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Thromboinflammatory Biomarkers in COVID-19: Systematic Review and Meta-analysis of 17,052 Patients

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Abstract

Objective: To evaluate differences in thromboinflammatory biomarkers between patients with severe coronavirus disease 2019 (COVID-19) infection/death and mild infection.

Patients and Methods: MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, EBSCO, Web of Science, and CINAHL databases were searched for studies comparing thromboinflammatory biomarkers in COVID-19 among patients with severe COVID-19 disease or death (severe/nonsurvivors) and those with nonsevere disease or survivors (nonsevere/survivors) from January 1, 2020, through July 11, 2020. Inclusion criteria were (1) hospitalized patients 18 years or older comparing severe/nonsurvivors vs nonsevere/survivors and (2) biomarkers of inflammation and/or thrombosis. A random-effects model was used to estimate the weighted mean difference (WMD) between the 2 groups of COVID-19 severity.

Results: We included 75 studies with 17,052 patients. The severe/nonsurvivor group was older, had a greater proportion of men, and had a higher prevalence of hypertension, diabetes, cardiac or cerebrovascular disease, chronic kidney disease, malignancy, and chronic obstructive pulmonary disease. Thromboinflammatory biomarkers were significantly higher in patients with severe disease, including D-dimer (WMD, 0.60; 95% CI, 0.49 to 0.71; I^2=83.85%), fibrinogen (WMD, 0.42; 95% CI, 0.18 to 0.67; I^2=61.88%; P<.001), C-reactive protein (CRP) (WMD, 35.74; 95% CI, 30.16 to 41.31; I^2=85.27%), high-sensitivity CRP (WMD, 62.68; 95% CI, 45.27 to 80.09; I^2=0%), interleukin 6 (WMD, 22.81; 95% CI, 17.90 to 27.72; I^2=90.42%), and ferritin (WMD, 506.15; 95% CI, 356.24 to 656.06; I^2=52.02%). Moderate to significant heterogeneity was observed for all parameters (I^2 > 25%). Subanalysis based on disease severity, mortality, and geographic region of the studies revealed similar inferences.

Conclusion: Thromboinflammatory biomarkers (D-dimer, fibrinogen, CRP, high-sensitivity CRP, ferritin, and interleukin 6) and marker of end-organ damage (high-sensitivity troponin I) are associated with increased severity and mortality in COVID-19 infection.

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As coronavirus disease 2019 (COVID-19) continues to spread across the world, there is accumulating evidence supporting the relative contribution of specific comorbidities and laboratory patterns among severely affected patients necessitating intensive care admission or resulting in mortality.[1-75] The US Food and Drug Administration recently approved remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized patients with severe disease (defined as patients with oxygen saturation of ≤94% while breathing room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation [ECMO]).[57] A 10-day course has been approved for COVID-19–infected patients who require invasive mechanical ventilation and/or ECMO and a 5-day course for patients not requiring mechanical ventilation and/or ECMO.[56] With the availability of potential treatment, the identification of clinical and laboratory predictors of severe disease is

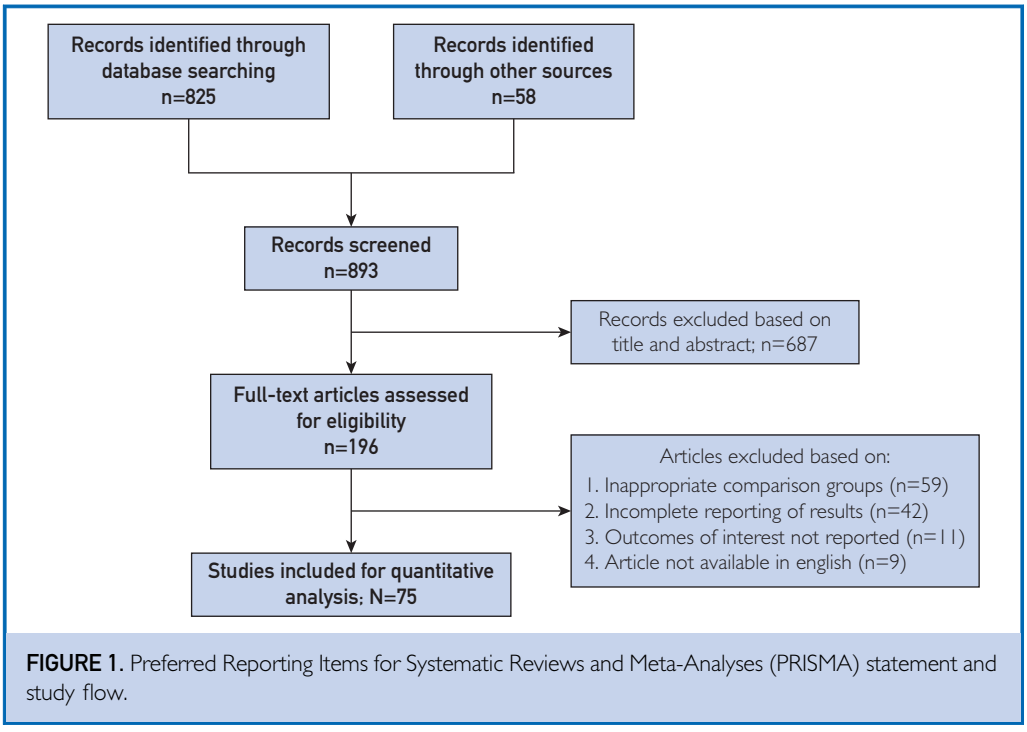

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and study flow.

urgently needed to further risk stratify patients and optimize the allocation of medications to improve clinical outcomes. Earlier meta-analyses have evaluated such predictors; however, at the time of their publication, limited data were available, reducing the confidence in their conclusions. Moreover, the data available at the time of prior meta-analyses were exclusively from China, where the COVID-19 infection initially spread. These analyses combined data from multiple studies with overlapping populations and could not account for any racial/ethnic differences in the thromboinflammatory milieu.[76-78] We hypothesized differences in the thromboinflammatory milieu according to disease severity and race/ethnicity. The aim of the current systematic review and meta-analysis was to (1) compare the differences in comorbidities and thromboinflammatory biomarkers between patients with severe COVID-19 infection/death (severe/nonsurvivors) due to COVID-19 infection and mild COVID-19 infection (nonsevere/survivors) and (2) assess the relative contribution of race/ethnicity in the thromboinflammatory milieu by comparing biomarkers between the Chinese population and that of countries other than China.

