


## RESEARCH ARTICLE

# Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis

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**Abstract**

Mortality rates of coronavirus disease-2019 (COVID-19) continue to rise across the world. Information regarding the predictors of mortality in patients with COVID-19 remains scarce. Herein, we performed a systematic review of published articles, from 1 January to 24 April 2020, to evaluate the risk factors associated with mortality in COVID-19. Two investigators independently searched the articles and collected the data, in accordance with PRISMA guidelines. We looked for associations between mortality and patient characteristics, comorbidities, and laboratory abnormalities. A total of 14 studies documenting the outcomes of 4659 patients were included. The presence of comorbidities such as hypertension (odds ratio [OR], 2.5; 95% confidence interval [CI], 2.1-3.1;  $P < .00001$ ), coronary heart disease (OR, 3.8; 95% CI, 2.1-6.9;  $P < .00001$ ), and diabetes (OR, 2.0; 95% CI, 1.7-2.3;  $P < .00001$ ) were associated with significantly higher risk of death amongst patients with COVID-19. Those who died, compared with those who survived, differed on multiple biomarkers on admission including elevated levels of cardiac troponin (+44.2 ng/L, 95% CI, 19.0-69.4;  $P = .0006$ ); C-reactive protein (+66.3  $\mu\text{g/mL}$ , 95% CI, 46.7-85.9;  $P < .00001$ ); interleukin-6 (+4.6 ng/mL, 95% CI, 3.6-5.6;  $P < .00001$ ); D-dimer (+4.6  $\mu\text{g/mL}$ , 95% CI, 2.8-6.4;  $P < .00001$ ); creatinine (+15.3  $\mu\text{mol/L}$ , 95% CI, 6.2-24.3;  $P = .001$ ); and alanine transaminase (+5.7 U/L, 95% CI, 2.6-8.8;  $P = .0003$ ); as well as decreased levels of albumin (-3.7 g/L, 95% CI, -5.3 to -2.1;  $P < .00001$ ). Individuals with underlying cardiometabolic disease and that present with evidence for acute inflammation and end-organ damage are at higher risk of mortality due to COVID-19 infection and should be managed with greater intensity.

**KEYWORDS**

cardiovascular disease, COVID-19, diabetes, meta-analysis

## 1 | INTRODUCTION

Since its emergence in Wuhan, China in late 2019, coronavirus disease-2019 (COVID-19) has rapidly become a global threat and was officially declared a pandemic by the World Health Organization on 11 March 2020. As of 30 April 2020, there have been more than 3.0 million global confirmed cases and greater than 230 000 fatalities due to COVID-19. The United States is now the epicenter of the outbreak, having recorded over 60 000 fatalities. However, the factors that predispose an individual to a higher risk of death from COVID-19 are poorly understood. To optimize patient care and appropriately deploy health care resources during this pandemic, effective patient risk stratification is essential.

Although prior COVID-19 meta-analyses have been published, they have focused on severity of disease rather than the clinical outcome of mortality.<sup>1-7</sup> These studies have begun to answer key clinical questions on COVID-19 evolution and outcomes, as well as potential risk factors leading to hospital and intensive care unit admission. Indeed, it is now understood that old age, male sex, elevated inflammatory markers, and comorbidities such as hypertension and cardiovascular disease are strong risk factors for COVID-19-related hospitalization.<sup>1,3-6</sup> To date, several important meta-analyses have reported on the relationships between COVID-19 disease severity and mortality with specific comorbidities,<sup>8-13</sup> lab and imaging results,<sup>7,14-17</sup> and medication use,<sup>18,19</sup> although the assessment of mortality was limited in sample size. We aimed to add to our understanding of COVID-19 by conducting a systematic meta-analysis of published articles to comprehensively elucidate predictors of mortality in hospitalized patients with COVID-19.

## 2 | METHODS

This article has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.<sup>20</sup>

### 2.1 | Data sources

We performed a retrospective, cross-sectional systematic review using PubMed, Google scholar, Web of Science, and China National Knowledge Infrastructure between 1 January 2020 and 24 April 2020 without language restriction. We used the following search terms: (a) "COVID 19 OR SARS-CoV-2 OR 2019-nCoV OR Coronavirus" (Title/Abstract) AND "Clinical characteristics OR clinical feature OR clinical manifestation" (All fields); (b) "COVID 19 OR SARS-CoV-2 OR 2019-nCoV OR Coronavirus" [Title/Abstract] AND "death OR died OR fatal OR mortality OR deceased OR non survivor OR non Survival" (All fields) AND "recovered OR discharged OR alive OR survivor OR survival" (All fields). We also searched the references of meta-analyses or systematic review articles to avoid missing any eligible articles.

