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; I²=83.85%), fibrinogen (WMD, 0.42; 95% CI, 0.18 to 0.67; I²=61.88%; P<.001), C-reactive protein (CRP) (WMD, 35.74; 95% CI, 30.16 to 41.31; I²=85.27%), high-sensitivity CRP (WMD, 62.68; 95% CI, 45.27 to 80.09; I²=0%), interleukin 6 (WMD, 22.81; 95% CI, 17.90 to 27.72; I²=90.42%), and ferritin (WMD, 506.15; 95% CI, 356.24 to 656.06; I²=52.02%). Moderate to significant heterogeneity was observed for all parameters (I² > 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.

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.1-7 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.50 With the availability of potential treatment, the identification of clinical and laboratory predictors of severe disease is...
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. 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. 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...
| Reference, year | Country     | Follow-up (d) | Groups                             | Type of study |
|----------------|-------------|---------------|------------------------------------|---------------|
| Bazzan et al.  | Italy       | 1.6           | Nonsurvivor vs survivor            | Retrospective |
| Bonetti et al. | Italy       | NA            | Nonsurvivor vs survivor            | Retrospective |
| Burian et al.  | Germany     | NA            | ICU vs non-ICU                     | Retrospective |
| Cen et al.     | China       | 28            | Severe vs nonsevere                | Retrospective |
| Chen et al.    | China       | NA            | Severe vs nonsevere                | Retrospective |
| Chen et al.    | China       | NA            | Severe/critical vs nonsevere       | Retrospective |
| Deng et al.    | China       | NA            | Nonsurvivor vs survivor            | Retrospective |
| Du et al.      | China       | 33            | Nonsurvivor vs survivor            | Prospective   |
| Duan et al.    | China       | NA            | Severe vs Nonsevere                | Retrospective |
| Fan et al.     | China       | NA            | Nonsurvivor vs survivor            | Retrospective |
| Fogarty et al. | Ireland     | NA            | Severe/critical vs nonsevere       | Prospective   |
| Fu et al.      | China       | 30            | Severe vs nonsevere                | Retrospective |
| Gan et al.     | China       | NA            | Nonsurvivor vs survivor            | Retrospective |
| Gao et al.     | China       | NA            | Severe vs nonsevere                | Retrospective |
| Gong et al.    | China       | NA            | Severe vs nonsevere                | Retrospective |
| Goshua et al.  | USA         | 40            | ICU vs non-ICU                     | Retrospective |
| Huang et al.   | China       | 10.5          | Critical/ICU vs non-ICU            | Prospective   |
| Javanian et al.| Iran        | NA            | Nonsurvivor vs survivor            | Retrospective |
| Ji et al.      | China       | NA            | Severe vs nonsevere                | Retrospective |
| Khamis et al.  | Oman        | NA            | ICU vs non-ICU                     | Retrospective |
| Li et al.      | China       | NA            | Severe vs nonsevere                | Retrospective |
| Li et al.      | China       | NA            | Severe vs nonsevere                | Prospective   |
| Li et al.      | China       | 30            | Nonsurvivor vs survivor            | Retrospective |
| Li et al.      | China       | NA            | Nonsurvivor vs survivor            | Retrospective |
| Li et al.      | China       | NA            | Severe vs nonsevere                | Retrospective |
| Liu et al.     | China       | NA            | Severe vs nonsevere                | Retrospective |
| Liu et al.     | China       | NA            | Severe vs nonsevere                | Retrospective |
| Liu et al.     | China       | NA            | Nonsurvivor vs survivor            | Retrospective |
| Liu et al.     | China       | 14            | Severe vs nonsevere                | Retrospective |
| Lv et al.      | China       | NA            | Severe vs nonsevere                | Retrospective |
| Ma et al.      | China       | NA            | Severe vs nonsevere                | Retrospective |
| Masetti et al. | Italy       | NA            | Nonsurvivor vs survivor            | Retrospective |
| Mao et al.     | China       | NA            | Severe vs nonsevere                | Retrospective |
| Middeldorp et al. | Netherlands | 15           | Critical/ICU vs non-ICU            | Prospective   |
| Ortíz-Brizuela et al. | Mexico | 13           | ICU vs non-ICU                     | Prospective   |
| Pan et al.     | China       | NA            | Severe vs nonsevere                | Retrospective |
| Qian et al.    | China       | NA            | Severe vs nonsevere                | Retrospective |
| Qin et al.     | China       | NA            | Severe vs nonsevere                | Retrospective |
| Rastad et al.  | Iran        | NA            | Nonsurvivor vs survivor            | Retrospective |
| Ruan et al.    | China       | 22            | Nonsurvivor vs survivor            | Retrospective |
| Salacup et al. | USA         | NA            | Nonsurvivor vs survivor            | Retrospective |
| Satıcı et al.  | Turkey      | NA            | Severe vs nonsevere                | Retrospective |
| Shahriarirad et al. | Iran | NA            | Nonsurvivor vs survivor            | Retrospective |
| Shi et al.     | China       | NA            | Nonsurvivor vs survivor            | Retrospective |
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