PATIENTS AND METHODS

This systematic review was performed according to Cochrane Collaboration guidance and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[79] The study was exempt from institutional review or ethical board review because of no access to patient-level data.

Search Strategy

We searched PubMed, The Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases from January 1, 2020, through July 11, 2020. We included prospective or retrospective studies that compared severe or fatal COVID-19 infection with mild COVID-19 infection or COVID-19 survivors. The search strategy is included in the Supplementary Appendix (available online at http://mcpiqojournal.org). The reference lists of all the retrieved articles were reviewed for further identification of potentially relevant studies. The identified studies were

TABLE 1. Characteristics of the 75 Included Studies[a]

Reference, year	Country	Follow-up (d)	Groups	Type of study
Bazzan et al,[1] 2020	Italy	11.6	Nonsurvivor vs survivor	Retrospective
Bonetti et al,[2] 2020	Italy	NA	Nonsurvivor vs survivor	Retrospective
Burian et al,[3] 2020	Germany	NA	ICU vs non-ICU	Retrospective
Cen et al,[4] 2020	China	28	Severe vs nonsevere	Retrospective
Chen et al (1),[5] 2020[b]	China	NA	Severe vs nonsevere	Retrospective
Chen et al (2),[6] 2020[b]	China	NA	Severe vs nonsevere	Retrospective
Chen et al (3),[7] 2020	China	NA	Severe/critical vs nonsevere	Retrospective
Deng et al,[8] 2020[b]	China	NA	Nonsurvivor vs survivor	Retrospective
Du et al,[9] 2020[c]	China	33	Nonsurvivor v. survivor	Prospective
Duan et al,[10] 2020[d]	China	NA	Severe vs Nonsevere	Retrospective
Fan et al,[11] 2020[e]	China	NA	Nonsurvivor vs survivor	Retrospective
Fogarty et al,[12] 2020	Ireland	NA	Severe/critical vs nonsevere	Prospective
Fu et al,[13] 2020	China	30	Severe vs nonsevere	Retrospective
Gan et al,[14] 2020[b]	China	NA	Nonsurvivor vs survivor	Retrospective
Gao et al,[15] 2020	China	NA	Severe vs nonsevere	Retrospective
Gong et al,[16] 2020[f]	China	NA	Severe vs nonsevere	Retrospective
Goshua et al,[17] 2020	USA	40	ICU vs non-ICU	Retrospective
Huang et al,[18] 2020[e]	China	10.5	Critical/ICU vs non-ICU	Prospective
Javanian et al,[19] 2020	Iran	NA	Nonsurvivor vs survivor	Retrospective
Ji et al,[20] 2020[g]	China	NA	Severe vs nonsevere	Retrospective
Khamis et al,[21] 2020	Oman	NA	ICU vs non-ICU	Retrospective
Li et al (1),[22] 2020	China	NA	Severe vs nonsevere	Retrospective
Li et al (2),[23] 2020	China	NA	Severe vs nonsevere	Prospective
Li et al (3),[24] 2020[b]	China	30	Nonsurvivor vs survivor	Retrospective
Li et al (4),[25] 2020[h]	China	NA	Nonsurvivor vs survivor	Retrospective
Li et al (5),[26] 2020[b]	China	NA	Nonsurvivor vs survivor	Retrospective
Liu et al (1),[27] 2020	China	NA	Severe vs nonsevere	Retrospective
Liu et al (2),[28] 2020	China	NA	Severe vs nonsevere	Retrospective
Liu et al (3),[29] 2020[b]	China	NA	Nonsurvivor vs survivor	Retrospective
Lu et al,[30] 2020	China	14	Severe vs nonsevere	Retrospective
Lv et al,[31] 2020[g]	China	NA	Severe vs nonsevere	Retrospective
Ma et al,[32] 2020	China	NA	Severe vs nonsevere	Retrospective
Masetti et al,[33] 2020	Italy	NA	Nonsurvivor vs survivor	Retrospective
Mao et al,[34] 2020[b]	China	NA	Severe vs nonsevere	Retrospective
Middeldorp et al,[35] 2020	Netherlands	15	Critical/ICU vs non-ICU	Prospective
Ortiz-Brizuela et al,[36] 2020	Mexico	13	ICU vs non-ICU	Prospective
Pan et al,[37] 2020[b]	China	NA	Severe vs nonsevere	Retrospective
Qian et al,[38] 2020	China	NA	Severe vs nonsevere	Retrospective
Qin et al,[39] 2020[b]	China	NA	Severe vs nonsevere	Retrospective
Rastad et al,[40] 2020	Iran	NA	Nonsurvivor vs survivor	Retrospective
Ruan et al,[41] 2020[b,e]	China	22	Nonsurvivor vs survivor	Retrospective
Salacup et al,[42] 2021	USA	NA	Nonsurvivor vs survivor	Retrospective
Satici et al,[43] 2020	Turkey	NA	Severe vs nonsevere	Retrospective
Shahriarirad et al,[44] 2020	Iran	NA	Nonsurvivor vs survivor	Retrospective
Shi et al,[45] 2020[g]	China	NA	Nonsurvivor vs survivor	Retrospective

