

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

Rahul Chaudhary, MD, MBA; Jalaj Garg, MD; Damon E. Houghton, MD; M. Hassan Murad, MD; Ashok Kondur, MD; Rohit Chaudhary, MS; Waldemar E. Wysokinski, MD; and Robert D. McBane, II, MD

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 Ddimer (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; l^2 =61.88%; P<.001), C-reactive protein (CRP) (WMD, 35.74; 95% CI, 30.16 to 41.31; l^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; $l^2=90.42\%$), and ferritin (WMD, 506.15; 95% CI, 356.24 to 656.06; $l^2=52.02\%$). 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.

© 2021 THE AUTHORS. Published by Elsevier Inc on behalf of Mayo Foundation for Medical Education and Research. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/) = Mayo Clin Proc Inn Qual Out 2021;5(2):388-402

From the Division of Hospital Internal Medicine (Rahul Chaudhary), Division of Vascular Medicine (D.E.H., W.E.W., R.D.M.), and Evidence-based Practice Center (M.H.M.), Mayo Clinic, Rochester, MN; Division of Cardiology, University of Pittsburgh Medical Center Heart and Vascular Institute, Pittsburgh, PA (Rahul Chaudhary); Division of Car-

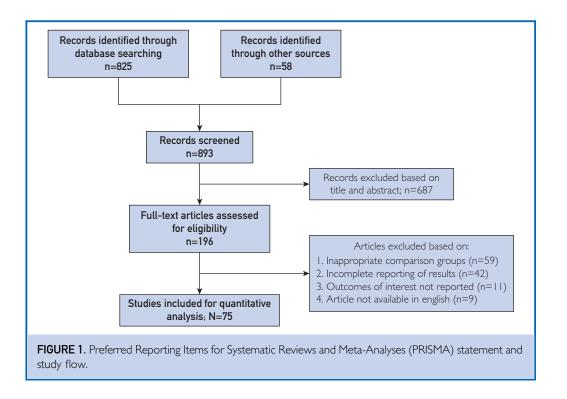
> Affiliations continued at the end of this article.

s 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 laboratoryconfirmed COVID-19 in hospitalized patients with severe disease (defined as patients with

oxygen saturation of \leq 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

Mayo Clin Proc Inn Qual Out = April 2021;5(2):388-402 = https://doi.org/10.1016/j.mayocpiqo.2021.01.009

www.mcpiqojournal.org
© 2021 THE AUTHORS. Published by Elsevier Inc on behalf of Mayo Foundation for Medical Education and Research. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).



urgently needed to further risk stratify patients and optimize the allocation of medications to improve clinical outcomes. Earlier metaanalyses 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 identified studies were studies. The

Country Folk taly taly Germany China China China China China China China China China China China China China China China China	ow-up (d) 11.6 NA NA 28 NA NA NA NA NA NA NA NA NA NA	Groups Nonsurvivor vs survivor Nonsurvivor vs survivor ICU vs non-ICU Severe vs nonsevere Severe vs nonsevere Severe vs nonsevere Severe/critical vs nonsevere Nonsurvivor vs survivor Severe vs Nonsevere Nonsurvivor vs survivor	Type of study Retrospective Retrospective Retrospective Retrospective Retrospective Retrospective Retrospective Prospective Retrospective Retrospective Retrospective
china China China China China China China China China China China China China	NA NA 28 NA NA NA 33 NA NA NA	Nonsurvivor vs survivor ICU vs non-ICU Severe vs nonsevere Severe vs nonsevere Severe vs nonsevere Severe/critical vs nonsevere Nonsurvivor vs survivor Nonsurvivor v. survivor Severe vs Nonsevere Nonsurvivor vs survivor	Retrospective Retrospective Retrospective Retrospective Retrospective Retrospective Prospective Retrospective
Germany China China China China China China China China China china	NA 28 NA NA NA 33 NA NA NA	ICU vs non-ICU Severe vs nonsevere Severe vs nonsevere Severe vs nonsevere Severe/critical vs nonsevere Nonsurvivor vs survivor Nonsurvivor v. survivor Severe vs Nonsevere Nonsurvivor vs survivor	Retrospective Retrospective Retrospective Retrospective Retrospective Prospective Retrospective
China China China China China China China China China China China	28 NA NA NA 33 NA NA NA	Severe vs nonsevere Severe vs nonsevere Severe vs nonsevere Severe/critical vs nonsevere Nonsurvivor vs survivor Nonsurvivor v. survivor Severe vs Nonsevere Nonsurvivor vs survivor	Retrospective Retrospective Retrospective Retrospective Prospective Retrospective
China China China China China China China China China	NA NA NA 33 NA NA NA	Severe vs nonsevere Severe vs nonsevere Severe/critical vs nonsevere Nonsurvivor vs survivor Nonsurvivor v. survivor Severe vs Nonsevere Nonsurvivor vs survivor	Retrospective Retrospective Retrospective Prospective Retrospective
China China China China China China reland China	NA NA 33 NA NA NA	Severe vs nonsevere Severe/critical vs nonsevere Nonsurvivor vs survivor Nonsurvivor v. survivor Severe vs Nonsevere Nonsurvivor vs survivor	RetrospectiveRetrospectiveRetrospectiveProspectiveRetrospective
China China China China China reland China	NA NA 33 NA NA NA	Severe/critical vs nonsevere Nonsurvivor vs survivor Nonsurvivor v. survivor Severe vs Nonsevere Nonsurvivor vs survivor	Retrospective Retrospective Prospective Retrospective
China China China China reland China	NA 33 NA NA NA	Nonsurvivor vs survivor Nonsurvivor v. survivor Severe vs Nonsevere Nonsurvivor vs survivor	Retrospective Prospective Retrospective
China China China reland China	33 NA NA NA	Nonsurvivor v. survivor Severe vs Nonsevere Nonsurvivor vs survivor	Prospective Retrospective
China China reland China	NA NA NA	Severe vs Nonsevere Nonsurvivor vs survivor	Retrospective
China reland China	NA NA	Nonsurvivor vs survivor	
reland China	NA		Retrospective
China			
	20	Severe/critical vs nonsevere	Prospective
China	30	Severe vs nonsevere	Retrospective
	NA	Nonsurvivor vs survivor	Retrospective
China	NA	Severe vs nonsevere	Retrospective
China	NA	Severe vs nonsevere	Retrospective
JSA	40	ICU vs non-ICU	Retrospective
China	10.5	Critical/ICU vs non-ICU	Prospective
ran	NA	Nonsurvivor vs survivor	Retrospective
China	NA	Severe vs nonsevere	Retrospective
Oman	NA	ICU vs non-ICU	Retrospective
China	NA	Severe vs nonsevere	Retrospective
China	NA	Severe vs nonsevere	Prospective
China	30	Nonsurvivor vs survivor	Retrospective
China	NA	Nonsurvivor vs survivor	Retrospective
China	NA	Nonsurvivor vs survivor	Retrospective
China	NA	Severe vs nonsevere	Retrospective
China	NA	Severe vs nonsevere	Retrospective
China	NA	Nonsurvivor vs survivor	Retrospective
China	14	Severe vs nonsevere	Retrospective
China	NA	Severe vs nonsevere	Retrospective
China	NA	Severe vs nonsevere	Retrospective
taly	NA	Nonsurvivor vs survivor	Retrospective
China	NA	Severe vs nonsevere	Retrospective
Netherlands	15	Critical/ICU vs non-ICU	Prospective
1exico	13	ICU vs non-ICU	Prospective
China	NA	Severe vs nonsevere	Retrospective
China	NA	Severe vs nonsevere	Retrospective
China	NA	Severe vs nonsevere	Retrospective
ran	NA	Nonsurvivor vs survivor	Retrospective
China	22	Nonsurvivor vs survivor	Retrospective
JSA	NA	Nonsurvivor vs survivor	Retrospective
Furkey	NA	Severe vs nonsevere	Retrospective
ran	NA	Nonsurvivor vs survivor	Retrospective
China	NA	Nonsurvivor vs survivor	Retrospective
	JSA China China	JSA 40 China 10.5 ran NA China NA </td <td>JSA40ICU vs non-ICUChina10.5Critical/ICU vs non-ICUanNANonsurvivor vs survivorChinaNASevere vs nonsevereDmanNAICU vs non-ICUChinaNASevere vs nonsevereChinaNASevere vs nonsevereChinaNASevere vs nonsevereChinaNASevere vs nonsevereChinaNASevere vs nonsevereChinaNANonsurvivor vs survivorChinaNANonsurvivor vs survivorChinaNANonsurvivor vs survivorChinaNASevere vs nonsevereChinaNASevere vs nonse</td>	JSA40ICU vs non-ICUChina10.5Critical/ICU vs non-ICUanNANonsurvivor vs survivorChinaNASevere vs nonsevereDmanNAICU vs non-ICUChinaNASevere vs nonsevereChinaNASevere vs nonsevereChinaNASevere vs nonsevereChinaNASevere vs nonsevereChinaNASevere vs nonsevereChinaNANonsurvivor vs survivorChinaNANonsurvivor vs survivorChinaNANonsurvivor vs survivorChinaNASevere vs nonsevereChinaNASevere vs nonse

Continued on next page

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.