### 2.2 | Study selection

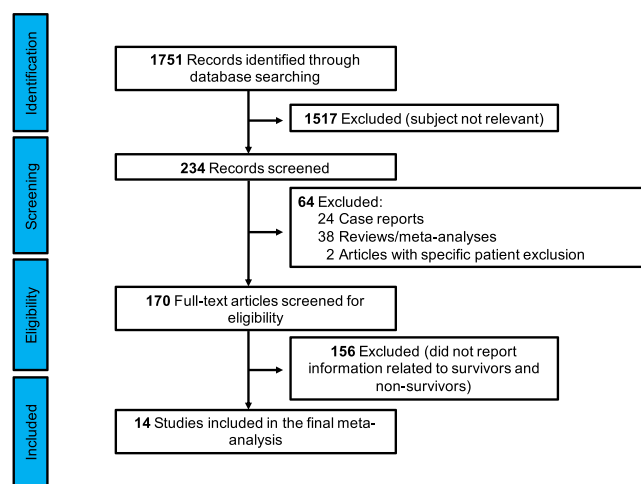
The results from the initial search were screened for relevance by titles and abstracts by two independent investigators. The full texts were reviewed for the eligibility criteria (Figure 1). Duplicate publications, reviews, editorials, case reports, family-based studies, and those that reported pediatric-only cases were excluded. Clinical studies that did not clearly report death as an outcome were excluded. In addition, if two or more studies were published based on the same sample of patients by the same author, only the article with the highest quality was included.

### 2.3 | Data extraction

Data extraction forms, including information on the authors, year of publication, country, region, hospital, sample size, age, gender, comorbidities (eg, hypertension and diabetes), clinical symptoms (eg, fever), and laboratory parameters (eg, creatinine and D-dimer) were obtained independently by two investigators (postdoctoral fellows with either MD or MBBS-PhD and clinical research experience). For one study published in Chinese, data were extracted by Drs. Tian and Jiang, who are fluent in Chinese. A third investigator checked the article list and corresponding data to ensure that no duplications were made and adjudicated any discrepancies.

### 2.4 | Quality assessment

For quality assessment, we used the Agency for Healthcare Research and Quality (AHRQ) score checklist to assess the methodological quality of cross-sectional studies in this meta-analysis.<sup>21</sup> Two independent assessors evaluated the quality of studies as low (0-3), moderate (4-7), or high (8-11). Although there were varying levels of



**FIGURE 1** Search and selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

confidence based on the AHRQ score (Table S1), we included all available studies to maximize the sample size and to enhance the generalizability of our findings.

## 2.5 | Data synthesis

A meta-analysis was performed using the program Review Manager (RevMan) (<https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman>) to compare clinical features (hypertension, coronary heart disease/cardiovascular disease, cerebrovascular disease, diabetes, chronic renal disease, smoking history, and chronic obstructive pulmonary disease [COPD]) between patients with COVID-19 who survived and those who did not survive. For laboratory data (ie, continuous measures), we calculated weighted mean differences and 95% confidence intervals (95% CI) in patients with COVID-19 who survived vs those who did not survive whenever two or more studies reported a given parameter. We used the generic inverse variance method in RevMan to weight studies involved in the meta-analysis. A random-effects meta-analysis model was assumed given the fact that the effects being estimated in different studies may not be identical but follow some distribution. The width of this distribution describes the degree

of heterogeneity. RevMan was also used to calculate measures of heterogeneity such as the  $\chi^2$  and  $I^2$  statistics and the Tau<sup>2</sup> statistic for random-effects analysis.<sup>22</sup>

## 3 | RESULTS

### 3.1 | Study search and characteristics

The systematic search of articles published on or before 24 April 2020, identified 170 topic-related articles, of which 14 articles were included in the final study (Figure 1).<sup>23-37</sup> The main characteristics of the included studies are reported in Table 1. The results of the meta-analyses are summarized in Tables 2 and 3. In total, 4659 patients were included in the studies from China (2025; 13 studies) and New York (2634; 1 study combining data from 12 hospitals). Overall, 2681 participants (57.5%) were male, and the mean age of the patients enrolled, excluding instances where only partial age ranges were analyzed, was 59.8 years. Across all patients, significant comorbidities included hypertension (43.6%), diabetes (23.8%), and coronary heart disease (CHD)/cardiovascular disease (12.4%). Fever (88.0%), fatigue (44.5%), and