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TABLE 1. Continued

Reference, year	Country	Follow-up (d)	Groups	Type of study
Sun et al,[46] 2020	China	NA	Severe vs nonsevere	Prospective
Tang et al (1),[47] 2020[b]	China	NA	Nonsurvivor vs survivor	Retrospective
Tang et al (2),[48] 2020[b]	China	28	Nonsurvivor vs survivor	Retrospective
Tian et al,[49] 2020[b,c,e]	China	30	Severe vs nonsevere	Retrospective
Vultaggio et al,[50] 2020	Italy	21	Severe vs nonsevere	Retrospective
Wan et al,[51] 2020[d]	China	NA	Severe vs nonsevere	Retrospective
Wang et al (1),[52] 2020[f]	China	34	Critical/ICU vs non-ICU	Retrospective
Wang et al (2),[53] 2020[f]	China	21	Nonsurvivor vs survivor	Retrospective
Wang et al (3),[54] 2020	China	NA	Severe vs nonsevere	Retrospective
Wang et al (4),[55] 2020	China	NA	Severe vs nonsevere	Retrospective
Wang et al (5),[56] 2020[b]	China	NA	Critical/ICU vs non-ICU	Retrospective
Wang et al (6),[57] 2020[b]	China	NA	Severe vs nonsevere	Retrospective
Wu et al (1),[58] 2020[e]	China	50	ARDS vs non-ARDS	Retrospective
Yan et al,[59] 2020[b]	China	NA	Nonsurvivor vs survivor	Retrospective
Yang et al (1),[60] 2020[e]	China	28	Nonsurvivor vs survivor	Retrospective
Yang et al (2),[61] 2020	China	NA	Severe vs nonsevere	Retrospective
Yang et al (3),[62] 2020	China	NA	Severe vs nonsevere	Retrospective
Yang et al (4),[63] 2020	China	NA	Nonsurvivor vs survivor	Retrospective
Ye et al,[64] 2020[c]	China	NA	Nonsurvivor vs survivor	Retrospective
Zeng et al,[65] 2021	China	30	ICU vs non-ICU	Retrospective
Zhang et al (1),[66] 2020	China	NA	Severe vs nonsevere	Retrospective
Zhang et al (2),[67] 2020	China	NA	Severe vs nonsevere	Prospective
Zhang et al (3),[68] 2020[b]	China	NA	Severe vs nonsevere	Retrospective
Zhang et al (4),[69] 2020[b]	China	36	Nonsurvivor vs survivor	Retrospective
Zhang et al (5),[70] 2020[f]	China	NA	Severe vs nonsevere	Retrospective
Zheng et al,[71] 2020	China	NA	Severe vs nonsevere	Retrospective
Zhou et al (1),[72] 2020[c,e]	China	21	Nonsurvivor vs survivor	Retrospective
Zhou et al (2),[73] 2020	China	NA	Severe vs nonsevere	Prospective
Zhu et al (1),[74] 2020	China	NA	Severe vs nonsevere	Retrospective
Zhu et al (2),[75] 2020	China	NA	Nonsurvivor vs survivor	Retrospective

[a]ARDS = acute respiratory distress syndrome; ICU = intensive care unit; NA = not available; USA = United States.
[b]Data from the same hospital—Tongji Hospital, China (n=18 exclusive; n=2 shared).
[c]Data from the same hospital—Wuhan Pulmonary Hospital, China (n=2 exclusive; n=2 shared).
[d]Data from the same hospital—Chongqing Three Gorges Hospital, China (n=2 exclusive).
[e]Data from the same hospital—Wuhan Jin Yin-tan Hospital, China (n=4 exclusive; n=2 shared).
[f]Data from the same hospital—Zhongnan Hospital of Wuhan University, China (n=4 exclusive).
[g]Data from the same hospital—Wuhan University Renmin Hospital, China (n=3 exclusive).
[h]Data compiled from >1 hospital noted above.

systematically assessed using the inclusion and exclusion criteria described subsequently.

Eligibility Criteria

Two reviewers (Rahul Chaudhary and J.G.) independently selected the studies and abstracted data on study characteristics, design, reported comorbidities, laboratory parameters, and reported clinical outcomes. Discrepancies between the 2 reviewers were resolved by discussion and consensus. The final results were reviewed by the senior investigators (W.E.W. and R.D.M.) (Figure 1). The eligibility criteria were (1) hospitalized patients 18 years or older comparing severe/nonsurvivor COVID-19–positive patients vs nonsevere/survivor COVID-19–positive patients and (2) reported biomarkers of inflammation

and/or thrombosis. Studies of pregnant women (due to inherent changes in markers of thromboinflammation during pregnancy) and reports with incomplete reporting of biomarkers were excluded. Abstracts, case reports, conference presentations, editorials, reviews, expert opinions, and literature not published in English were excluded.

Outcome Definition

Severe COVID-19 was designated when the patients had one of the following criteria: (1) respiratory distress with respirations of 30 or more per minute, (2) pulse oximeter oxygen saturation of 93% or less at rest, and (3) oxygenation index (arterial partial pressure of oxygen/inspired oxygen fraction) of 300 mm Hg or lower. Nonsevere patients met all the following conditions: (1) epidemiological history, (2) fever or other respiratory symptoms, (3) typical computed tomographic evidence of abnormalities of viral pneumonia, and (4) positive result of the reverse transcription–polymerase chain reaction for COVID-19 RNA. For studies with the categorization of illness in multiple grades of severity, the values from the 2 most extreme groups, eg, critical vs mild illness, were chosen for analysis. The acute cardiac injury was determined if serum levels of cardiac biomarkers (eg, troponin I) were above the 99th percentile upper reference limit or if new abnormalities were detected on electrocardiography and/or echocardiography.

Risk of Bias Appraisal

Assessment of risk of bias for each study was performed using the Newcastle-Ottawa Scale for cohort studies.[80] This tool addresses the domains of patient selection, comparability of groups, and outcome assessment.

Statistical Analyses

We used the random-effects model to pool results across studies and estimate the weighted mean difference (WMD) and odds ratio (OR). We evaluated heterogeneity of effects using the Higgins I-squared (I^2) statistic with heterogeneity defined as $I^2<25\%$ as nonsignificant heterogeneity, between 25% and 50% as mild heterogeneity, between 50% and 75% as moderate heterogeneity and greater than 75% as high heterogeneity. We evaluated the assumption of combining data from patients with severe disease with nonsurvivors and combining nonsevere disease data with survivors by doing each analysis separately. We also compared the results of studies with patients from China vs other locations. A 2-tailed $P<.05$ was considered statistically significant. Meta-analysis was performed using the Comprehensive Meta-Analysis software package, version 3.3.070 (Biostat Solutions, LLC).