| Reference, year | Country | Follow-up (d) | Groups | Type of study |
|-----------------|---------|---------------|--------|---------------|
| Sun et al, 2020 | China   | NA            | Severe vs nonsmoke | Prospective |
| Tang et al (1), 2020 | China | NA | Nonsurvivor vs survivor | Retrospective |
| Tang et al (2), 2020 | China | 28 | Nonsurvivor vs survivor | Retrospective |
| Tian et al, 2020 | China | 30 | Severe vs nonsmoke | Retrospective |
| Vultaggio et al, 2020 | Italy | 21 | Severe vs nonsmoke | Retrospective |
| Wan et al, 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Wang et al (1), 2020 | China | 34 | Critical/ICU vs non-ICU | Retrospective |
| Wang et al (2), 2020 | China | 21 | Nonsurvivor vs survivor | Retrospective |
| Wang et al (3), 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Wang et al (4), 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Wang et al (5), 2020 | China | NA | Critical/ICU vs non-ICU | Retrospective |
| Wang et al (6), 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Wu et al (1), 2020 | China | 50 | ARDS vs non-ARDS | Retrospective |
| Yan et al, 2020 | China | NA | Nonsurvivor vs survivor | Retrospective |
| Yang et al (1), 2020 | China | 28 | Nonsurvivor vs survivor | Retrospective |
| Yang et al (2), 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Yang et al (3), 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Yang et al (4), 2020 | China | NA | Nonsurvivor vs survivor | Retrospective |
| Ye et al, 2020 | China | NA | Nonsurvivor vs survivor | Retrospective |
| Zeng et al, 2020 | China | 30 | ICU vs non-ICU | Retrospective |
| Zhang et al (1), 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Zhang et al (2), 2020 | China | NA | Severe vs nonsmoke | Prospective |
| Zhang et al (3), 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Zhang et al (4), 2020 | China | 36 | Nonsurvivor vs survivor | Retrospective |
| Zhang et al (5), 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Zheng et al, 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Zhou et al (1), 2020 | China | 21 | Nonsurvivor vs survivor | Retrospective |
| Zhou et al (2), 2020 | China | NA | Severe vs nonsmoke | Prospective |
| Zhu et al (1), 2020 | China | NA | Severe vs nonsmoke | Retrospective |
| Zhu et al (2), 2020 | China | NA | Nonsurvivor vs survivor | Retrospective |

*ARDS = acute respiratory distress syndrome; ICU = intensive care unit; NA = not available; USA = United States.

*Data from the same hospital—Tongji Hospital, China (n=18 exclusive; n=2 shared).

*Data from the same hospital—Wuhan Pulmonary Hospital, China (n=2 exclusive; n=2 shared).

*Data from the same hospital—Chongqing Three Gorges Hospital, China (n=2 exclusive).

*Data from the same hospital—Wuhan Jin Yin-tan Hospital, China (n=4 exclusive; n=2 shared).

*Data from the same hospital—Zhongnan Hospital of Wuhan University, China (n=4 exclusive).

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

*Data compiled from >1 hospital noted above.
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. 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 $P < 0.05$ 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. 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, all studies were retrospective. Most of the 75 studies were reported from China (80.0% [n=60]), while other studies were from Italy, Iran, the United States, Oman, Turkey, Mexico, Germany, Ireland, and the Netherlands. 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
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]; I²=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]; I²=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]; I²=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]; I²=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]; I²=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]; I²=0%; P<.001), interleukin 6 (IL-6) (49.3±35.7 vs 12.5±12.3 pg/mL; WMD, 22.81 [95% CI, 17.90 to 27.72]; I²=90.42%; P<.001) (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 two 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 by race/ethnicity in thromboinflammatory marker analysis (Supplemental Table 5).