**TABLE 1** Included studies

Author	Publication date (MM/DD)	Sample size (survivor/nonsurvivor)	Country	Hospital (dates of data collection)
Richardson et al <sup>30</sup>	04/22	2634 (2081/553)	USA	12 Hospitals within the Northwell Health system, New York (03/04/2020 to 04/04/2020)
Chen et al <sup>24</sup>	04/11	55 (36/19)	China	Patients $\geq$ 65 y from Zhongnan Hospital (01/01/2020 to 02/10/2020)
Chen et al <sup>25</sup>	04/11	274 (161/113)	China	Tongji Hospital (until 02/28/2020)
Du et al <sup>27</sup>	04/08	179 (158/21)	China	Wuhan Pulmonary Hospital (12/25/2019 to 02/07/2020)
Cao et al <sup>23</sup>	04/02	102 (85/17)	China	Adults patients at Zhongnan Hospital (01/03/2020 to 02/01/2020)
Zhou et al <sup>37</sup>	03/28	191 (137/54)	China	$\geq$ 18 y old patients from Jinyintan and Wuhan Pulmonary Hospital (until 01/31/2020)
Zhang et al <sup>36</sup>	03/23	315 (268/47)	China	Wuhan Union Hospital West Area (01/12/2020 to 02/03/2020)
Deng et al <sup>26</sup>	03/20	225 (116/109)	China	Branch hospitals of Tongji Hospital and Wuhan Central Hospital (01/01/2020 to 02/01/2020)
He et al <sup>28</sup>	03/15	54 (28/26)	China	Severe patients at Tongji Hospital (02/03/2020 to 02/24/2020)
Wu et al <sup>34</sup>	03/13	84 (40/44)	China	Patients with ARDS at Jinyintan Hospital (12/25/2019 to 01/26/2020)
Tang et al <sup>33</sup>	03/13	183 (162/21)	China	Tongji Hospital (01/12/2020 to 02/03/2020)
Ruan et al <sup>31,32</sup>	03/03	150 (82/68)	China	Jinyintan and Tongji Hospital (date was not described)
Li et al <sup>29</sup>	03/03	161 (96/65)	China	Wuhan Red Cross Hospital (01/21/2020 to 01/26/2020)
Yang et al <sup>35</sup>	02/24	52 (20/32)	China	Patients in ICU at Jinyintan Hospital (late December 2019 to 01/26/2020)

Abbreviation: ICU, intensive care unit.

**TABLE 2** Summary of meta-analyses for patient demographics, comorbidities, and clinical manifestations

Variable	No. of Studies	Survived		Deceased		OR (95% CI)	Meta-analysis P-value
		Total (survived)	No. with risk factor (%)	Total (deceased)	No. with risk factor (%)		
Male sex	14	3470	1900 (54.8)	1189	781 (65.7)	1.78 (1.30-2.42)	.0003
<i>Comorbidities</i>							
Hypertension	11	3192	1251 (39.2)	1071	608 (56.8)	2.53 (2.07-3.09)	<.00001
CHD/CVD	12	1227	96 (7.8)	615	132 (21.5)	3.81 (2.11-6.85)	<.00001
Cerebrovascular disease	6	652	13 (2.0)	296	31 (10.5)	4.92 (1.54-15.68)	.007
Diabetes	12	3212	682 (21.2)	1103	344 (31.2)	1.97 (1.67-2.31)	<.00001
Smoking	4	414	16 (3.9)	264	16 (6.1)	1.77 (0.83-3.81)	.14
Chronic renal disease	6	769	3 (0.4)	318	15 (4.7)	9.41 (3.23-27.40)	<.0001
COPD	4	283	9 (3.2)	167	9 (5.4)	2.09 (0.49-8.90)	.32
<i>Clinical manifestations</i>							
Fever	10	931	807 (86.7)	542	488 (90.0)	1.31 (0.77-2.23)	.31
Fatigue	9	1063	452 (42.5)	448	221 (49.3)	1.62 (1.06-2.48)	.03
Myalgia	10	1159	249 (21.5)	545	110 (20.2)	1.04 (0.78-1.37)	.80
Diarrhea	7	899	129 (14.3)	424	68 (16.0)	0.98 (0.70-1.37)	.88
Hemoptysis	3	435	15 (3.4)	243	9 (3.7)	1.76 (0.62-4.99)	.29

Abbreviations: CI, confidence interval; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; OR, odds ratio.

myalgia (21.1%) were common clinical manifestations. Overall, 1189 patients died (25.5%). The mortality rate amongst Chinese patients was 31.4% and for New York was 21.0%. However, unlike the New York study, some of the Chinese studies only included critically ill patients in their studies and, therefore, a comparison cannot be performed.