 $^{\rm b}\mbox{Data}$ from the same hospital—Tongji Hospital, China (n=18 exclusive; n=2 shared).

 $^{c}\mbox{Data}$ from the same hospital—Wuhan Pulmonary Hospital, China (n=2 exclusive; n=2 shared).

 $^{\rm d}\textsc{Data}$ 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).

 $^{\mathrm{f}}\mathrm{Data}$ from the same hospital—Zhongnan Hospital of Wuhan University, China (n=4 exclusive).

^gData from the same hospital—Wuhan University Renmin Hospital, China (n=3 exclusive).

^hData 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) posresult the itive of 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 studies were from Italy,^{1,2,33,50} other 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

 $(171\pm34 \text{ vs } 197\pm30 \times 10^9/\text{L}; \text{WMD}, -11.75$ [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 $(2.9\pm3.1 \text{ vs})$ 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 $(13.9\pm2.0 \text{ vs})$ 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 $(36.6\pm8.7 \text{ vs } 35.1\pm5 \text{ s};$ 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), highsensitivity (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) $(49.3\pm35.7 \text{ vs } 12.5\pm12.3 \text{ pg/L};$ 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 $\mu g/L$, 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 μ kat/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 propopulation nounced in the Chinese (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 metaanalysis 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

Study	Statistic	s for each	<u>study</u>	Sa	imple size		Weighted mean difference	
-	Difference			pro 5:20			(random-effects model)	Relativ
	in means	error	P value	Severe/nonsurvivor	Nonsevere/survivor	Total		weigh
Bazzan et al.	2.70	1.66	.10	9	79	88		0.11
Bonetti et al.	1.08	0.32	<.01	70	74	44		1.68
Burian et al.	0.78	0.80	.33	28	37	65		0.43
Cen et al.	0.80	0.24	<.01	222	720	942		2.21
Chen et al. (2)	2.30	0.97	.02		10	21		0.30
Du et al.	0.60	0.23	.01	21	158	179		2.28
Duan et al.	0.08	0.04	.07	20	328	348		3.70
an et al.	0.99	0.04	.07	47	26	73	Γ_	2.23
	0.20	0.24	.00	33	50	83		3.50
ogarty et al.								
u et al.	0.13	0.04	<.01	16	59	75		3.73
an et al.	3.00	0.88	<.01	39	56	95		0.36
iao et al.	0.28	0.10	<.01	15	28	43		3.39
iong et al.	0.24	0.20	.25	28	161	189		2.52
ioshua et al.	3.50	0.85	<.01	48	20	68		0.39
luang et al.	1.90	0.62	<.01	13	28	41		0.66
et al.	1.30	0.38	<.01	9	70	79		1.37
hamis et al.	1.90	0.55	<.01	24	39	63		0.81
et al. (2)	0.40	0.15	.01	120	136	256	-	2.94
et al. (3)	0.30	0.16	.06	25	68	93	-	2.89
et al. (4)	3.20	0.97	<.01	122	1327	1449		0.30
et al. (5)	1.40	0.35	<.01	15	87	102		1.54
. ,	3.39	1.08	<.01	25	58	83		0.25
u et al. (1)				11	67	78		2.14
iu et al. (2)	0.17	0.25	.50					
u et al. (3)	3.67	1.11	<.01	34	302	336		0.24
u et al.	0.41	0.10	<.01	22	243	265		3.35
v et al.	10.07	3.01	<.01	84	115	199	\longrightarrow	0.03
la et al.	0.20	0.06	<.01	20	64	84	—	3.64
lasetti et al.	3.48	1.04	<.01	33	196	229		0.26
1ao et al.	0.50	0.15	<.01	88	126	214	-	2.98
1iddeldorp et al.	0.90	0.32	.01	75	123	198		1.66
Ortiz-brizuela et al.	2.75	0.82	<.01	29	111	140		0.41
an et al.	2.85	1.09	.01	89	35	124		0.24
Dian et al.	1.50	2.77	.59	9	82	91		0.04
alacup et al.	0.67	0.26	.01	52	190	242		2.08
atici et al.	0.62	0.45	.17	55	626	681		1.08
un et al.	1.79	0.34	<.01	9	8	17		1.56
	1.51	0.45	<.01	21	162	183		1.09
ang et al. (1)		0.45		134	315	449		
ang et al. (2)	3.23		<.01					0.30
ian et al.	1.20	0.33	<.01	148	84	232		1.63
Van et al.	0.30	0.07	<.01	40	95	135		3.55
/ang et al. (1)	2.48	0.74	<.01	36	102	138		0.50
/ang et al. (2)	0.25	0.08	<.01	19	88	107	—	3.51
/ang et al. (3)	0.15	0.07	.02	39	46	85	•	3.59
/ang et al. (5)	10.50	2.43	<.01	14	14	28	$ \longrightarrow$	0.05
/ang et al. (6)	5.30	1.70	<.01	15	30	45		0.10
/u et al. (I)	0.64	0.19	<.01	84	117	201	-	2.62
an et al.	4.54	1.29	<.01	39	9	48		0.18
ang et al. (2)	0.40	0.12	<.01	33	103	136		3.23
ang et al. (2)	16.06	6.10	.01	24	69	93		0.01
ang et al. (5) ang et al. (4)	5.65	1.69	<.01	50	176	226		0.01
e et al. (+)	1.46	0.44	<.01	52	297	349		1.13
eng et al.	0.22	0.08	<.01	55	406	461	<u>_</u>	3.54
hang et al. (1)	0.20	0.06	<.01	58	82	140		3.64
hang et al. (2)	0.40	0.08	<.01	16	293	309	-	3.50
hang et al. (4)	0.89	2.79	.75	5	14	19		0.04
hang et al. (5)	5.85	2.21	.01	27	47	74	│	0.06
hou et al. (1)	4.60	1.16	<.01	54	137	191		0.22
hou et al. (2)	-0.01	0.10	.92	5	12	17	•	3.38
hu et al. (1)	0.06	0.05	.19	16	111	127		3.70
'hu et al. (2)	0.33	0.15	.02	29	73	102	T _e	3.02
	0.60	0.06	<.01	2583	8789	11,372	•	2.02
-						1		
						-8.00	-4.00 0.00 4.00 8.00	0

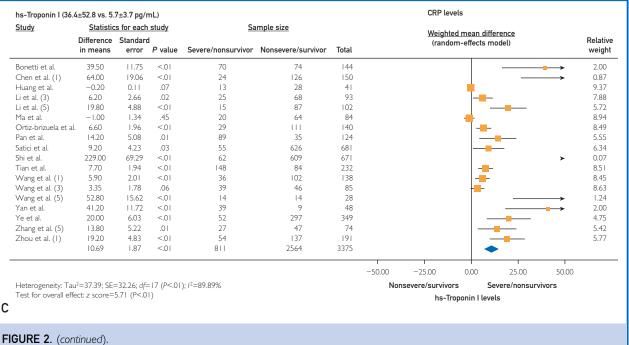
А

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).