**DISCUSSION**

This systematic review and meta-analysis of 74 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...
A high-sensitivity (hs) troponin I levels (36.4 vs 23.2 mg/L) (A), C-reactive protein (CRP) levels (52.8 vs 5.7 mg/L) (B), and D-dimer levels (2.9±3.1 vs 0.8±0.8 mg/dL) (C), were compared 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).
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, haptoglobin 1, 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. 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. 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. Our findings resonate with those of prior analyses. 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. 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. Coronaviruses have a unique affinity to the host angiotensin-converting enzyme 2 receptors, which are expressed in the vascular endothelium. 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. However, D-dimer levels need to be interpreted with caution in

| Study       | difference in means | standard error | p value | sample size | weighted mean difference | relative weight |
|-------------|---------------------|----------------|---------|-------------|---------------------------|----------------|
| Bonetti et al. | 39.50               | 11.75          | <.01    | 364         | 20                        | 2.00           |
| Chen et al. (1) | 64.00               | 19.06          | <.01    | 25          | 126                       | 0.87           |
| Huang et al.  | −0.20               | 0.11           | .07     | 13          | 28                        | 9.37           |
| Li et al. (3)  | 6.20                | 2.66           | .02     | 25          | 68                        | 7.88           |
| Li et al. (5)  | 19.80               | 4.88           | <.01    | 15          | 87                        | 5.72           |
| Ma et al.     | −1.00               | 1.34           | .45     | 20          | 64                        | 8.94           |
| Ortiz-Brizuela et al. | 6.60             | 1.96           | <.01    | 29          | 111                       | 8.49           |
| Pan et al.    | 14.20               | 5.08           | .01     | 89          | 35                        | 5.55           |
| Sato et al.   | 9.20                | 4.23           | .03     | 55          | 626                       | 6.34           |
| Shi et al.    | 229.00              | 69.29          | <.01    | 62          | 609                       | 0.07           |
| Tian et al.   | 7.70                | 1.94           | <.01    | 148         | 84                        | 8.51           |
| Wang et al. (1) | 5.90             | 2.01           | <.01    | 36          | 102                       | 8.45           |
| Wang et al. (3) | 3.35               | 1.78           | .06     | 39          | 46                        | 8.63           |
| Wang et al. (5) | 52.80              | 15.62          | <.01    | 14          | 14                        | 1.24           |
| Yan et al.    | 41.20               | 11.72          | <.01    | 39          | 9                         | 2.00           |
| Ye et al.     | 20.00               | 6.03           | <.01    | 52          | 297                       | 4.75           |
| Zhang et al. (5) | 13.80              | 5.22           | .01     | 27          | 47                        | 5.42           |
| Zhou et al. (1) | 19.20               | 4.83           | <.01    | 34          | 137                       | 5.77           |
| 10.69         | 1.87               | <.01           | 811     | 2564        | 307                       |                |

**FIGURE 2.** (continued.)
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.

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. In a study by Herold et al 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. 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. 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.
making the values 1000 times smaller or higher. 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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**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)**