RESULTS

A total of 893 studies were identified after the exclusion of duplicate or irrelevant references (Figure 1). After a detailed evaluation, 75 relevant studies were included incorporating a total of 17,052 hospitalized COVID-19–positive patients.[1-75] There were a total of 3664 patients in the severe/nonsurvivor COVID-19 group and 13,388 patients in the nonsevere/survivor group. Except for 9 prospective cohort studies,[9,12,18,23,35,36,46,67,73] all studies were retrospective. Most of the 75 studies were reported from China (80.0% [n=60]), while other studies were from Italy,[1,2,33,50] Iran,[19,40,44] the United States,[17,42] Oman,[21] Turkey,[43] Mexico,[36] Germany,[3] Ireland,[12] and the Netherlands.[35] All studies used reverse transcription–polymerase chain reaction for COVID-19 diagnosis. The overall characteristics of the included studies are described in Table 1 and Supplemental Tables 1 through 4 (available online at http://mcpiqojournal.org).

Risk of Bias

We deemed all the studies to be at a high risk of bias because of unadjusted analyses and variability in groups with comorbidities and prognostic factors.

Meta-analysis in the Combined Group of Disease Severity and Mortality

Among demographics, patients in the severe/nonsurvivor group were older, a greater proportion were men, and had a higher prevalence of hypertension, diabetes, cardiac or cerebrovascular disease, chronic kidney disease, chronic liver disease, malignancy, and chronic obstructive pulmonary disease compared to the nonsevere/survivor group (Supplemental Table 1).

The platelet count was statistically lower in the severe/nonsurvivor COVID-19 group

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(171±34 vs 197±30 $\times 10^9$/L; WMD, −11.75 [95% CI, −16.10 to −7.39]; I^2=76.32%; P<.001). Thromboinflammatory biomarkers were elevated in the severe/nonsurvivor group compared with the nonsevere/survivor group, including D-dimer levels (2.9±3.1 vs 0.8±0.8 mg/dL [to convert values to nmol/L, multiply by 5.476]; WMD, 0.60 [95% CI, 0.49 to 0.71]; I^2=83.85%; P<.001) (Figure 2A), prothrombin time (13.9±2.0 vs 12.7±1.3 s; WMD, 0.75 [95% CI, 0.57 to 0.78]; I^2=37.01%; P<.001), activated partial thromboplastin time (36.6±8.7 vs 35.1±5 s; WMD, 0.81 [95% CI, 0.03 to 1.59]; I^2=70.84%; P=.04), fibrinogen (4.4±1.1 vs 4.0±1.1 g/L; WMD, 0.42 [95% CI, 0.18 to 0.67]; I^2=61.88%; P<.001), C-reactive protein (CRP) (71.3±39.4 vs 23.2±19.1 mg/L; WMD, 35.74 [95% CI, 30.16 to 41.31]; I^2=85.27%; P<.001) (Figure 2B), high-sensitivity (hs)−CRP (96.6±24.9 vs 22.9±6.5 mg/L; WMD, 62.68 [95% CI, 45.27 to 80.09]; I^2=0%; P<.001), interleukin 6 (IL-6) (49.3±35.7 vs 12.5±12.3 pg/L; WMD, 22.81 [95% CI, 17.90 to 27.72]; I^2=90.42%; P<.001), ferritin (1367.0±744.5 vs 635.1±323.0 ng/mL [to convert values to μg/L, multiply by 1]; WMD, 506.15 [95% CI, 356.24 to 656.06]; I^2=52.02%; P<.001), hs-troponin I (36.4±52.8 vs 5.7±3.7 pg/mL [to convert values to μg/L, multiply by 1]; WMD, 10.69 [95% CI, 7.02 to 14.36]; I^2=89.89%; P<.001) (Figure 2C), and lactate dehydrogenase (LDH) (448.6±147.1 vs 267.5±67.3 U/L [to convert values to μkat/L, multiply by 0.0167]; WMD, 155.40 [95% CI, 114.41 to 196.40]; I^2=88.07%; P<.001).

As expected, the severe/nonsurvivor group had higher mortality (OR, 28.14 [95% CI, 14.99 to 52.83]; I^2=0%; P<.001), higher incidence of acute cardiac injury (OR, 12.86 [95% CI, 5.11 to 32.41]; I^2=75.12%; P<.001), and higher incidence of acute respiratory distress syndrome (OR, 59.83 [95% CI, 30.40 to 117.76]; I^2=73.41%; P<.001) compared with the nonsevere/survivor group.

Sensitivity Analyses

Sensitivity analysis was performed by separating disease severity from survivorship. Thus, a separate analysis was done comparing severe vs nonsevere disease, and another analysis compared survivors to nonsurvivors. In general, both analyses provided similar conclusions (Table 2). Additionally, the WMDs in thromboinflammatory biomarkers were compared between studies conducted in China (n=60) and other countries (n=15) to address the overlap of the study population in the published studies from China (Table 1). The non-Chinese population had a higher comorbidity burden, including hypertension, diabetes, cardiac or cerebrovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease. Otherwise, results were similar in the 2 populations (Supplemental Table 5, available online at http://mcpiqojournal.org). Also, there were significant differences between the groups in the WMD for platelet count, fibrinogen level, and hs-troponin I level. The difference in D-dimer levels between the severe/nonsurvivor and the nonsevere/survivor groups was more pronounced in the non-Chinese population. In contrast, the difference between the 2 groups in the CRP levels was more pronounced in the Chinese population (Supplemental Table 5). Similar results were noted when studies were stratified between China and Europe/United States to determine racial/ethnic differences in thromboinflammatory profile (Supplemental Table 5).