Difference Standar Value Severe/nonstruvior Nonseversuvivor Tola Verde order λ also λ	Study	<u>Statistic</u>	s for each	1 mg/L) study	Sa	<u>mple size</u>		Weighted mean difference
origit at J 105 35 31.35 <01					Severe/nonsurvivor	Nonsevere/survivor	Total	Net 1
urian et al. 7.60 2.20 <01 28 37 65 37 40 22 40 37 45 38 40 129 116 225 47 38 40 129 116 225 47 38 40 129 116 225 48 40 129 129 129 129 129 129 129 129 129 129	Sonetti et al	105 35	3 25	< 01	70	74	44	
ane et al. -19.39 5.87 <01								
Unroge al. (0.603) 31.80 < (0.603) 31.80 < (0.603)								
Numerical 5940 1986 01 21 158 179 120 an et al. 66.10 1925 <01								
hun et al. 0400 15.44 0.1 20 338 949 949 949 949 949 949 949 <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>								
an et al. 66.10 1925 <01 47 26 73 1 et al. 2770 868 <01 16 59 75 ain et al. 2770 868 <01 16 59 75 ain et al. 2770 868 <01 15 28 43 et al. 2061 774 01 15 28 43 ain et al. 776 120 01 29 161 100 et al. (1) 32.11 <01 24 39 63 et al. 1100 32.11 <01 25 58 83 et al. (1) 6.930 17.03 <01 25 68 93 et al. (1) 38.00 125 58 83 et al. (1) 38.00 126 01 25 68 83 et al. (1) 38.00 126 01 25 68 83 et al. (1) 38.00 126 01 25 68 83 et al. (1) 38.00 126 01 25 18 83 et al. (1) 38.00 126 01 25 18 83 et al. (2) 8.01 25 18 83 et al. (2) 8.01 29 02 11 67 78 et al. (2) 9.02 01 98 166 214 et al. (2) 8.01 29 02 11 67 78 et al. (2) 9.02 01 98 166 214 et al. (2) 8.01 29 01 12 26 02 16 78 et al. (2) 9.02 01 98 166 214 et al. (2) 8.01 29 01 13 166 214 et al. (2) 8.01 29 01 19 166 22 19 0 et al. (2) 8.02 00 19 8 17 0 at at 32.99 9.58 001 99 81 124 et al. (2) 8.07 01 9 8 17 at at 32.99 9.58 001 99 81 124 et al. (2) 8.07 01 9 8 17 at at 32.99 0.90 001 93 01 266 2957 et al. 2.00 0.01 9 8 17 at at 32.90 9.07 01 9 8 17 et al. (2) 13.0 1.02 113 et al. (2) 10 29 01 14 148 29 et al. (3) 13.0 1.02 176 226 et al. (4) 13.70 779 01 15 30 45 et al. (4) 13.70 779 01 16 193 209 et al. (4) 13.70 779 01 15 30 45 et al. (4) 13.70 779 01 16 193 209 et al. (4) 13.70 77								
operty et al. 56.90 15.69 <01 33 50 83 out et al. 7770 80.80 <01								
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $								
ain et al. 77,0 28,34 < 0.01								
aio et al. 20.61 7.74 0.0 15 2.8 43								
iong et al. 30.50 11.72 .01 28 161 189								
waran etal. 4485 1322 <01 9 8 81 100 etal. (7) 700 2309 <01 9 70 79 hamis etal. 11100 3211 <01 24 39 63 feital. (1) 761 2331 <01 25 68 93 etal. (1) 8400 2548 <01 122 1337 1449 uetal. (1) 3800 1125 <01 25 58 833 uetal. (1) 8400 2548 <01 122 1337 1449 uetal. (2) 2830 1229 02 11 67 28 28 83 uetal. (2) 2830 1229 02 11 67 28 28 83 uetal. (2) 2830 1229 02 11 67 28 28 83 uetal. (3) 758 <01 44 115 199 uetal. (3) 758 <01 44 115 199 uetal. (3) 758 <01 48 126 29 uetal. (4) 70 78 0 <01 73 3 196 229 0 0 103 0 01 28 0 01 88 126 214 140 0 2362 07 33 196 229 0 0 103 0 01 226 66 46 12 177 63 0 01 28 0 11 26 61 22 24 3 265 184 24 3200 1958 <01 48 126 214 140 0 140 0 2362 07 33 196 229 0 0 193 0.0 301 2656 2957 0 0 19 82 91 111 140 140 0 14 22 29 0.2 11 60 188 126 124 14 210 746 <01 22 190 23 124 140 0 14 22 133 0 10 301 2656 2957 0 10 28 124 0 14 140 0 14 22 133 0 10 301 2656 2957 0 10 28 124 0 14 140 0 15 199 141 140 0 14 23 144 2405 746 <01 28 166 452 144 240 746 <01 28 166 452 144 240 746 <01 52 190 242 145 208 146 213 146 214 2900 103 0.1 301 2656 2957 147 28 148 240 746 <01 52 190 242 149 242 149 240 746 <01 52 190 242 140 241 27 141 240 746 <01 52 190 242 140 242 141 2900 1073 0.1 301 2656 2957 141 240 746 <01 52 190 242 141 290 1073 0.1 301 2656 2957 141 240 740 746 <01 52 190 242 141 240 740 74 1.1 11 102 113 141 250 90 77 <01 63 145 208 142 140 150 157 30 45 144 144 28 144 28 145 208 145 208 146 141 28 147 44 148 290 148 141 28 149 445 208 149 445 208 140 445 208 140 445 208 141 27 141 446 28 141 27 141 44 28 141 27 141 44 28 141 27 141 44 28 141 44 28 142 456 150 155 30 45 144 144 28 145 208 146 144 148 147 28 148 144 148 148 128 149 144 144 28 149 149 149 149 149 140 149 149 149 149 149 149 149 149 149 149								
et al. 9700 2309 < 01 9 70 79 tet al. (1) 7764 2331 < 01 25 58 833 tet al. (1) 7764 2331 < 01 25 58 833 tet al. (1) 840 1165 < 01 122 1327 1449 uet al. (2) 2830 1125 02 11 67 78 uet al. (2) 2830 1125 02 11 67 78 uet al. (2) 2830 1125 02 11 67 78 tet al. (3) 724 235 01 94 115 199 tet al. (1) 1930 545 01 92 11 67 78 tet al. (2) 2830 01 958 01 94 115 199 tet al. (2) 2830 01 958 01 94 115 199 tet al. (2) 2830 01 958 01 94 115 199 tet al. (2) 270 80 00 122 123 196 229 tet al. (2) 270 80 00 128 162 219 tet al. (2) 727 80 00 129 111 140 tet al. (2) 727 80 00 129 111 140 tet al. (2) 727 80 00 129 111 140 tet al. (2) 727 74 215 < 01 29 111 140 tet al. (2) 77 74 01 286 166 452 10 an et al. 2229 755 < 01 68 82 130 tet al. 42470 7, 746 01 286 166 452 10 an et al. 2230 7, 746 01 286 166 452 10 an et al. 2470 7, 746 01 286 166 452 10 an et al. 1820 2755 < 01 62 69 671 10 an et al. 1820 2755 < 01 62 69 671 10 an et al. 1820 2755 < 01 62 609 671 10 an et al. 1820 2755 < 01 62 609 671 10 an et al. 1820 2755 < 01 62 609 671 10 an et al. 1820 2755 < 01 62 609 671 10 an et al. 1820 275 10 an et al. 1820 2755 < 01 62 609 671 10 an et al. 1820 2755 < 01 62 609 671 10 an et al. 1820 275 10 an et al. 1830 2076 < 01 40 95 135 10 an et al. 1830 2076 < 01 40 95 135 10 an et al. 1830 2076 < 01 40 95 135 10 an et al. 1830 2076 < 01 40 95 135 10 an et al. 1830 2076 < 01 50 076 226 10 an et al. 1830 2076 < 01 40 95 135 10 an et al. 314 160 10 an et al. 600 314 04 148 84 222 10 an et al. 610 31 822 < 01 33 113 161 10 an et al. 610 31 822 < 01 33 113 161 10 an et al. 610 155 146 411 127 10 an et al. 155 146 411 10 an et al. 151 140 10 an et								
hamis et al. (1) 100 32,11 < 01 24 39 63 i et al. (2) 796 (23) < 01 25 58 83 i et al. (2) 693 (703 < 01 25 58 83 i et al. (2) 693 (703 < 01 25 58 83 i et al. (2) 840 (25 01 25 58 83 i et al. (2) 840 (25 01 22 243 265 i et al. (2) 928 (01 23 64 84 i et al. (2) 928 (01 29 111 140 i et al. (2) 925 (2) 9 25 i et al. (2) 928 (01 28 126 i et al. (2) 93 0 01 301 2656 2957 i et al. (2) 93 0 1 301 2656 2957 i et al. (2) 90 013 0 1 301 2656 2957 i et al. (2) 90 013 0 1 301 2656 2957 i et al. (2) 90 75 < 01 9 88 17 i et al. (2) 90 75 < 01 9 88 17 i et al. (2) 90 75 < 01 9 88 17 i et al. (2) 90 75 < 01 9 88 17 i et al. (2) 90 76 < 01 9 88 17 i et al. (2) 90 76 < 01 9 88 17 i et al. (2) 90 76 < 01 9 88 17 i et al. (2) 90 907 < 01 9 88 17 i et al. (2) 90 907 < 01 9 88 17 i et al. (3) 707 799 < 01 66 193 209 i et al. (4) 0107 674 11 11 102 113 i et al. (1) 180 052 < 01 53 045 i et al. (1) 170 799 < 01 66 193 209 i et al. (4) 03170 799 < 01 66 193 209 i et al. (4) 03170 799 < 01 66 193 209 i et al. (5) 03 1875 < 01 55 046 461 i et al. (1) 180 522 < 01 58 82 140 i et al. (1) 180 522 < 01 58 82 140 i et al. (1) 180 522 < 01 58 82 140 i et al. (1) 180 522 < 01 58 82 140 i et al. (1) 180 522 < 01 58 82 140 i et al. (1) 180 522 < 01 58 82 140 i et al. (1) 180 522 < 01 58 82 140 i et al. (2) 7159 2117 < 01 18 93 111 i fill i hang et al. (3) 7159 2117 < 01 18 93 111 i fill i hang et al. (3) 7159 2117 < 01 18 93 111 i fill i hang et al. (4) 130 522 < 01 58 82 122 309 i et al. (5) 7159 2117 < 01 18 93 111 i fill i hang et al. (3) 7159 2117 < 01 18 93 111 i hang et al.								