| Parameter                  | Severe vs nonsevere | Nonsurvivor vs survivor |
|----------------------------|---------------------|-------------------------|
|                            | Mean±SD             | WMD/OR (95% CI)         | Mean±SD             | WMD/OR (95% CI)         |
| Platelet count (x 10^9/L)  | 179±33 vs 195±32    | WMD: −8.01 (−1.45 to −1.51); P<.001 | 159±33 vs 201±28    | WMD: −26.33 (−35.99 to −16.66); P<.001 |
|                           | (n=5135)            |                          | (n=4518)            |                          |
| D-dimer (mg/dL)            | 2.9±3.7 vs 0.8±0.9  | WMD: 0.43 (0.32 to 0.54); P<.001 | 3±1.8 vs 0.9±0.7    | WMD: 1.35 (0.99 to 1.71); P<.001 |
|                           | (n=5863)            | r²=83.08%               | (n=5509)            | r²=85.58%               |
| Prothrombin time (s)       | 13.7±2.9 vs 12.4±1.2| WMD: 0.53 (0.39 to 0.66); r²=0.0%; P<.001 | 14.3±1.6 vs 13.1±1.2| WMD: 1.01 (0.77 to 1.26); r²=35.39%; P<.001 |
|                           | (n=2533)            |                          | (n=3951)            |                          |
| aPTT (s)                   | 33.5±5 vs 33.6±5    | WMD: 0.38 (−0.84 to 1.61); r²=76.51%; P=.54 | 41.1±11 vs 37.1±4.6 | WMD: 1.14 (0.12 to 2.16); r²=59.94%; P=.03 |
|                           | (n=2559)            |                          | (n=2797)            |                          |
| Fibrinogen (g/L)           | 4.3±1.5 vs 3.5±1.2  | WMD: 0.62 (0.26 to 0.99); r²=59.14%; P<.001 | 4.6±0.6 vs 4.4±0.7  | WMD: 0.23 (−0.09 to 0.56); r²=58.32%; P=.16 |
|                           | (n=1100)            |                          | (n=3520)            |                          |
| CRP (mg/L)                 | 59.2±34.8 vs 19.1±16.3| WMD: 30.42 (24.31 to 36.53); r²=85.74%; P<.001 | 97±37.1 vs 31.7±22  | WMD: 58.58 (41.23 to 75.93); r²=84.39%; P<.001 |
|                           | (n=6099)            |                          | (n=7987)            |                          |
| hs-CRP (mg/L)              | 102±43±32 vs 25.4±4.8| WMD: 62.72 (37.97 to 87.46); r²=130.7%; P<.001 | Not enough data     | Not enough data          |
|                           | (n=486)             |                          |                      |                          |
| Interleukin 6 (pg/L)       | 49.2±32.1 vs 12.6±13.1| WMD: 28.14 (19.93 to 36.35); r²=91.41%; P<.001 | 49.4±46.7 vs 12.2±10.6| WMD: 15.30 (7.06 to 25.53); r²=86.71%; P<.001 |
|                           | (n=2385)            |                          | (n=1958)            |                          |
| Ferritin (ng/mL)           | 1109±737 vs 584±319 | WMD: 320.92 (1197.54 to 444.30); r²=120.6%; P<.001 | 1626±947 vs 687±341 | WMD: 700.21 (497.52 to 902.90); r²=27.06%; P<.001 |
|                           | (n=1154)            |                          | (n=3179)            |                          |
| hs-Troponin I (pg/ml)      | 225±23.5 vs 5.5±4.5 | WMD: 5.39 (1.84 to 8.94); r²=88.81%; P<.001 | 50.2±70.3 vs 6.3±3  | WMD: 18.68 (10.92 to 26.44); r²=75.69%; P<.001 |
|                           | (n=972)             |                          | (n=2403)            |                          |
| LDH (U/L)                  | 377±94 vs 242±54    | WMD: 124.04 (75.42 to 172.66); r²=90.08%; P<.001 | 561±134 vs 303±70   | WMD: 188.77 (153.07 to 224.47); r²=125.7%; P<.001 |
|                           | (n=3371)            |                          | (n=5784)            |                          |
| Mortality                  | 30.1% (115 of 383) vs 1.3% (11 of 862) | OR: 28.14 (14.99 to 52.83); r²=0%; P<.001 | NA                  | NA                          |
|                           | (n=1319)            |                          |                      |                          |
| Acute cardiac injury       | 24.8% (38 of 153) vs 9.0% (36 of 402) | OR: 4.73 (1.64 to 13.67); r²=57.83%; P<.001 | 56.6% (172 of 304) vs 3.8% (64 of 1668) | OR: 43.83 (15.54 to 123.65); r²=59.33%; P<.001 |
|                           | (n=555)             |                          | (n=1972)            |                          |
| ARDS                       | 67.2% (76 of 133) vs 3.6% (12 of 338) | OR: 33.49 (16.75 to 66.98); r²=17.30%; P<.001 | 81.9% (334 of 408) vs 4.4% (94 of 2155) | OR: 73.80 (29.66 to 1183.61); r²=83.2%; P<.001 |
|                           | (n=471)             |                          | (n=2563)            |                          |

*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.