DISCUSSION

This systematic review and meta-analysis of 75 published articles and 17,052 COVID-19−positive patients is the largest meta-analysis on the topic and provides a comprehensive analysis of demographic factors and thromboinflammatory biomarkers associated with COVID-19 severity and mortality. In our article, we summarize all the available evidence on the biomarkers of both thrombosis and inflammation in patients with COVID-19 and further analyze the published literature on the differential impact of region and race/ethnicity in the COVID-19 thromboinflammatory milieu. Major findings of our study were (1) severe COVID-19 infection involved older patients with a high proportion of men; (2) comorbidities associated with disease severity and COVID-19−associated mortality included hypertension, diabetes, chronic kidney disease, cardiac or cerebrovascular disease, malignancy, and chronic obstructive pulmonary disease; (3) patients with severe COVID-19

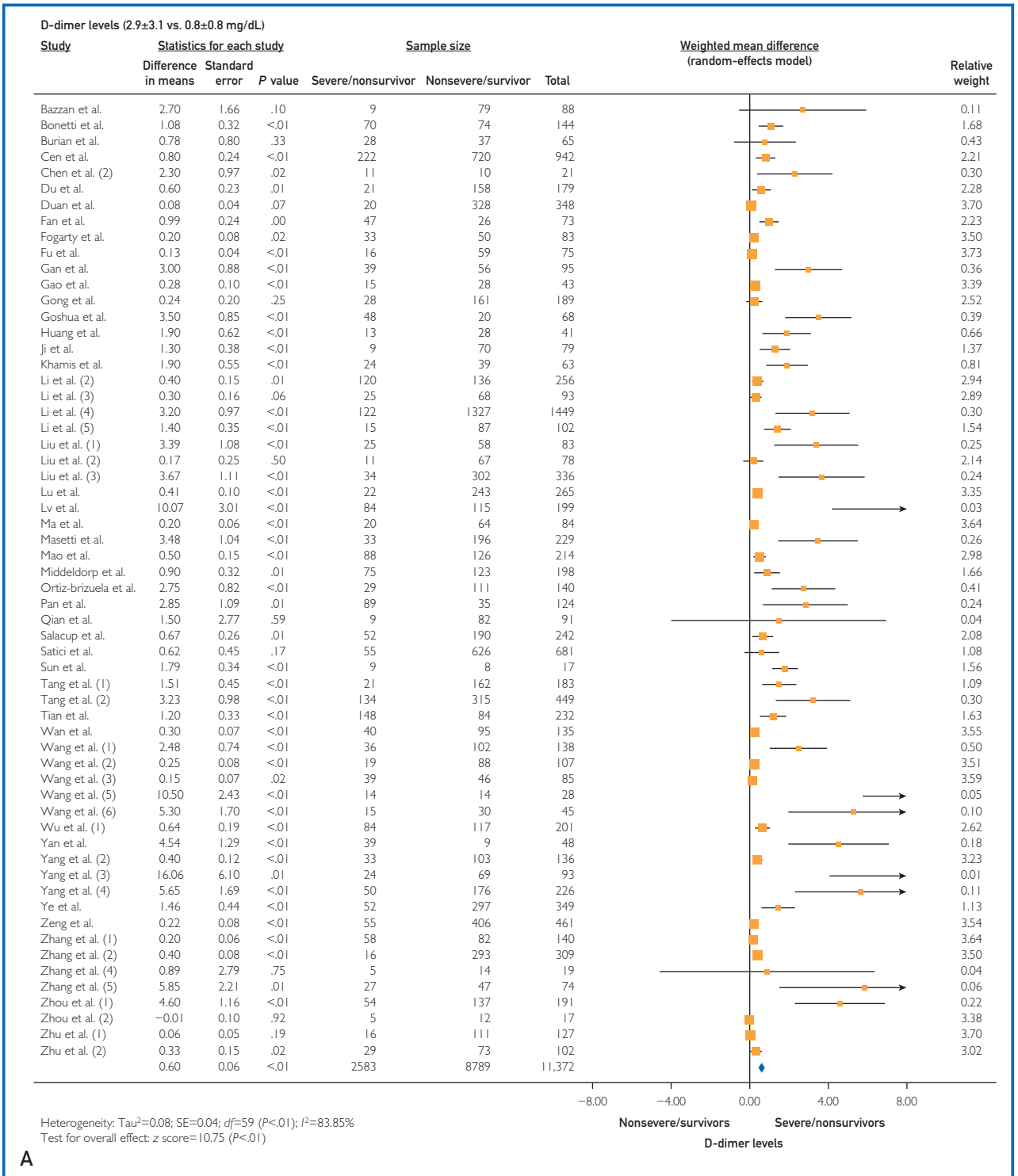

FIGURE 2. Forest plots showing differences in thromboinflammatory biomarkers between severe/nonsurvivor and nonsevere/survivor groups for D-dimer levels (2.9±3.1 vs 0.8±0.8 mg/dL) (A), C-reactive protein (CRP) levels (71.3±39.4 vs 23.2±19.1 mg/L) (B), and high-sensitivity (hs) troponin I levels (36.4±52.8 vs 5.7±3.7 pg/mL).