Older age was associated with a higher risk of death (Figure S1A, mean difference 15.6; 95% CI, 12.5-18.6,  $P < .00001$ ). Furthermore, male sex was associated with a higher risk of mortality (Table 2 and Figure S1B; odds ratio [OR], 1.8; 95% CI, 1.3-2.4,  $P = .0003$ ).

### 3.2 | Clinical symptoms

There was no clear association between death and the presence of fever, myalgia, diarrhea, or hemoptysis in COVID-19 patients (Figure S2). Fatigue was more prevalent in patients that succumbed to COVID-19 versus those that survived (Figure S2B, OR, 1.6; 95% CI, 1.1-2.5,  $P = .03$ ). We also observed a nonsignificant trend to suggest that increased length of time between the onset of symptoms and hospital admission correlated with a greater odds for death (Figure S3, +0.8 days; 95% CI, -0.5 to 2.1;  $P = .22$ ).

### 3.3 | Comorbidities

In our meta-analysis, we found several comorbidities were associated with risk of mortality due to COVID-19 (summarized in Table 2). The presence of hypertension (Figure 2A, OR, 2.5; 95% CI,

2.1-3.1;  $P < .00001$ ), diabetes (Figure S4A, OR, 2.0; 95% CI, 1.7-2.3;  $P < .00001$ ), CHD/cardiovascular disease (Figure S4B, OR, 3.8; 95% CI, 2.1-6.9;  $P < .00001$ ), cerebrovascular disease (Figure S4C, OR, 4.9; 95% CI, 1.5-15.7;  $P = .007$ ), and chronic renal disease (Figure S5A, OR, 9.4; 95% CI, 3.2-27.4;  $P < .0001$ ) were all associated with significantly higher risk of death amongst patients with COVID-19. Of those analyzed, hypertension was the most prevalent comorbidity amongst patients that died (56.8%), followed by diabetes (31.2%) and CHD/cardiovascular disease (21.5%). We found no significant association between COPD (Figure S5B, OR, 2.1; 95% CI, 0.5-8.9;  $P = .32$ ) or smoking (Figure S5C, OR, 1.8; 95% CI, 0.8-3.8;  $P = .14$ ) and death, but these comorbidities were only reported in four of the 14 studies.

### 3.4 | Laboratory results

Common laboratory tests were evaluated for their association with mortality (Table 3, Figure 2, and Figures S6-S10). Several cardiovascular disease biomarkers were higher in the nonsurvivor group. Cardiac troponin, a marker of myocardial injury, was significantly higher in nonsurvivors (Figure 2B, +44.2 ng/L, 95% CI, 19.0-69.4;  $P = .0006$ ). N-terminal pro-brain natriuretic peptide, a marker of heart failure or cardiac strain, was also elevated in nonsurvivors (Figure S6A, +903 pg/mL, 95% CI, 718-1089;  $P < .00001$ ). Levels of the inflammatory markers interleukin-6 (IL-6; Figure S6B, +4.6 ng/mL, 95% CI, 3.6-5.6;  $P < .00001$ ), C-reactive protein (CRP, Figure 2C, +66.3 μg/mL, 95% CI, 46.7-85.9;  $P < .00001$ ), and erythrocyte sedimentation rate (ESR; Figure S6C, +6.9 mm/h, 95% CI, 3.4-10.4;  $P = .0001$ ) were higher in nonsurvivors.