1/1000 = conversion factors: To convert D-dimer values to nmmol/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 kat/L, multiply by 0.0167.
infection. Comorbidities conferring higher risk coupled with thrombinflammatory 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://mcpqojournal.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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REFERENCES
1. Bazzan M, Montanari B, Sciascia S, Cosseddu D, Noribato C, Roccatello D. Low ADAMTS 13 plasma levels are predictors of mortality in COVID-19 patients. Intern Emerg Med. 2020; 15(5):861-863.
2. 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.
3. Burian E, Jungmann F, Kaisis GA, et al. Intensive care risk estimation in COVID-19 pneumonia based on clinical and imaging parameters: experiences from the Munich cohort. J Clin Med. 2020;9(5):1514.
4. Chen 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.
5. Chen C, Chen C, Yan JF, 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 Xu Guan Bing Za Zhi. 2020;48(7):567-571.
6. 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.
7. 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.
8. 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.
9. Du RH, Liang LR, Yang CQ, 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):200524]. Eur Respir J. 2020;55(5):2000524.
10. 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(1):6-2622.
11. 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 LN, Neelaiah C, et al. COVID-19 coagulopathy in Caucasian patients. Br J Haematol. 2020;189(6):1044-1049.
13. 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. Thorax Res. 2020;19:3-8.
14. 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.
15. 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.
16. Geng J, Ou J, Qu X, et al. A tool for early prediction of severe coronavirus disease 2019 (COVID-19): a multicenter study using the risk nomogram in Wuhu and Guangdong, China. Clin Infect Dis. 2020;71(15):833-840.
17. Goshua G, Pine AB, Mezlish ML, et al. Endothelopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol. 2020;7(8):e575-e582.
18. 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(10233):496]. Lancet. 2020;395(10233):497-506.
19. 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.
20. Ji M, Yuan L, Shen W, et al. Characteristics of disease progress of mortality in patients with coronavirus disease 2019 in Wuhan, China. J Med Virol. 2020;92(e1):1-1-1-1-105.
21. Khans M, Al-Zakwani I, Al Naamani H, et al. Clinical characteristics and outcomes of the first 63 adult patients hospitalised with COVID-19: an experience from Oman. J Infect Public Health. 2020;13(7):906-913.
22. 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.

23. Li Y, Zhao K, Wei H, et al. Dynamic relationship between D-dimer and COVID-19 severity. Br J Haematol. 2020;190(1):e24-e27.

24. Li Y, Yang L, Gui S, et al. Association of clinical and radiographic findings with the outcomes of 93 patients with COVID-19 in Wuhan, China. Throm Res. 2020;101(4):613-612.

25. Li Q, Mao L, Jin H, Wang M, et al. Hematological features of persons with COVID-19. Leukemia. 2020;34(8):2163-2172.

26. 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.

27. Liu X, Li Z, Liu S, et al. Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. Acta Pharmac Sin B. 2020;10(7):1205-1215.

28. 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 J, Li SK. Laboratory findings and a combined multifactorial approach to predict death in critically ill patients with COVID-19: a retrospective study. Epi- demiol Infect. 2020;148:e129.

30. Lu H, Aj I, 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/10.1016/j.ijert.2020.02.002.005301. Preprint posted online February 23, 2020.

31. Lv Z, Cheng S, Le J, et al. Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. Micrbes Infect. 2020;22(4):S5-199.

32. 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/10.1016/j.ijert.2020.03.034.124. Preprint posted online March 23, 2020.

33. 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.

34. Mao L, Jin H, Wang M, et al. Neurological manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China: a prospective cohort study. J Thromb Haemost. 2020;18(1):427.

35. 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-Brieldia E, Villanueva-Reza M, Gonzalez-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.

37. 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.

38. 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. QJM. 2020;113(7):474-481.

39. 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.

40. 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;12:257.

41. 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.

42. Salacup G, Lin KB, Gu 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.

43. Sabit C, Demirkol MA, Atunak ES, et al. Performance of pneumonia severity index and CURB-65 in predicting 30-day mortality in patients with COVID-19. Int J Infect Dis. 2020;98:84-89.

44. Shahriari 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;42(22):2070-2079.

46. Sun Y, Dong Y, Wang L, et al. Characteristics and prognostic factors of disease severity in patients with COVID-19: the Beijing experience. J Autonomn. 2020;12:102473.

47. 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.

48. 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.

51. 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.

52. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with novel coronavirus 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.

54. 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.

55. 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.