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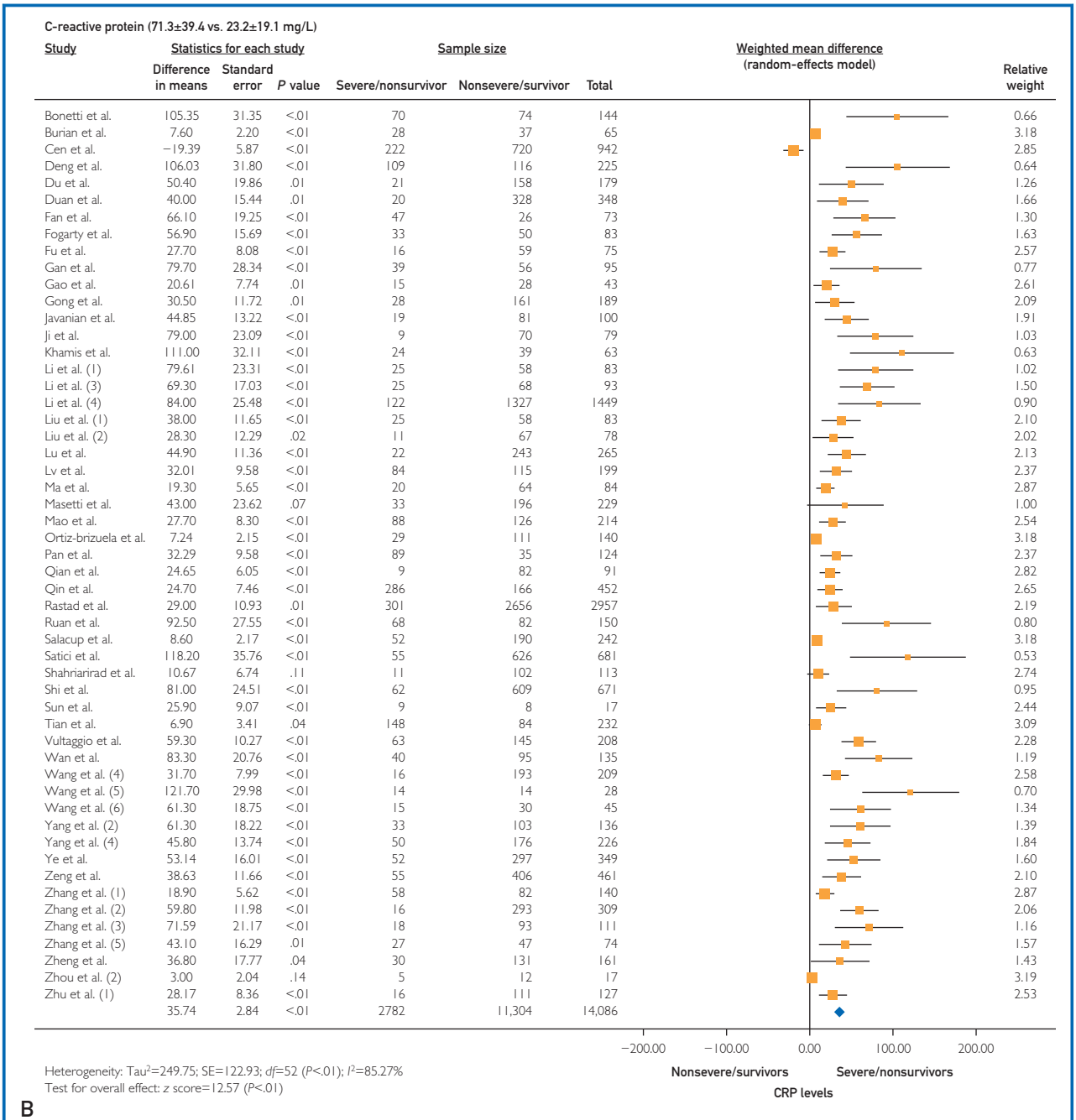

FIGURE 2. (*continued*).

had lower platelet counts compared with patients with nonsevere COVID-19; and (4) the severe/nonsurvivor COVID-19 group had elevated markers of thrombosis, inflammation, and cardiac injury: elevated D-dimer, fibrinogen, CRP, hs-CRP, IL-6, ferritin, hs-troponin I, and LDH levels.

COVID-19 has been described as a thromboinflammatory syndrome.[81,82] Among patients with severe disease and mortality,

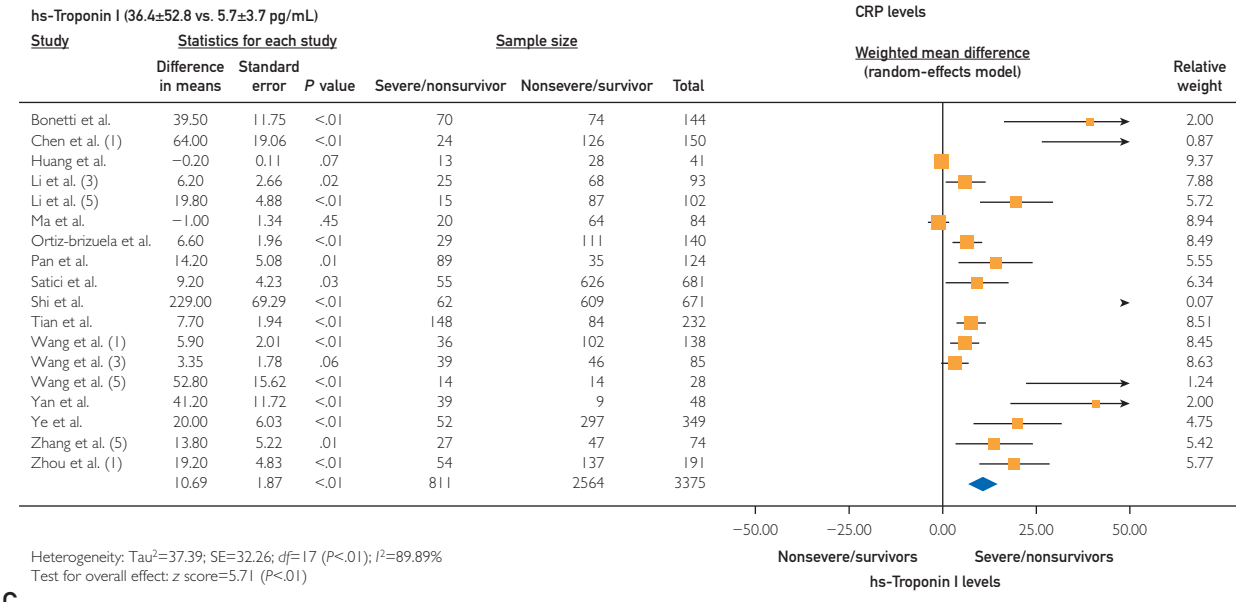

FIGURE 2. (*continued*).