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $								
iet al. (2) 6930 1703 c01 25 68 93 iet al. (1) 8400 2548 c01 122 1377 144 iet al. (2) 2830 1229 02 11 67 78 u et al. (1) 3800 11.65 c01 22 243 265 u et al. (2) 2830 12.99 02 11 67 78 at al. 32.01 958 c01 22 243 265 iet al. 41.90 13.65 c01 22 243 265 iet al. 41.90 13.65 c01 22 243 265 iet al. 41.90 13.65 c01 22 243 265 iet al. 41.90 23.62 07 33 196 229 iet al. 41.74 2.15 c01 29 111 140 iet al. 72.70 8.30 c01 88 126 214 iet al. 72.70 8.30 c01 88 126 214 iet al. 72.70 8.30 c01 89 35 124 jan et al. 32.29 958 c01 99 82 91 jan et al. 32.62 05 c01 9 82 91 jan et al. 24.65 6.05 c01 9 82 91 jan et al. 24.60 2.17 c01 22 190 242 iet al. 10.67 6.74 .11 11 02 iatci et al. 11.00 24.51 c01 55 626 681 iet al. 11.00 24.51 c01 52 190 242 iet al. 11.00 24.51 c01 52 190 242 iet al. 11.00 24.51 c01 52 190 242 iet al. 11.00 24.51 c01 62 269 671 iet al. 11.00 24.51 c01 9 8 17 iet al. 41.90 37.67 c01 9 8 17 iet al. 41.90 37.67 c01 9 8 17 iet al. 41.90 37.67 c01 9 8 17 iet al. 41.90 27.7 c01 63 145 208 iet al. 41.90 27.7 c01 63 145 208 iet al. 65.0 31.77 c01 9 8 17 iet al. 61.00 24.51 c01 62 209 671 iet al. 61.00 18.75 c01 9 13 303 136 iet al. 64.00 27.7 c01 63 145 208 iet al. 61.30 18.75 c01 15 30 45 iet al. 61.30 18.75 c01 15 30 45 iet al. 61.00 18.77 c01 52 12.77 349 iet al. 61.61 30 18.75 c01 16 23 309 iet al. 61.61 30 18.75 c01 16 193 309 iet al. 61.60 1.30 18.75 c01 16 193 309 iet al. 61.60 1.30 18.75 c01 16 193 309 iet al. 61.61 11.61 127 iet al. 61.61 11.61 127 iet al. 61.61 11.61 127 iet al. 61.61 11.61 127 iet al. 61.61 11.61 12.77 iet al. 61.61 11.61 12.77 iet al. 61.61 11.61 12.77 iet al. 61.61 11.61 12.77 iet al. 61.61 11.78 12.77 iet al. 61.61 11.78 12.77 iet al. 61.61 11.78 12.77 iet al. 61.61 11.78 12.77 i								
iet al. $(1)^{\circ}$ 80.00 25.48 c.01 22 1327 1449 000 25.48 c.01 22 1327 1449 000 25.48 c.01 22 1327 1449 000 25.48 c.01 22 143 265 200 20 11 6.7 78 200 200 11 6.7 78 200 200 11 6.7 78 200 200 11 6.7 78 200 200 11 6.7 78 200 200 11 6.7 78 200 200 11 6.7 78 200 200 11 6.7 78 200 200 11 6.7 78 200 200 11 6.7 78 200 200 11 6.7 78 200 200 11 6.7 78 200 200 100 200 200 200 200 200 200 200								
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $								
u et al. 22.9 0.0 11 67 78 20 vet al. 32.01 9.58 <01								
ue tal. 4490 1.36 <0 22 243 265 vetal 320 9.88 <0 84 15 99 fa et al. 1930 5.65 <0 20 64 84 15 199 fa et al. 1930 5.65 <0 20 64 84 15 29 fa et al. 2070 8.30 <0 88 126 214 an et al. 32.29 9.58 <0 89 35 124 jan et al. 24.55 6.05 <0 9 82 91 jan et al. 24.55 6.05 <0 9 82 91 jan et al. 24.55 6.05 <0 9 82 91 jan et al. 24.50 $0.07 8.6 0.05 6.6 4.65 2 $ jan et al. 24.00 $10.93 0.0 0.03 0.0 0.266 6.6 4.52 $ jan et al. 25.00 $10.93 0.0 0.30 0.0 266 6.6 4.52 $ jan et al. 25.00 $10.93 0.0 0.30 0.0 255 6.26 6.81 $ jan et al. 18.20 $35.76 <0.0 55 6.26 6.81 $ jan et al. 86.0 2.17 <0 52 190 242 jan et al. 86.0 2.17 <0 62 6.69 6.71 jan et al. 81.00 2.45 1 <0 62 6.69 6.71 jan et al. 83.0 20.76 <0 9 8 17 jan et al. 69.0 3.41 0.4 148 84 232 van et al. 83.0 20.76 <0 9 8 17 jan et al. 69.0 3.41 0.4 148 84 232 van et al. 83.0 20.76 <0 9 8 17 jan et al. 69.0 3.41 0.4 148 84 232 van et al. 83.0 20.76 <0 9 8 17 jan et al. 69.0 3.41 0.4 148 84 232 van et al. 83.30 20.76 <0 40 95 135 van et al. 83.30 20.76 <0 50 176 226 van et al. 83.30 20.76 <0 50 176 226 van et al. 83.30 10.77 <0 53 8.2 140 van et al. 83.30 10.61 52 2.97 349 van et al. (0) 5.2 2.97 349 van et al. (0) 5.3 1.16 (1) jan et al. (0) 5.2 2.97 349 van et al. (0) 5.3 1.16 (1) jan et al. (0) 5.2 2.91 33 103 11.6 (1) jan et al. (1) 1.80 5.52 <0 58 8.2 140 van et al. (2) 5.80 1.178 <0 55 122 1.17 <0 18 9.3 111 jan et al. (1) 1.80 5.52 <0 58 8.2 140 van et al. (2) 5.80 1.178 <0 127 47 74 74 74 jan et al. (3) 5.41 2.01 16 2.93 309 jan et al. (4) 5.80 1.177 4 30 1.16 1.11 1.127 van et al. (2) 5.80 1.178 <0 126 1.11								
vert al. 32.01 9.58 -<01 P4 115 99 ta et al. 19.30 5.65 -<01 20 64 84 19.30 5.65 -<01 20 64 84 19.30 5.65 -<01 20 64 84 10.01 23.62 0.7 33 196 229 10.02 64 84 10.02 64 10.02 7 10.02 64 10.02 7 10.02	iu et al. (2)							
hat al. 19.30 5.65 $< < colspan=10^{-1}$ 20 64 84 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>								
fasetti et al. 43.00 23.62 .07 33 196 229 .010 fao et al. 27.70 8.30 <01	v et al.							
lage et al. 27.70 8.30 <01 88 126 214 25 Drizz-brizulea et al. 724 2.15 <01 29 111 140 23 an et al. 32.29 958 <01 89 35 124 23 jan et al. 24.65 6.05 <01 29 616 452 2.3 jan et al. 24.70 10.93 .01 301 2656 2957 2.1 uan et al. 92.50 27.55 <01 68 82 150 00 24.2 0 2.1 uan et al. 106.67 <01 52 190 24.2 0 0.0 alacu et al. 10.67 6.74 .11 110 102 113 0.7 27.7 0.1 22.2 0.9 21.2 23.1 an et al. 6.90 3.41 .04 148 84 23.2 22.2 23.1 23.1 23.1 23.1 23.1 <	1a et al.							
htte-britelae et al. 724 2,15 <0,01 29 111 140 31, an et al. 3229 9,58 <01 89 35 124 23 an et al. 2465 6,05 <01 9 82 91 23 jan et al. 2465 6,05 <01 9 82 91 24 jan et al. 2467 7,46 <01 286 166 452 62 jan et al. 2900 1093 01 301 2656 2957 62 uan et al. 9250 2755 <01 68 82 150 68 alacup et al. 8,60 2,17 <01 52 190 242 7 tai et al. 118,20 35,76 <01 55 626 681 7 jan et al. 2590 9,07 <01 9 8 17 7 jan et al. 2590 9,07 <01 9 8 17 7 jan et al. 2590 9,07 <01 9 8 17 7 jan et al. 2590 9,07 <01 9 8 17 7 jan et al. 6,00 3,41 04 148 84 232 7 jan et al. 8,30 20,76 <01 40 95 135 7 Vang et al. 6,01 3,177 9 <01 16 193 209 7 Vang et al. 6,01 3,178 <01 45 208 7 Vang et al. 6,01 3,18,75 <01 15 30 45 7 Vang et al. 6,01 3,18,75 <01 15 30 45 7 Vang et al. 6,01 3,18,72 <01 63 145 208 7 Vang et al. 6,01 3,18,72 <01 63 145 208 7 Vang et al. 6,01 3,18,72 <01 63 145 208 7 Vang et al. 6,01 3,18,72 <01 63 145 209 7 Vang et al. 6,01 3,18,72 <01 33 103 136 7 et al. 33,020,76 <01 14 14 28 7 Vang et al. 6,01 3,18,72 <01 33 103 136 7 et al. 33,020,76 <01 15 30 45 7 Vang et al. 6,01 3,18,72 <01 30 136 7 et al. 33,1166 <01 52 297 399 7 Vang et al. 6,01 3,177 <01 50 176 226 7 Hang et al. 6,01 3,177 <01 50 176 226 7 Hang et al. 6,01 3,18,22 <01 33 103 136 7 et al. 33,1166 <01 52 297 399 7 jan et al. 6,01 6,29 309 7 	1asetti et al.	43.00	23.62	.07	33	196	229	I
an et al. 32.29 9.58 <01 89 35 124 23 gan et al. 24.65 6.05 <01 9 82 91 24 astad et al. 29.00 10.93 01 301 2656 2957 26 astad et al. 29.20 10.93 01 301 2656 2957 21 au et al. 92.50 7.755 <01 68 82 150 22 alacup et al. 8.60 2.17 <01 52 190 242 2 alacup et al. 10.67 74 1.1 111 102 113 20 the et al. 10.82 0.77 <0.1 62 669 671 27 bit et al. 4.1 0.0 24.51 <0.1 62 669 671 27 bit et al. 4.1 0.0 24.51 <0.1 62 669 671 27 bit et al. 4.1 0.0 24.51 <0.1 62 669 671 27 bit et al. 4.1 0.0 24.51 <0.1 62 669 671 27 bit et al. 5.30 10.27 <0.1 63 145 208 27 Van et al. 8.30 20.76 <0.1 40 95 135 20 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 84 232 47 Van et al. 6.90 3.41 0.44 148 14 28 47 Van et al. 6.90 3.44 0.45 14 14 28 47 Van et al. 6.90 3.44 0.45 14 14 28 47 Van et al. 6.90 3.47 0.15 30 45 47 Jan get al. (2) 6.130 18.72 0.1 15 30 45 47 Jan get al. (3) 1.79 2.1.17 0.1 18 93 111 47 Jan get al. (4) 4.580 13.74 0.1 50 176 226 47 Jan get al. 38.63 11.66 0.1 55 406 461 47 Jan get al. (3) 7.59 2.1.17 0.1 18 93 111 47 Jan get al. (3) 7.59 2.1.17 0.1 18 93 111 47 Jan get al. (3) 7.59 2.1.17 0.1 18 93 111 47 Jan get al. (3) 7.59 2.1.17 0.1 18 93 111 47 Jan get al. (3) 7.59 2.1.17 0.1 18 93 111 47 Jan get al. (4) 4.580 13.1 1.61 47 Jan get al. (4) 4.580 13.1 1.61 47 Jan get al. (2) 3.00 2.04 1.4 5 12 17 Jan Jan de Jan	1ao et al.	27.70	8.30	<.01	88	126	214	2
