of responses to COVID-19 and the problem related to this SARS-CoV-2 pandemic may be directly assigned to the bias identified in the different articles and experimental designs.

A meta-analysis was also performed in order to help identify possible quantitative prognostic factors for COVID-19-related thrombotic events and to support physicians on the best clinical scenario and timing for prescribing anticoagulants agents. With the quantitative analysis, thrombotic events might be expected in COVID-19 patients with D-dimer values above 3.17 μg/mL. In addition, it may be considered that neutrophils count and C-reactive protein levels were not prognostic factors to thrombotic events in COVID-19 patients. Finally, COVID-19 patients with coagulopathy were 2.23 years older than COVID-19 patients without thrombotic events. Nonetheless, due to high level of heterogeneity in age, these data can be classified as unreliable. This high level of heterogeneity on age might be explained by the dissimilar approaches on managing the pandemic adopted by different medical staff in the world.[51] Still, coagulopathy associated with SARS-CoV-2 appears to be more frequent in patients older than 60 years.

Even so, limited information remains on SARS-CoV-2 and its relationship with thrombotic conditions. Suitable diagnostics examinations and appropriate therapies should be investigated by further randomized studies, including in vivo experiments with different animal models and observational studies to establish other reliable prognostic factors and guidelines for feasible and effective patients' treatments.

5 | CONCLUSION

COVID-19 patients may develop thrombotic events if they are older than 60 years and if they present D-dimer levels above 3.17 μg/mL. It is suggested that D-dimer levels should be assessed for early diagnosis of thrombotic events in COVID-19 patients. Some comorbidities, such as hypertension, cardiovascular diseases, diabetes, respiratory diseases, chronic kidney disease and active cancer, are also relevant and require attention in COVID-19 thromboembolic events.

Clearly, investigation and efforts towards establishing the profile of COVID-19 patients with higher risk for thrombotic events are needed in order to guide enhanced clinical and therapeutic approaches and to increase chances of inpatients survival.

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CONFLICT OF INTEREST

There is no conflict of interest involving any author in the present study.

AUTHOR CONTRIBUTIONS

Initial Concept: Gabbai-Armelin, PR and Brighenti, FL; Keywords and data searching: Gabbai-Armelin, PR, Brighenti, FL and De Oliveira, AB; Articles selection and data extraction: Gabbai-Armelin, PR and De Oliveira, AB; Prospero registration: Miranda, ML, Gabbai-Armelin, PR, De Oliveira, A.B and Ferrisse, TM; Introduction writing: Sales, LS, Barbosa, ERO and Gabbai-Armelin, PR; Methodology section: Gabbai-Armelin, PR, De Oliveira, A.B and Ferrisse, TM; Results writing: Salomão, KB, Gabbai-Armelin, PR, De Oliveira, A.B and Ferrisse, TM; Quality analysis: De Oliveira, AB and Ferrisse, TM; Meta-analysis: Ferrisse, TM; Discussion: Gabbai-Armelin, PR, Brighenti, F.L, De Oliveira, A.B and Ferrisse, TM; Conclusions: Gabbai-Armelin, PR; De Oliveira, AB; Ferrisse, T.M and Brighenti, FL; Overall paper checking and writing: Gabbai-Armelin, PR; De Oliveira, AB; Ferrisse, T.M, Brighenti, F.L, Salomão, KB, Miranda, ML, Sales, LS and Barbosa, ERO.

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