diffuse endothelial dysfunction, widespread coagulopathy, and complement-induced thrombosis have been noted to result in the development of systemic microangiopathy and thromboembolism.[83] The diffuse endothelial dysfunction, coupled with a hyperinflammatory response to the COVID-19 infection, is the harbinger of cytokine storm associated with poor clinical outcomes.[84] Inflammation and vascular endothelial dysfunction predominantly affect the lungs in the early stages, resulting in diffuse alveolar damage and formation of pulmonary microthrombi affecting both ventilation and perfusion (termed *pulmonary intravascular coagulopathy*), which is distinct from disseminated intravascular coagulation.[85-88] Our findings resonate with those of prior analyses.[77,78,89-94] With incremental evidence, the thromboinflammatory biomarkers continue to hold their importance in predicting poor prognosis and severity of COVID-19 infection, especially D-dimer, CRP, and LDH.[48,58,72,95,96]

We observed that a substantial proportion of patients with severe COVID-19 infection had comorbidities of hypertension, diabetes, chronic kidney disease, cardiac or cerebrovascular disease, and chronic obstructive pulmonary disease. All these disorders are associated with endothelial dysfunction manifested by reduced nitric oxide bioavailability as an early event in their pathogenesis.[97-101] Coronaviruses have a unique affinity to the host angiotensin-converting enzyme 2 receptors, which are expressed in the vascular endothelium.[102,103] The enhanced endothelial dysfunction due to COVID-19 among patients with preexisting endothelial dysfunction (due to comorbidities) promotes the likelihood of a cytokine storm leading to adverse clinical outcomes and death.

Our analysis further revealed that patients with severe COVID-19 infection and mortality with COVID-19 had higher levels of D-dimer and fibrinogen. Increased D-dimer levels support the notion of pulmonary intravascular coagulopathy as an early form of disseminated intravascular coagulation and support secondary fibrinolytic conditions in these patients. Several prior studies have reported the association of elevated D-dimer levels with poor prognosis of patients.[78,104] However, D-dimer levels need to be interpreted with caution in

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COVID-19–infected patients. The major issues identified with measuring D-dimer levels include the following. First, D-dimer has poor specificity, and elevated levels are often seen with advanced age, African American race, female sex, active malignancy, surgery, pregnancy, immobility, cocaine use, connective tissue disorders, end-stage renal disease, and prior thromboembolic disease. Second, D-dimer reflects a later stage in the hemostatic process and is released when a clot is degraded by the fibrinolytic processes. Third, the studies reporting D-dimer levels had considerable variation in the units for D-dimer levels, making the pooling of the uncorrected levels unreliable. Finally, D-dimer levels do not capture the dynamic effects of functional interactions among platelets, endothelium, and fibrinolytic processes.[105]

The elevation in the inflammatory biomarkers, including CRP, hs-CRP, ferritin, and IL-6 among severe COVID-19 infections noted in our analysis, is in agreement with findings reported in previous publications.[90,106] In a study by Herold et al[106] with 89 COVID-19–positive patients, biomarkers of inflammation, including IL-6 and CRP, were highly predictive of the need for mechanical ventilation, and LDH was highly predictive of respiratory failure.

Prior studies have found racial/ethnic differences in the baseline levels of thromboinflammatory biomarkers, including D-dimer levels and CRP.[107] Because the inherent differences in the thromboinflammatory milieu across races could theoretically affect clinical outcomes, especially in COVID-19 infection, we evaluated the differences in a subgroup analysis. Most reported studies included only the East Asian population (80% of studies with Chinese patients) with only 15 studies from other countries. Among the included studies, the non-Chinese study participants had a higher prevalence of comorbidities, including hypertension, diabetes, cardiac or cerebrovascular disease, chronic kidney disease, chronic liver disease, and chronic obstructive pulmonary disease. Also, the difference in the D-dimer levels between the severe/nonsurvivor and the nonsevere/survivor groups was more pronounced in the non-Chinese population. In contrast, the difference between CRP levels was more pronounced in the Chinese population (Supplemental Table 5). It can be hypothesized that a difference in the comorbidity burden and thromboinflammatory milieu between the East Asians, Whites, and African Americans could be contributory to the higher case fatality rate noted in Europe and the United States. However, because of the limited published literature from other countries, our confidence in these estimates is low. It remains to be determined whether racial differences in the thromboinflammatory milieu affect COVID-19 outcomes.

Our study has several limitations. In our analysis, we combined the subgroups of severe COVID-19 with nonsurvivors, which could lead to potential confounders. We addressed the confounders by performing a subgroup analysis comparing severe vs nonsevere COVID-19 and nonsurvivors vs survivors, and the results were consistent with the main analysis (Table 2). Additionally, the included studies had heterogeneous populations with differing burdens of comorbidities and not all outcomes were available in all included studies. This issue was reflected in the Higgins I^2 statistic with 57% reflecting significant heterogeneity and 29% reflecting moderate heterogeneity in the analyzed biomarkers. Another confounder was that most of the studies were Chinese with potential overlapping populations artificially amplifying the effect of certain comorbidities and biomarkers (multiple studies reported from the same hospital, Table 1). To address this limitation, WMDs among thromboinflammatory biomarkers were compared according to the country of origin of the study, ie, Chinese vs non-Chinese (Supplemental Table 5). However, because data from non-Chinese countries was lacking, a definite conclusion could not be drawn about the differential weightage of comorbidities and biomarkers among racial/ethnic groups. As the literature continues to increase, it would be imperative to identify the potential role of genetics in the prevalence of poor clinical outcomes among African Americans and Whites compared with East Asians. Another problem with the available data was that the values for D-dimer levels (concerning units of measurement) varied considerably among the studies, and several studies misreported the measuring unit,

TABLE 2. Weighted Mean Differences and Odds Ratios for Biomarkers and Outcomes for the 2 Comparisons of Severe vs Nonsevere (47 Studies, 7388 Patients) and Nonsurvivor vs Survivor (28 Studies, 9664 Patients)[a,b]