jan et al. 24.65 605 <01	Ortiz-brizuela et al.	7.24	2.15	<.01	29	111	140	3
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	'an et al.	32.29	9.58	<.01	89	35	124	2
astad et al. 2900 1093 0.1 301 2656 2957 $-$ 2.1 uan et al. 92.50 27.55 <.01	Qian et al.	24.65	6.05	<.01	9	82	91	2
uan et al. 92.50 27.55 <0.1 68 82 150 $<$ 0.8 $alacup et al.$ 8.60 2.17 <0.1 52 190 242 $alacup et al.$ $alacu et al.$ $alacu et al.$	Qin et al.	24.70	7.46	<.01	286	166	452	2
alacup et al. 8.60 2.17 < 01 52 190 242 31 tatici et al. 118.20 35.76 < 01 55 626 681 0 bahnairad et al. 10.67 6.74 11 111 11 11 11 11 11 11 11 11 11 11 1	astad et al.	29.00	10.93	.01	301	2656	2957	2
alacup et al. 8.60 2.17 < 01 52 190 242 31 at ici et al. 118.20 35.76 < 01 55 626 681 05 113 10 11 11 11 11 11 11 11 11 11 11 11 11	Ruan et al.	92.50	27.55	<.01	68	82	150	O
atici et al. 118.20 35.76 <01 55 626 681 $$ 055 habriarizad et al. 10.67 6.74 .11 11 102 113 055 un et al. 25.90 9.07 <01 9 8 17 099 un et al. 6.90 3.41 0.4 148 84 232 300 ultagio et al. 59.30 10.27 <01 63 145 208 $$ 2.2 Van et al. 83.30 20.76 <01 40 95 135 $$ 2.5 Vang et al. (6) 61.30 18.75 <01 15 30 45 $$ 1.3 ang et al. (2) 61.30 18.75 <01 15 30 45 $$ 1.3 ang et al. (2) 61.30 18.75 <01 55 406 461 $$ 2.1 hang et al. (2) 61.30 18.75 <01 55 406 461 $$ 2.1 hang	alacup et al.		2.17	<.01	52	190	242	
hahriariaria de tal. 10.67 6.74 .11 11 102 113 27 hi et al. 81.00 24.51 <01								
hi et al. 81.00 24.51 <01 62 609 671 0.9 un et al. 25.90 9.07 <01 9 8 17 2.4 ian et al. 6.90 3.41 .04 148 84 232 3.0 Utaggio et al. 59.30 10.27 <01 63 145 208 2.4 Van et al. 83.30 20.76 <0.1 40 95 135 1.1 Vang et al. (5) 121.70 29.98 <0.1 14 14 28 0.7 Vang et al. (6) 61.30 18.75 <0.1 15 30 45 0.7 Vang et al. (6) 61.30 18.22 <01 33 103 136 0.7 ang et al. (7) 64 0.1 55 406 461 0.7 et al. 53.14 16.01 <0.1 52 2.97 349 0.1 hang et al. (2) 53.81 1.66 <0.1 55 406 461 0.7 hang et al. (2) 55.80 11.98 <0.1 16 2.2 hang et al. (3) 71.59 21.17 <0.1 18 93 111 0.4 hang et al. (2) 55.80 11.98 <0.1 16 2.93 309 0.20 hang et al. (3) 71.59 21.17 <0.1 18 93 111 0.4 hang et al. (4) 43.10 16.29 0.1 27 47 74 1.4 hang et al. (5) 43.10 16.29 0.1 27 47 74 1.4 hang et al. (2) 59.80 11.98 <0.1 16 1.30 131 161 0.4 hang et al. (2) 3.00 2.04 1.14 5 112 17 0.20 0.00 100.00 200.00 hang et al. (1) 18.90 5.62 <0.1 27 47 74 1.4 5 12 17 0.4 3.0 hang et al. (2) 3.00 2.04 1.14 5 12 17 0.4 3.0 hang et al. (2) 3.00 2.04 1.14 5 12 17 0.4 3.0 hang et al. (3) 71.59 21.17 <0.1 18 93 111 0.4 0.4 0.4 0.5 0.5 0.4 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5								
un et al. 25.90 9.07 < 01 9 8 17 24 ian et al. 6.90 3.41 04 148 84 232 30 Van et al. 83.30 20.76 < 01 63 145 208 22 Van et al. 83.30 20.76 < 01 40 95 135 1.1 Vang et al. (5) 121.70 29.98 < 01 14 14 28								
ian et al. 6.90 3.41 0.4 148 84 232 30 Van et al. 83.30 20.76 <01								
ultaggio et al. 59.30 10.27 <0.1 63 145 208 \rightarrow 22 Van et al. 83.30 20.76 <0.1 40 95 135 \rightarrow 1.1 Van et al. (5) 12.170 29.98 <0.1 14 14 28 \rightarrow 2.5 Van et al. (6) 61.30 18.75 <0.1 15 30 45 133 ang et al. (6) 61.30 18.75 <0.1 15 30 45 133 ang et al. (6) 61.30 18.75 <0.1 50 176 226 133 ang et al. (6) 13.74 <0.1 55 406 461 $$ 2.1 $bhang$ et al. (1) 18.90 5.62 <0.1 58 82 140 $$ 2.0 $bhang$ et al. (5) 43.10 1629 0.1 27 47 74 74 $$								
Van et al. 83.30 20.76 $<$ 01 40 95 135 1.1 Van et al. 83.30 20.76 $<$ 01 16 193 209 $<$ 2.5 Vang et al. (6) 121.70 29.98 $<$ 01 14 14 28 $<$ 7.7 $<$ 2.5 Vang et al. (6) 61.30 18.75 $<$ 01 15 30 45 $<$ 1.3 'ang et al. (2) 61.30 18.75 $<$ 01 15 30 45 $<$ 1.3 'ang et al. (2) 61.30 18.75 $<$ 01 50 176 226 $<$ 1.3 'e et al. 53.14 16.01 $<$ 01 52 297 349 $=$ 6 $<$ 1.6 'hang et al. (1) 18.90 5.62 $<$ 01 58 82 140 $=$ 6 $=$ 6 $<$ 2.8 'hang et al. (3) 71.59 21.17 $<$ 01 18 93 111 $=$ 6 $=$ 6 $<$ 1.0 'hang et al. (36.80 17.77 0.4 30 1								
Vang et al. (4) 31.70 7.99 <0.1 16 193 209 \rightarrow 25 Vang et al. (5) 121.70 29.98 <0.1 14 14 28 \rightarrow 0.7 Vang et al. (6) 61.30 18.75 <0.1 15 30 45 1.3 ang et al. (2) 61.30 18.22 <0.1 33 103 136 $ 1.3$ ang et al. (4) 45.80 13.74 <0.1 50 176 226 $ 1.8$ ang et al. (1) 18.90 5.62 <0.1 55 406 461 $ 2.1$ hang et al. (1) 18.90 5.62 <0.1 58 82 140 $ 2.0$ 2.0 <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>								
Vang et al. (5) 121.70 29.98 <01 14 14 28 0.7 Vang et al. (6) 61.30 18.75 <01 15 30 45 1.3 ang et al. (2) 61.30 18.22 <01 33 103 136 1.3 ang et al. (4) 45.80 13.74 <01 50 176 226 1.8 e et al. 53.14 16.01 <01 52 297 349 1.6 feng et al. 38.63 11.66 <01 55 406 461 -2.0 hang et al. (1) 18.90 5.62 <01 58 82 140 -4 2.8 hang et al. (3) 71.59 21.17 <01 18 93 111 -4 1.5 hang et al. (5) 43.10 16.29 01 27 47 74 -4 4.5 hu et al. (1) 28.17 8.36 <01 16 111 127 -20.00								
Vang et al. (6) 61.30 18.75 < 01 15 30 45 13 ang et al. (2) 61.30 18.22 < 01 33 103 136 13 ang et al. (4) 45.80 13.74 < 01 50 176 226 1.8 iang et al. (4) 45.80 13.74 < 01 52 297 349 1.6 ieng et al. 38.63 11.66 < 01 55 406 461 1.2 thang et al. (2) 59.80 11.98 < 01 16 2.9 309 1.1 thang et al. (5) 43.10 16.29 01 27 47 74 1.1 thang et al. (5) 43.10 16.29 01 27 47 74 1.5 theng et al. 36.80 17.77 04 30 131 161 1.4 thou et al. (1) 28.17 8.36 < 01 16 111 127 2.6 -20.00 -100.00 0.00 100.00 200.00 100.00 200.00								
ang et al. (2) 61.30 18.22 <01								
ang et al. (4) 45.80 13.74 <01								
e et al. 53.14 16.01 <01								
leng et al. 38.63 11.66 <.01								
hang et al. (1) 18.90 5.62 <.01								
thang et al. (2) 59.80 11.98 <.01								
hang et al. (3) 71.59 21.17 <01								
hang et al. (5) 43.10 16.29 .01 27 47 74 1.5 heng et al. 36.80 17.77 .04 30 131 161 1.4 hou et al. (2) 3.00 2.04 .14 5 12 17 3.1 hu et al. (1) 28.17 8.36 <.01								
theng et al. 36.80 17.77 .04 30 131 161 1.4 theou et al. (2) 3.00 2.04 .14 5 12 17 3.1 thu et al. (1) 28.17 8.36 <.01								
hou et al. (2) 3.00 2.04 .14 5 12 17 3.1 hu et al. (1) 28.17 8.36 <.01 16 111 127 2.5 35.74 2.84 <.01 2.782 11,304 14,086								
Thu et al. (1) 28.17 8.36 <01								
35.74 2.84 <.01								
Heterogeneity: Tau ² =249.75; SE=122.93; df=52 (P<.01); l ² =85.27% Nonsevere/survivors Severe/nonsurvivors Tech for an unit of the constraint of the con	lhu et al. (I)							2
Heterogeneity: Tau ² =249.75; SE=122.93; df=52 (P<.01); l ² =85.27% Nonsevere/survivors Severe/nonsurvivors		35.74	2.84	<.01	2782	11,304	14,086	•
Ideerogeneity: Tau ² =249.75; SE=122.93; df=52 (P<.01); l ² =85.27% Nonsevere/survivors Severe/nonsurvivors							-3	<u> </u>
	Heterogeneity: Tau ²	=249.75; SE	=122.93; d	f=52 (P<.0)1); / ² =85.27%		-	
			(·				UNF LEVELS