**TABLE 3** Summary of meta-analyses for laboratory results

Laboratory test	No. of studies tested	Mean difference (95% CI) nonsurvivor-survivor	Meta-analysis P-value
Albumin	7	-3.7 (-5.3 to -2.1)	<.00001
ALT	7	5.7 (2.6-8.8)	.0003
APTT	6	1.3 (-1.3 to 4.0)	.32
AST	6	15.2 (7.7-22.7)	<.0001
BUN	5	3.0 (1.6-4.4)	<.0001
CD4+ T Cell count	2	-50.0 (-82.6 to -17.4)	.003
CD8+ T Cell count	2	-82.9 (-151.3 to -14.4)	.02
Creatine kinase	5	87 (21-153)	.010
Creatinine	8	15.3 (6.2-24.3)	.001
CRP	8	66.3 (46.7-85.9)	<.00001
D-Dimer	8	4.6 (2.8-6.4)	<.00001
ESR	6	6.9 (3.4-10.4)	.0001
Hemoglobin	6	-1.2 (-3.9 to 1.4)	.35
IL-6	3	4.6 (3.6-5.6)	<.00001
Lactate dehydrogenase	5	290 (256-325)	<.00001
Lymphocyte count	9	-0.34 (-0.41 to -0.27)	<.00001
NT-proBNP	3	903 (718-1089)	<.00001
Platelet count	7	-35.9 (-53.3 to -18.5)	<.0001
Procalcitonin	4	0.21 (0.11-0.31)	<.0001
PT	7	1.15 (0.43-1.87)	.002
Total Bilirubin	6	4.8 (3.4-6.1)	<.00001
Troponin I	3	44.2 (19.0-69.4)	.0006
WBC count	9	3.8 (3.1-4.5)	<.00001

Abbreviations: ALT, alanine transaminase; APTT, activated partial thromboplastin time; aspartate aminotransferase; BUN, blood urea nitrogen; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; NT-proBNP, N-terminal pro-brain natriuretic peptide; PT, prothrombin time; WBC, white blood cell count.

Levels of lactate dehydrogenase (Figure S6D, +290.2 U/L, 95% CI, 255.9-324.6;  $P < .00001$ ) and creatine kinase (Figure S6E, +86.8 U/L, 95% CI, 21.0-152.6;  $P = .01$ ) were also elevated in nonsurvivors compared with survivors. Across four studies, there was a higher level of procalcitonin (Figure S6F, +0.2 ng/mL, 95% CI, 0.1-0.3;  $P < .0001$ ) in the nonsurvivor group, which may be indicative of sepsis in these patients.<sup>38</sup>

Blood coagulation measurements revealed a greater risk of coagulopathy in patients in the nonsurvival group. Platelet count was significantly lower (Figure S7A,  $-35.9 \times 10^9/L$ , 95% CI,  $-53.3$  to  $-18.5$ ;  $P < .0001$ ) in the nonsurvival group whereas D-dimer (Figure 2D, +4.6 pg/mL, 95% CI, 2.8-6.4;  $P < .00001$ ) was higher. In addition,

prothrombin time was mildly elevated in the nonsurvival group (Figure S7B, +1.2 second, 95% CI, 0.4-1.9;  $P = .002$ ). However, we found no significant association between activated partial thromboplastin time and mortality (Figure S7C).

Liver and renal biomarker levels generally revealed worse function in the nonsurvival group. With regard to liver function tests, total bilirubin (Figure S8A, +4.8  $\mu\text{mol/L}$ , 95% CI, 3.4-6.1;  $P < .00001$ ), alanine transaminase (Figure S8B, ALT, +5.7 U/L, 95% CI, 2.6-8.8;  $P = .0003$ ), and aspartate transaminase (Figure S8C, AST, +15.2 U/L, 95% CI, 7.7-22.7;  $P < .0001$ ) levels were higher in the nonsurvival group. Albumin levels were lower in the nonsurvival group (Figure S8D,  $-3.7 \text{ g/L}$ , 95% CI,  $-5.3$  to  $-2.1$ ;  $P < .00001$ ). In addition, levels of creatinine (Figure S9A, +15.3  $\mu\text{mol/L}$ , 95% CI, 6.2-24.3;  $P = .001$ ), and blood urea nitrogen (BUN; Figure S9B, +3.0  $\mu\text{mol/L}$ , 95% CI, 1.6-4.4;  $P < .0001$ ) were consistently higher amongst those patients who died, demonstrating that worse renal function at the time of hospital admission was associated with increased mortality. Baseline severity of chronic renal disease or hemodialysis status were unknown.