56. Wang F, Yang Y, Deng K, et al. Clinical characteristics of 28 patients with diabetes and COVID-19 in Wuhan, China. Endocr Pract. 2020;26(6):668-674.

57. Wang F, Hou H, Luo Y, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI Insight. 2020;5(10):e137999.

58. 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.

59. 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.
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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. J Clin Pharm Ther. 2020;45(4):609-616.

61. Yang Q, Xie L, Zhang W, et al. Analysis of the clinical characteristics, drug treatments and prognoses of 136 patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: a propensity score-matching analysis. Resp Res. 2020;22(1):172.

62. Ye W, Chen G, Li X, et al. Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19. J Infect. 2020;80(6):441-447.

63. 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. J Med Virol. 2021;93(1):434-440.

64. Zhang J.J., Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Aliment Pharmacol Ther. 2020;57(7):1730-1741.

65. Zhang Y, Tan Y, Ling Y, et al. Viral and host factors related to the clinical outcome of COVID-19. Nature. 2020;583(7816):437-440.

66. 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.

67. Zhang Y, Cao W, Li W, et al. High natural anticoagulant, coagulant factor and anti-phospholipid antibody in critically ill COVID-19 patients. J Thromb Thrombolysis. 2020;50(3):580-586.

68. 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.

69. Zheng F, Tang W, Li H, Huang Y-X, Xie Y-L, Zhou Z-G. Clinical characteristics of 161 cases of coronavirus disease 2019 (COVID-19) in Changsha. Eur Rev Med Pharmacol Sci. 2020;24(6):3404-3410.

70. 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):1029, 1038]. Lancet. 2020;395(10229):1029-1038.

71. Zhou Y, Zhang T, Tian J, Xiong S. Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus. Arq Palmit Med. 2020;9(2):428-436.

72. Zhu Z, Cai T, Fan L, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020;95:332-339.

73. 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.

74. Zhu J, Zhong Z, Ji P, et al. Clinico-pathological characteristics of 8697 patients with COVID-19 in China: a meta-analysis [published correction appears in Fam Med Community Health. 2020;8(2):e000406]. Fam Med Community Health. 2020;8(2):e000406.

75. 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.

76. 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.

77. 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.

78. Wells GA, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 3, 2021.

79. Cicci F, Beretta L, Scandroglio AM, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroGLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc. 2020;22(2):95-97.

80. Henry BM, Vilse J, Beront S, Favaloro EJ, Lipi 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.

81. Perico L, Benigni A, Caiarighi F, Ng LFP, Renia L, Renuzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 2021;17(1):46-64.

82. Zeng Y, Zhang B, Zhang X, Yi C. Clinical characteristics of 9 cancer patients with SARS-CoV-2 infection. J Clin Med. 2020;5(4):7.

83. McGonagle D, Sharif K, O’Regan A, Bridgewood C. Interleukin-6 use in COVID-19 pneumonia related macrophage activation syndrome. Aut Immun Rev. 2020;19(6):102537.

84. Fox SE, Akmatbekov A, Herbst 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.

85. Plentz T, Haußbauer JD, Niehans 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.

86. Lax SF, Sklak K, Zechari 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.

87. Xiong M, Liang X, Wei Y-D. Changes in blood coagulation in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Br J Haematol. 2020;190(6):1050-1052.

88. Zheng 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.

89. Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. J Med Virol. 2020;92(10):1875-1883.

90. Zhang Z-L, Hou Y-L, Li D-T, Li F-Z. Laboratory findings of COVID-19: a systematic review and meta-analysis. Sclod J Clin Lab Invest. 2020;80(6):441-447.

91. Henry BM, de Oliveira PHS, Beront S, Piebani M, Lipi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chim Acta. 2020;510:105211.

92. Zhang Z, Peng F, Xue B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. Int J Infect Dis. 2020;95:332-339.

93. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Infect. 2020;80(6):441-447.
98. Honing ML, Morrison PJ, Banga JD, Stroes ES, Rabelink TJ. Nitric oxide availability in diabetes mellitus. *Diabetes Metab Rev*. 1998;14(3):241-249.

99. Kinlay S, Ganz P. Role of endothelial dysfunction in coronary artery disease and implications for therapy. *Am J Cardiol*. 1997; 80(9A):11-16.

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. Manzano 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(1):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.