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, hstroponin I, and LDH levels.

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



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 endothelium.^{102,103} the vascular 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

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, Ddimer 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 al¹⁰⁶ 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,

Studies, 7388 Patients) and Nonsurvivor vs Survivor (28 Studies, 9664 Patients) ^{a.b}							
	Severe v	rs nonsevere	Nonsurvivor vs survivor				
Parameter	Mean±SD	WMD/OR (95% CI)	Mean±SD	WMD/OR (95% CI)			
Platelet count (×10 ⁹ /L)	179±33 vs 195±32 (n=5135)	WMD: -8.01 (-14.51 to -1.51); I ² =63.76%; P<.001	59±33 vs 20 ±28 (n=45 8)	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); l ² =83.08%; P<.001	3±1.8 vs 0.9±0.7 (n=5509)	WMD: 1.35 (0.99 to 1.71); 1 ² =85.58%; P<.001			
Prothrombin time (s)	3.5±2.3 vs 2.4± .2 (n=2533)	WMD: 0.53 (0.39 to 0.66); l ² =0%; P<.001	4.3± .6 vs 3. ± .2 (n=395)	WMD: 1.01 (0.77 to 1.26); l ² =35.39%; P<.001			
aPT⊤ (s)	33.5±5 vs 33.6±5 (n=2559)	WMD: 0.38 (-0.84 to 1.61); l ² =76.51%; P=.54	41.1±11 vs 37.1±4.6 (n=2797)	WMD: 1.14 (0.12 to 2.16); l 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); l ² =59.14%; P<.001	4.6±0.6 vs 4.4±0.7 (n=3520)	WMD: 0.23 (-0.09 to 0.56); l 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); l ² =85.74%; P<.001	97±37.1 vs 31.7±22 (n=7987)	WMD: 58.58 (41.23 to 75.93); l 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); l 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); l ² =91.41%; P<.001	49.4±46.7 vs 12.2±10.6 (n=1958)	WMD: 15.30 (7.06 to 25.53); l ² =86.71%; P<.001			
Ferritin (ng/mL)	09±37 vs 584±3 9 (n= 54)	WMD: 320.92 (1197.54 to 444.30); I ² =12.06%; P<.001	626±947 ∨s 687±341 (n=3179)	WMD: 700.21 (497.52 to 902.90); / 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); l ² =88.81%; P<.001	50.2±70.3 vs 6±3 (n=2403)	WMD: 18.68 (10.92 to 26.44); l ² =75.69%; P<.001			
LDH (U/L)	377±94 vs 242±54 (n=3371)	WMD: 124.04 (75.42 to 172.66); 1 ² =90.08%; P<.001	561±134 vs 303±70 (n=5784)	WMD: 188.77 (153.07 to 224.47); <i>I</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); l 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			

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}

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

^bSI 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 (Ddimer, 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 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

Affiliations (Continued from the first page of this article.): diology, Medical College of Wisconsin, Milwaukee (J.G.); Division of Cardiology, Garden City Hospital, Garden City, MI (A.K.); and Deakin University, Melbourne, Australia (Rohit Chaudhary).