Immune cell counts that differed between the nonsurvival and survival groups included a higher white blood cell count (Figure S10A,  $+3.8 \times 10^9/L$ , 95% CI, 3.1-4.5;  $P < .00001$ ) and lower absolute lymphocyte count (Figure S10B,  $-0.34 \times 10^9/L$ , 95% CI,  $-0.41$  to  $-0.27$ ;  $P < .00001$ ). In the two studies where T lymphocyte counts were available, CD4<sup>+</sup> cell count (Figure S10C,  $-50.0 \times 10^9/L$ , 95% CI,  $-82.6$  to  $-17.4$ ;  $P = .003$ ), and CD8<sup>+</sup> cell count (Figure S10D,  $-82.9 \times 10^9/L$ , 95% CI,  $-151.3$  to  $-14.4$ ;  $P = .02$ ) were lower in the nonsurvivor group.

## 4 | DISCUSSION

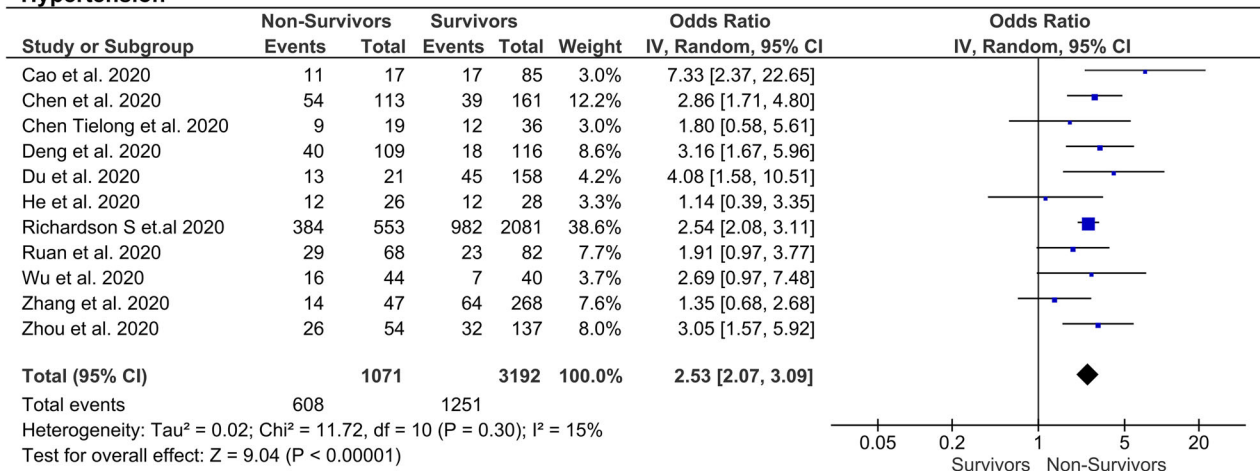
Our systematic review and meta-analysis of 14 published articles involving 4659 patients is the first to provide a comprehensive analysis of the demographic features, comorbidities, and laboratory abnormalities that are associated with mortality in COVID-19. Across all studies included in the meta-analysis, a quarter of hospitalized patients died, which is higher than previously reported.<sup>5</sup> The majority of patients across both groups were male, which supports previous studies.<sup>3,5,6</sup> However, we report for the first time that a higher proportion of admitted men died than did admitted women.

Consistent with other meta-analyses, hypertension was a common underlying condition amongst all patients across the collected studies (39.9%), and the prevalence was substantially higher (56.8%) in the nonsurvival group.<sup>3,5,6</sup> We observed that hypertension confers a greater than 2.5-fold increase in the odds of death from COVID-19, supporting previous studies.<sup>8,12</sup> The second most prevalent comorbidity we assessed was diabetes, which was observed in approximately a quarter of all patients. Diabetes was associated with a two-fold higher odds of death from COVID-19, which is consistent with previous meta-analyses.<sup>9,10</sup> Here, we found ~12% of hospitalized patients have underlying CHD/cardiovascular disease, which was also associated with a 3.8-fold increase in the odds of death.