Parameter	Severe vs nonsevere		Nonsurvivor vs survivor	
	Mean±SD	WMD/OR (95% CI)	Mean±SD	WMD/OR (95% CI)
Platelet count ($\times 10^9$/L)	179±33 vs 195±32 (n=5135)	WMD: −8.01 (−14.51 to −1.51); I^2=63.76%; ***P*<.001**	159±33 vs 201±28 (n=4518)	WMD: −26.33 (−35.99 to −16.66); I^2=84.75%; ***P*<.001**
D-dimer (mg/dL)	2.9±3.7 vs 0.8±0.9 (n=5863)	WMD: 0.43 (0.32 to 0.54); I^2=83.08%; ***P*<.001**	3±1.8 vs 0.9±0.7 (n=5509)	WMD: 1.35 (0.99 to 1.71); I^2=85.58%; ***P*<.001**
Prothrombin time (s)	13.5±2.3 vs 12.4±1.2 (n=2533)	WMD: 0.53 (0.39 to 0.66); I^2=0%; ***P*<.001**	14.3±1.6 vs 13.1±1.2 (n=3951)	WMD: 1.01 (0.77 to 1.26); I^2=35.39%; ***P*<.001**
aPTT (s)	33.5±5 vs 33.6±5 (n=2559)	WMD: 0.38 (−0.84 to 1.61); I^2=76.51%; ***P*=.54**	41.1±11 vs 37.1±4.6 (n=2797)	WMD: 1.14 (0.12 to 2.16); I^2=59.94%; ***P*=.03**
Fibrinogen (g/L)	4.3±1.5 vs 3.5±1.2 (n=1100)	WMD: 0.62 (0.26 to 0.99); I^2=59.14%; ***P*<.001**	4.6±0.6 vs 4.4±0.7 (n=3520)	WMD: 0.23 (−0.09 to 0.56); I^2=58.32%; ***P*=.16**
CRP (mg/L)	59.2±34.8 vs 19.1±16.3 (n=6099)	WMD: 30.42 (24.31 to 36.53); I^2=85.74%; ***P*<.001**	97±37.1 vs 31.7±22 (n=7987)	WMD: 58.58 (41.23 to 75.93); I^2=84.39%; ***P*<.001**
hs-CRP (mg/L)	102.4±32 vs 25.4±4.8 (n=486)	WMD: 62.72 (37.97 to 87.46); I^2=13.07%; ***P*<.001**	Not enough data	Not enough data
Interleukin 6 (pg/L)	49.2±32.1 vs 12.6±13.1 (n=2385)	WMD: 28.14 (19.93 to 36.35); I^2=91.41%; ***P*<.001**	49.4±46.7 vs 12.2±10.6 (n=1958)	WMD: 15.30 (7.06 to 25.53); I^2=86.71%; ***P*<.001**
Ferritin (ng/mL)	1109±371 vs 584±319 (n=1154)	WMD: 320.92 (1197.54 to 444.30); I^2=12.06%; ***P*<.001**	1626±947 vs 687±341 (n=3179)	WMD: 700.21 (497.52 to 902.90); I^2=27.06%; ***P*<.001**
hs-Troponin I (pg/mL)	22.5±23.5 vs 5.5±4.5 (n=972)	WMD: 5.39 (1.84 to 8.94); I^2=88.81%; ***P*<.001**	50.2±70.3 vs 6±3 (n=2403)	WMD: 18.68 (10.92 to 26.44); I^2=75.69%; ***P*<.001**
LDH (U/L)	377±94 vs 242±54 (n=3371)	WMD: 124.04 (75.42 to 172.66); I^2=90.08%; ***P*<.001**	561±134 vs 303±70 (n=5784)	WMD: 188.77 (153.07 to 224.47); I^2=12.57%; ***P*<.001**
Mortality	30.1% (115 of 383) vs. 1.3% (11 of 862) (n=1319)	OR: 28.14 (14.99 to 52.83); I^2=0%; ***P*<.001**	NA	NA
Acute cardiac injury	24.8% (38 of 153) vs. 9.0% (36 of 402) (n=555)	OR: 4.73 (1.64 to 13.67); I^2=57.83%; ***P*<.001**	56.6% (172 of 304) vs. 3.8% (64 of 1,668) (n=1972)	OR: 43.83 (15.54 to 123.65); I^2=59.33%; ***P*<.001**
ARDS	67.2% (76 of 133) vs. 3.6% (12 of 338) (n=471)	OR: 33.49 (16.75 to 66.98); I^2=17.30%; ***P*<.001**	81.9% (334 of 408) vs. 4.4% (94 of 2,155) (n=2563)	OR: 73.80 (29.66 to 1183.61); I^2=83.21%; ***P*<.001**

[a]aPTT = activated partial thromboplastin time; ARDS = acute respiratory distress syndrome; CRP = C-reactive protein; hs = high-sensitivity; LDH = lactate dehydrogenase; NA = not applicable; OR = odds ratio; WMD = weighted mean difference.

[b]SI conversion factors: To convert D-dimer values to nmol/L, multiply by 5.476; to convert ferritin values to μg/L, multiply by 1; to convert hs-troponin I values to μg/L, multiply by 1; to convert LDH values to μkat/L, multiply by 0.0167.

making the values 1000 times smaller or higher.[105] While performing our analysis, these values were adjusted to reflect appropriate differences between the 2 groups. Additionally, substantial heterogeneity among studies coupled with the high risk of bias (due to unadjusted analyses and unbalanced groups) reduces confidence in the interpretation of the results. Publication bias is also highly likely in a field that primarily consists of small unregistered observational studies.

CONCLUSION

Thromboinflammatory biomarkers (D-dimer, fibrinogen, CRP, hs-CRP, ferritin, and IL-6) and indicators of cardiac damage (hs-troponin I) on admission were associated with the severity and mortality of COVID-19

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infection. Comorbidities conferring higher risk coupled with thromboinflammatory biomarkers might assist in the development of risk prediction models for the severity and prognosis of COVID-19. Such models could potentially aid in the selection of patients to receive early therapeutic strategies, eg, remdesivir therapy, and improve clinical outcomes.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **COVID-19** = coronavirus disease 2019; **CRP** = C-reactive protein; **ECMO** = extracorporeal membrane oxygenation; **hs** = high-sensitivity; **IL-6** = interleukin 6; **LDH** = lactate dehydrogenase; **OR** = odds ratio; **WMD** = weighted mean difference

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