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Rahul Chaudhary, MD, MBA, Department of Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Chaudhary. rahul@mayo.edu; rahulchaudhary1234@gmail.com; Twitter: @RahulCh91915963).

ORCID

Rahul Chaudhary: b https://orcid.org/0000-0002-3276-385X; Damon E. Houghton: b https://orcid.org/0000-0002-6065-9523; M. Hassan Murad: b https://orcid.org/ 0000-0001-5502-5975; Ashok Kondur: b https://orcid. d.org/0000-0002-5115-7003; Waldemar E. Wysokinski: b https://orcid.org/0000-0002-8119-6206; Robert D. McBane: b https://orcid.org/0000-0001-8727-8029

REFERENCES

- Bazzan M, Montaruli B, Sciascia S, Cosseddu D, Norbiato C, Roccatello D. Low ADAMTS 13 plasma levels are predictors of mortality in COVID-19 patients. *Intern Emerg Med.* 2020; 15(5):861-863.
- Bonetti G, Manelli F, Patroni A, et al. Laboratory predictors of death from coronavirus disease 2019 (COVID-19) in the area of Valcamonica, Italy. *Clin Chem Lab Med*. 2020;58(7):1100-1105.
- Burian E, Jungmann F, Kaissis GA, et al. Intensive care risk estimation in COVID-19 pneumonia based on clinical and

imaging parameters: experiences from the Munich cohort. *| Clin Med.* 2020;9(5):1514.

- Cen Y, Chen X, Shen Y, et al. Risk factors for disease progression in patients with mild to moderate coronavirus disease 2019—a multi-centre observational study. *Clin Microbiol Infect.* 2020;26(9):1242-1247.
- Chen C, Chen C, Yan JT, Zhou N, Zhao JP, Wang DW. Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19 [in Chinese]. *Zhonghua Xin Xue Guan Bing Za Zhi.* 2020;48(7):567-571.
- Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest.* 2020;130(5):2620-2629.
- Chen X, Zhao B, Qu Y, et al. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019. *Clin Infect Dis.* 2020;71 (8):1937-1942.
- Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. *Chin Med J (Engl)*. 2020; 133(11):1261-1267.
- Du R-H, Liang L-R, Yang C-Q, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study [published correction appears in *Eur Respir J.* 2020;56(3):2050524]. *Eur Respir J.* 2020;55(5): 2000524.
- Duan J, Wang X, Chi J, et al. 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;92(11):2616-2622.
- Fan H, Zhang L, Huang B, et al. Cardiac injuries in patients with coronavirus disease 2019: not to be ignored. Int J Infect Dis. 2020;96:294-297.
- 12. Fogarty H, Townsend L, Ni Cheallaigh C, et al. COVID 19 coagulopathy in Caucasian patients. *Br J Haematol*. 2020;189(6):1044-1049.
- Fu J, Kong J, Wang W, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: a retrospective study in Suzhou China. *Thromb Res.* 2020;192:3-8.
- Gan J, Li J, Li S, Yang C. Leucocyte subsets effectively predict the clinical outcome of patients with COVID-19 pneumonia: a retrospective case-control study. Front Public Health. 2020;8:299.
- Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020;92(7):791-796.
- Gong J, Ou J, Qiu X, et al. A tool for early prediction of severe coronavirus disease 2019 (COVID-19): a multicenter study using the risk nomogram in Wuhan and Guangdong, China. *Clin Infect Dis.* 2020;71(15):833-840.
- Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a singlecentre, cross-sectional study. *Lancet Haematol.* 2020;7(8): e575-e582.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in *Lancet*. 2020;395(10223):496]. *Lancet*. 2020;395(10223):497-506.
- Javanian M, Bayani M, Shokri M, et al. Clinical and laboratory findings from patients with COVID-19 pneumonia in Babol North of Iran: a retrospective cohort study. *Rom J Intern Med.* 2020;58(3):161-167.
- Ji M, Yuan L, Shen W, et al. Characteristics of disease progress in patients with coronavirus disease 2019 in Wuhan, China. *Epidemiol Infect.* 2020;148:e94.
- Khamis F, Al-Zakwani I, Al Naamani H, et al. Clinical characteristics and outcomes of the first 63 adult patients hospitalized with COVID-19: an experience from Oman. J Infect Public Health. 2020;13(7):906-913.

- Li K, Wu J, Wu F, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. *Invest Radiol.* 2020;55(6):327-331.
- Li Y, Zhao K, Wei H, et al. Dynamic relationship between Ddimer and COVID-19 severity. Br J Haematol. 2020;190(1): e24-e27.
- 24. Li L, Yang L, Gui S, et al. Association of clinical and radiographic findings with the outcomes of 93 patients with COVID-19 in Wuhan, China. *Theranostics*. 2020;10(14): 6113-6121.
- **25.** Li Q, Cao Y, Chen L, et al. Hematological features of persons with COVID-19. *Leukemia*. 2020;34(8):2163-2172.
- Li K, Chen D, Chen S, et al. Predictors of fatality including radiographic findings in adults with COVID-19. Respir Res. 2020;21(1):146.
- Liu X, Li Z, Liu S, et al. Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. Acta Pharm Sin B. 2020;10(7):1205-1215.
- Liu W, Tao Z-W, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J (Engl)*. 2020;133(9): 1032-1038.
- 29. Liu Q, Song NC, Zheng ZK, Li JS, Li SK. Laboratory findings and a combined multifactorial approach to predict death in critically ill patients with COVID-19: a retrospective study. *Epidemiol Infect.* 2020;148:e129.
- 30. Lu H, Ai J, Shen Y, et al. A descriptive study of the impact of diseases control and prevention on the epidemics dynamics and clinical features of SARS-CoV-2 outbreak in Shanghai, lessons learned for metropolis epidemics prevention. *medRxiv*. https://doi.org/10.1101/2020.02.19.20025031. Preprint posted online February 23, 2020.
- Lv Z, Cheng S, Le J, et al. Clinical characteristics and coinfections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. *Microbes Infect.* 2020;22(4-5):195-199.
- Ma K-L, Liu Z-H, Cao C-F, et al. COVID-19 myocarditis and severity factors: an adult cohort study. *medRxiv*. https://doi. org/10.1101/2020.03.19.20034124. Preprint posted online March 23, 2020.
- Masetti C, Generali E, Colapietro F, et al; Humanitas Covid-19 Task Force. High mortality in COVID-19 patients with mild respiratory disease. Eur J Clin Invest. 2020;50(9):e13314.
- Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-690.
- Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(8):1995-2002.
- 36. Ortiz-Brizuela E, Villanueva-Reza M, González-Lara MF, et al. Clinical and epidemiological characteristics of patients diagnosed with COVID-19 in a tertiary care center in Mexico City: a prospective cohort study [published correction appears in *Rev Invest Clin.* 2020;72(4):252-258]. *Rev Invest Clin.* 2020; 72(3):165-177.
- Pan F, Yang L, Li Y, et al. Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): a case-control study. Int J Med Sci. 2020;17(9): 1281-1292.
- Qian G-Q, Yang N-B, Ding F, et al. Epidemiologic and clinical characteristics of 91 hospitalized patients with COVID-19 in Zhejiang, China: a retrospective, multi-centre case series. Q/M. 2020;113(7):474-481.
- Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with coronavirus 19 (COVID-19) in Wuhan, China. *Clin Infect Dis*. 2020;71(15):762-768.
- Rastad H, Karim H, Ejtahed H-S, et al. Risk and predictors of in-hospital mortality from COVID-19 in patients with diabetes and cardiovascular disease. *Diabetol Metab Syndr.* 2020;12:57.

- Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China [published correction appears in Intensive Care Med. 2020;46(6):1294-1297]. Intensive Care Med. 2020;46(5):846-848.
- Salacup G, Lo KB, Gul F, et al. Characteristics and clinical outcomes of COVID-19 patients in an underserved-inner city population: a single tertiary center cohort. J Med Virol. 2021; 93(1):416-423.
- Satici C, Demirkol MA, Altunok ES, et al. Performance of pneumonia severity index and CURB-65 in predicting 30day mortality in patients with COVID-19. Int J Infect Dis. 2020;98:84-89.
- 44. Shahriarirad R, Khodamoradi Z, Erfani A, et al. Epidemiological and clinical features of 2019 novel coronavirus diseases (COVID-19) in the South of Iran. BMC Infect Dis. 2020; 20(1):427.
- 45. Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J. 2020;41(22):2070-2079.
- Sun Y, Dong Y, Wang L, et al. Characteristics and prognostic factors of disease severity in patients with COVID-19: the Beijing experience. J Autoimmun. 2020;112:102473.
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.
- Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* 2020;18(5):1094-1099.
- 49. Tian J, Yuan X, Xiao J, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. *Lancet Oncol.* 2020;21(7): 893-903.
- 50. Vultaggio A, Vivarelli E, Virgili G, et al. Prompt predicting of early clinical deterioration of moderate-to-severe COVID-19 patients: usefulness of a combined score using IL-6 in a preliminary study. J Allergy Clin Immunol Pract. 2020;8(8): 2575-2581.e2.
- Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. 2020;92(7):797-806.
- Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069.
- 53. Wang D, Yin Y, Hu C, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. *Crit Care*. 2020;24(1):188.
- Wang C-Z, Hu S-L, Wang L, Li M, Li H-T. Early risk factors of the exacerbation of coronavirus disease 2019 pneumonia. *J Med Virol.* 2020;92(11):2593-2599.
- Wang G, Wu C, Zhang Q, et al. C-reactive protein level may predict the risk of COVID-19 aggravation. Open Forum Infect Dis. 2020;7(5):ofaa153.
- Wang F, Yang Y, Dong K, et al. Clinical characteristics of 28 patients with diabetes and COVID-19 in Wuhan, China. Endocr Pract. 2020;26(6):668-674.
- Wang F, Hou H, Luo Y, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCl Insight. 2020;5(10):e137799.
- Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-943.
- Yan Y, Yang Y, Wang F, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Res Care. 2020;8(1):e001343.

- 60. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020;8(5):475-481.
- Yang Q, Xie L, Zhang W, et al. Analysis of the clinical characteristics, drug treatments and prognoses of 136 patients with coronavirus disease 2019. J Clin Pharm Ther. 2020;45(4):609-616.
- Yang A-P, Li H-M, Tao W-Q, et al. Infection with SARS-CoV-2 causes abnormal laboratory results of multiple organs in patients. Aging (Albany NY). 2020;12(11):10059-10069.
- 63. Yang Q, Zhou Y, Wang X, et al. Effect of hypertension on outcomes of adult inpatients with COVID-19 in Wuhan, China: a propensity score-matching analysis. *Respir Res.* 2020;21(1):172.
- 64. Ye W, Chen G, Li X, et al. Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19. Respir Res. 2020;21(1):169.
- 65. Zeng Z, Ma Y, Zeng H, et al. Simple nomogram based on initial laboratory data for predicting the probability of ICU transfer of COVID-19 patients: multicenter retrospective study. / Med Virol. 2021;93(1):434-440.
- Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-1741.
- Zhang X, Tan Y, Ling Y, et al. Viral and host factors related to the clinical outcome of COVID-19. *Nature*. 2020;583(7816): 437-440.
- Zhang J, Yu M, Tong S, Liu L-Y, Tang L-V. Predictive factors for disease progression in hospitalized patients with coronavirus disease 2019 in Wuhan, China. J Clin Virol. 2020;127:104392.
- Zhang Y, Cao W, Jiang W, et al. Profile of natural anticoagulant, coagulant factor and anti-phospholipid antibody in critically ill COVID-19 patients. J Thromb Thrombolysis. 2020; 50(3):580-586.
- Zhang Q, Wei Y, Chen M, Wan Q, Chen X. Clinical analysis of risk factors for severe COVID-19 patients with type 2 diabetes. J Diabetes Complications. 2020;34(10):107666.
- Zheng F, Tang W, Li H, Huang Y-X, Xie Y-L, Zhou Z-G. Clinical characteristics of 161 cases of corona virus disease 2019 (COVID-19) in Changsha. *Eur Rev Med Pharmacol Sci.* 2020; 24(6):3404-3410.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published corrections appear in *Lancet.* 2020;395(10229):1038]. *Lancet.* 2020;395(10229): 1054-1062.
- Zhou Y, Zhang Z, Tian J, Xiong S. Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus. *Ann Palliat Med.* 2020;9(2):428-436.
- Zhu Z, Cai T, Fan L, et al. Clinical value of immuneinflammatory parameters to assess the severity of coronavirus disease 2019. *Int J Infect Dis.* 2020;95:332-339.
- Zhu Y, Du Z, Zhu Y, Li W, Miao H, Li Z. Evaluation of organ function in patients with severe COVID-19 infections. *Med Clin (Barc)*. 2020;155(5):191-196.
- Zhu J, Zhong Z, Ji P, et al. Clinicopathological characteristics of 8697 patients with COVID-19 in China: a meta-analysis [published correction appears in *Fam Med Community Health*. 2020;8(2):e000406corr1]. *Fam Med Community Health*. 2020;8(2):e000406.
- Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. J Infect. 2020;80(6):656-665.
- 78. Shah S, Shah K, Patel SB, et al. Elevated D-dimer levels are associated with increased risk of mortality in COVID-19: a systematic review and meta-analysis. medRxiv. https://doi.org/10. 1101/2020.04.29.20085407. Preprint posted online May 5, 2020.

- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
- Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/ clinical_epidemiology/oxford.asp. Accessed March 3, 2021.
- Ciceri F, Beretta L, Scandroglio AM, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. *Crit Care Resusc.* 2020;22(2):95-97.
- 82. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clin Chim Acta*. 2020;507:167-173.
- Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 2021;17(1):46-64.
- Zeng Y, Zhang B, Zhang X, Yi C. Clinical characteristics of 9 cancer patients with SARS-CoV-2 infection. *Chin Med.* 2020;15:47.
- McGonagle D, Sharif K, O'Regan A, Bridgewood C. Interleukin-6 use in COVID-19 pneumonia related macrophage activation syndrome. *Autoimmun Rev.* 2020;19(6): 102537.
- 86. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med*. 2020;8(7):681-686.
- Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology*. 2020;77(2):198-209.
- Lax SF, Skok K, Zechner P, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med. 2020;173(5):350-361.
- Xiong M, Liang X, Wei Y-D. Changes in blood coagulation in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Br | Haematol. 2020;189(6):1050-1052.
- Zeng F, Huang Y, Guo Y, et al. Association of inflammatory markers with the severity of COVID-19: a meta-analysis. Int J Infect Dis. 2020;96:467-474.
- Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: a systematic review and metaanalysis. J Med Virol. 2020;92(10):1875-1883.
- Zhang Z-L, Hou Y-L, Li D-T, Li F-Z. Laboratory findings of COVID-19: a systematic review and meta-analysis. Scand J Clin Lab Invest. 2020;80(6):441-447.
- Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med.* 2020;58(7):1021-1028.
- Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and metaanalysis. J Infect. 2020;81(2):e16-e25.
- Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, Creactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020;127:104370.
- Fan BE, Chong VCL, Chan SSW, et al. Hematologic parameters in patients with COVID-19 infection [published correction appears in Am J Hematol. 2020;95(11):1442]. Am J Hematol. 2020;95(6):E131-E134.
- Hermann M, Flammer A, Lüscher TF. Nitric oxide in hypertension. J Clin Hypertens (Greenwich). 2006;8(12, suppl 4):17-29.

- Honing ML, Morrison PJ, Banga JD, Stroes ES, Rabelink TJ. Nitric oxide availability in diabetes mellitus. *Diabetes Metab Rev.* 1998;14(3):241-249.
- Kinlay S, Ganz P. Role of endothelial dysfunction in coronary artery disease and implications for therapy. Am J Cardiol. 1997; 80(9A):111-16I.
- 100. Malhotra R, Hess D, Lewis GD, Bloch KD, Waxman AB, Semigran MJ. Vasoreactivity to inhaled nitric oxide with oxygen predicts long-term survival in pulmonary arterial hypertension. Pulm Circ. 2011;1 (2):250-258.
- 101. Marrazzo F, Spina S, Zadek F, et al. Protocol of a randomised controlled trial in cardiac surgical patients with endothelial dysfunction aimed to prevent postoperative acute kidney injury by administering nitric oxide gas. *BMJ Open*. 2019;9(7):e026848.
- 102. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res.* 2020;126(10):1456-1474.

- 103. Bavishi C, Maddox TM, Messerli FH. Coronavirus disease 2019 (COVID-19) infection and renin angiotensin system blockers. *JAMA Cardiol.* 2020;5(7):745-747.
- 104. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis [letter]. Thromb Haemost. 2020;120(5):876-878.
- 105. Chaudhary R, Kreutz RP, Bliden KP, Tantry US, Gurbel PA. Personalizing antithrombotic therapy in COVID-19: role of thromboelastography and thromboelastometry [letter]. *Thromb Haemost.* 2020;120(11):1594-1596.
- 106. Herold T, Jurinovic V, Amreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020;146(1):128-136.e4.
- 107. Chaudhary R, Bliden KP, Kreutz RP, et al. Race-related disparities in COVID-19 thrombotic outcomes: beyond social and economic explanations. *EClinicalMedicine*. 2020;29: 100647.