The prevailing data seems to suggest patients with underlying cardiovascular disease are more prone to severe outcomes of COVID-19,

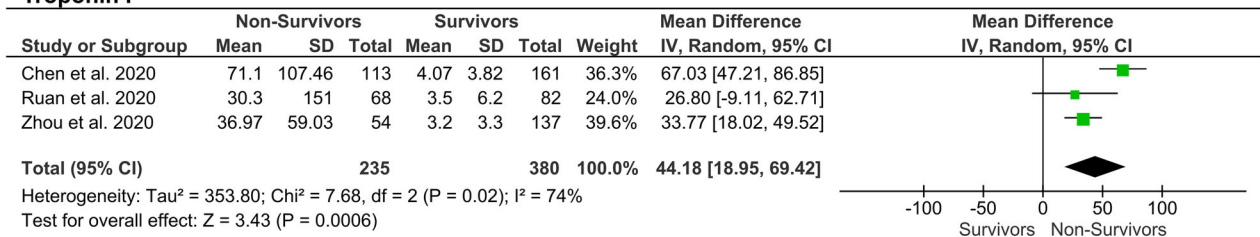
(A)

**Hypertension**



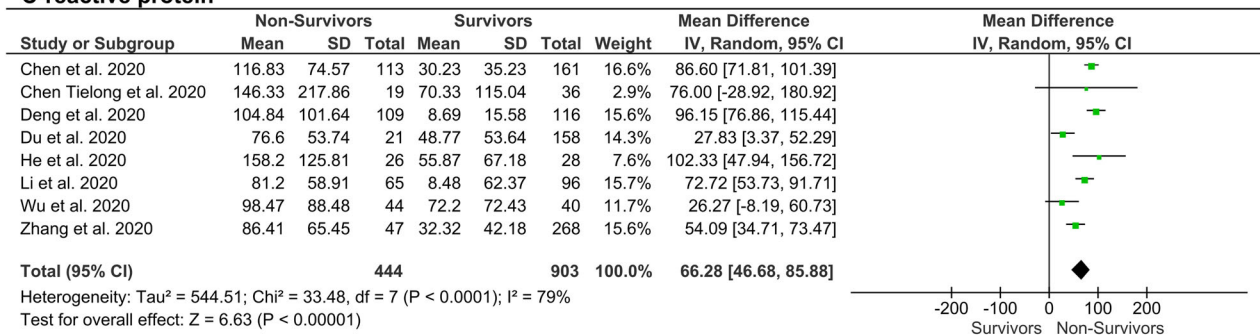
(B)

**Troponin I**



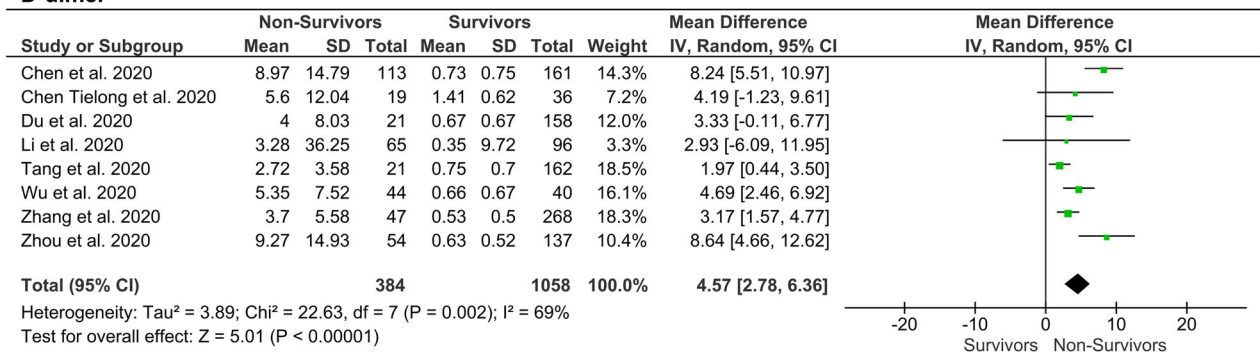
(C)

**C-reactive protein**



(D)

**D-dimer**



**FIGURE 2** Key factors associated with an increased risk of COVID-19 mortality. Forest plots demonstrating the association between COVID-19 mortality and the presence of hypertension (A), and levels of troponin I (B), C-reactive protein (C), and D-dimer (D). Sizes of data markers indicate weight of studies. CI, confidence intervals; COVID-19, coronavirus disease-2019; df, degrees of freedom; IV, inverse variance

including death, as we found in our meta-analyses.<sup>1,5,6,8,16,39-45</sup> The mechanisms underlying the association between cardiovascular disease and COVID-19 remain to be determined but might be due to infection-related demand ischemia that devolves into myocardial injury or myocardial dysfunction and/or a viral-induced inflammatory storm causing shock and ensuing ischemic-related injury. In addition, a previous case report found evidence for direct viral infection of the myocardium.<sup>46</sup> Our meta-analysis found evidence that both myocardial injury and increased inflammation were more prevalent in the nonsurvival group. We and others have shown that higher levels of troponin I are found in nonsurvivors compared with survivors of COVID-19.<sup>15,16,43,45</sup> Furthermore, we found that increased levels of inflammatory markers, such as CRP, IL-6, and ESR, were also observed in the nonsurvival group.

In the current study, levels of BUN, creatinine, albumin, total bilirubin, ALT, and AST were indicative of abnormal kidney and liver function at the time of admission in nonsurvivors compared with survivors. Mortality was also associated with lower platelet count and elevated D-dimer levels, suggesting a possible coagulopathy in these patients. Moreover, we observed that patients in the nonsurvival group were more likely to have a higher WBC count and lower lymphocyte and CD4<sup>+</sup>/CD8<sup>+</sup> T cell counts. Taken together, these findings suggest that initial laboratory assessment is important for risk stratification of patients with COVID-19 and that those demonstrating markers of end-organ dysfunction, inflammation, or coagulopathy are at increased risk of a poor outcome.

Whether the virus alters biomarker levels directly, or that abnormal baseline levels predispose a higher individual risk for mortality to COVID-19, is not currently understood. Various infections, including those caused by the severe acute respiratory syndrome (SARS) family of viruses, cause endothelial dysfunction, which is characterized by a diminished ability to produce nitric oxide and the release of inflammatory markers, such as CRP, ICAM-1 and VCAM-1.<sup>47,48</sup> The unique marked affinity of coronaviruses to the host angiotensin-converting enzyme 2 receptor, which is expressed in endothelial cells of blood vessels, means a direct effect of SARS-coronavirus 2 (SARS-CoV-2) on the vascular endothelium is distinctly possible.<sup>39,43,45,49-51</sup> Endothelial dysfunction manifested by reduced nitric oxide bioavailability is thought to be an early event in hypertension, diabetes, CHD, and even kidney dysfunction, which were shown here to be significantly associated with mortality in patients with COVID-19.<sup>52-56</sup> Interestingly, nitric oxide donors inhibit SARS-CoV infection of cells and improve cell survival.<sup>57</sup> It is possible, therefore, that underlying endothelial dysfunction, which is further exacerbated by COVID-19 infection, promotes a sequela leading to adverse clinical events and death. Further studies will need to be conducted to investigate the specific role of endothelial dysfunction and nitric oxide in COVID-19 infection.

#### 4.1 | Limitations

The studies included in this meta-analysis were not randomized controlled trials, but retrospective studies, which are the only

studies available during this pandemic. Furthermore, as with all meta-analyses, the limitations are mainly the availability of data, possible underlying heterogeneity of data, and the potential for publication bias. This was particularly apparent in analyzing some of the comorbidities (eg, COPD and cerebrovascular disease) and laboratory abnormalities, which were not uniformly assessed across all 14 studies. In general, few studies that report associations with death in COVID-19 are available at this time. Since all but one of our included studies were from China, the overall generalizability of the meta-analysis results must be interpreted with caution. Additional data from other geographical areas will be required to have a more complete picture of the predictors of mortality in COVID-19. The current understanding of COVID-19 epidemiology will be enhanced when clinical data from nations across the globe are available. Furthermore, because of the lack of access to individual patient data, we were unable to perform multivariable regression analyses to adjust for potential confounders in the nonsurvival vs survival groups (eg, age).

## 5 | CONCLUSIONS

In this meta-analysis, we found that baseline cardiometabolic disease and evidence of increased acute inflammation and end-organ damage (cardiac, renal, liver, and hematologic) on admission were associated with increased risk of mortality due to COVID-19 infection. This information adds important pieces of clinical knowledge to the armamentarium that physicians need to manage patients with COVID-19 and may help to inform discussions between patients and caregivers about risk stratification, management strategies, and allocation of health care resources and personnel during the COVID-19 pandemic.

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#### CONFLICT OF INTERESTS

The authors confirm that there are no financial conflicts of interest.

#### AUTHOR CONTRIBUTIONS

WT, WJ, and RM conceived, designed, and planned the study. WT, WJ, RHL, and RM performed the literature search, screened the manuscripts, extracted the data, and performed some data analyses. JY, JIR, and XG performed the meta-analysis. HHS and LW performed data analysis. CJN and RM drafted the manuscript and interpreted the data. All authors interpreted the data and made significant contributions to manuscript editing.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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