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RESEARCH ARTICLE

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Association between markers of immune response at hospital admission and COVID-19 disease severity and mortality: A meta-analysis and meta-regression

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Abstract

Background: To determine the utility of admission laboratory markers in the assessment and prognostication of coronavirus disease-2019 (COVID-19), a systematic review and meta-analysis were conducted on the association between admission laboratory values in hospitalized COVID-19 patients and subsequent disease severity and mortality.

Material and Methods: Searches were conducted in MEDLINE, Pubmed, Embase, and the WHO Global Research Database from December 1,2019 to May 1, 2020 for relevant articles. A random effects meta-analysis was used to calculate the weighted mean difference (WMD) and 95% confidence interval (95% CI) for each of 27 laboratory markers. The impact of age and sex on WMDs was estimated using meta-regression techniques for 11 markers.

Results: In total, 64 studies met the inclusion criteria. The most marked WMDs were for neutrophils (ANC) at 3.82×10^9/L (2.76, 4.87), lymphocytes (ALC) at -0.34×10^9/L (−0.45, −0.23), interleukin-6 (IL-6) at 32.59 pg/mL (23.99, 41.19), ferritin at 814.14 ng/mL (551.48, 1076.81), C-reactive protein (CRP) at 66.11 mg/L (52.16, 80.06), D-dimer at 5.74 mg/L (3.91, 7.58), LDH at 232.41 U/L (178.31, 286.52), and high sensitivity troponin I at 90.47 pg/mL (47.79, 133.14) when comparing fatal to nonfatal cases. Similar trends were observed comparing severe to non-severe groups. There were no statistically significant associations between age or sex and WMD for any of the markers included in the meta-regression.

Conclusion: The results highlight that hyper inflammation, blunted adaptive immune response, and intravascular coagulation play key roles in the pathogenesis of COVID-19. Markers of these processes are good candidates to identify patients for early intervention and, importantly, are likely reliable regardless of age or sex in adult patients.

KEYWORDS

COVID-19, laboratory values, meta-analysis, meta-regression, systematic review

1 | INTRODUCTION

The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), known as coronavirus disease-2019 (COVID-19), is primarily a respiratory condition that can range from being asymptomatic to causing respiratory failure and other potentially fatal complications.[1] Approximately 20% of cases develop severe dyspnea due to an often-bilateral viral pneumonia that

requires hospitalization.[2] The virus has caused a global pandemic with growing case numbers, but early studies of seroprevalence estimate that the proportion of infected individuals does not exceed 20% even in regions with large case burdens, leaving most of the population susceptible.[3-5] As such, hospitals across the world remain at risk of spikes in patient load that may stretch or exceed their capacity, thereby contributing to worsening COVID-19 morbidity and mortality.

As has been demonstrated with other health conditions, clinical tools incorporating laboratory parameters have been invaluable to the efficient use of health care resources, and improvement of patient outcomes.[6] Such tools are often based on an understanding of disease pathophysiology, and in the case of COVID-19, cytokine storm syndrome and thromboinflammation have surfaced as central and interconnected factors in the development of severe and fatal illness.[7-9] These disease processes can be monitored using various biochemical and hematologic markers that are routinely measured at the time of hospitalization, potentially contributing to the accurate prediction of severity and mortality among patients hospitalized for COVID-19 and allowing for early intervention.[10,11] However, the development of useful predictive tools incorporating laboratory parameters will require studies with large sample sizes covering broad population groups to be accurate and generalizable. Usually, individual studies are small and hence meta-analyses could provide critical evidence needed for clinical and policy decisions.

To date, meta-analyses assessing the impact of COVID-19 on laboratory markers have suffered from various methodological and reporting issues, including a lack of consideration for potentially overlapping datasets, incorrect estimation of study means and error, and not including data on mortality.[10,11] In addition, given the importance of age and sex as predictors of disease severity, the contribution of these factors to any associations between laboratory parameters and COVID-19 severity has not received adequate attention.[2,10,11] To resolve these limitations, we first conducted a systematic review and meta-analysis on the association between admission laboratory values and disease severity and mortality in patients hospitalized for COVID-19. We then assessed the contributions of age and sex to the observed associations using meta-regression techniques.

2 | METHODS

2.1 | Search strategy

A broad initial search was conducted on March 17, 2020 in PubMed, Ovid Embase, and Ovid Medline, limited to publications from 2019 onwards. In addition, the WHO Global Research Database[12] was manually searched up to March 17, 2020 for relevant publications. Shortly after, a search strategy was created by Wolters Kluwer,[13] which was used to supplement the search in Medline.

An updated search was run on May 1, 2020 to capture additional publications entered into PubMed and Embase since March 16, 2020. The PubMed strategy included the new MeSH supplementary concepts, "severe acute respiratory syndrome coronavirus 2" and "COVID-19." We combined the COVID-19 PubMed strategy provided by the Stephen B. Thacker CDC Library[14] with the newly released Embase strategy by Wolters Kluwer[15] and translated them for the appropriate databases. To expand the search while maintaining relevance to the topic, we searched keywords in multipurpose or.mp fields. Conference abstracts were excluded from Embase, and additional limiters, including English language and entry dates, were applied in both databases. The search strategies are presented in Supplement 1. Backward chaining was employed to identify potentially relevant references in the included studies and published reviews.

2.2 | Screening and data extraction

Articles were imported to Covidence, a systematic review manager.[16] The majority of duplicate records were automatically excluded at the article importing stage. Two reviewers (JK and MD) independently screened the titles, abstracts, and full texts based on eligibility criteria. Studies were eligible for inclusion if they provided hospital-based data and reported summary values (eg, mean) with precision estimates (eg, standard deviation (SD)). Studies were excluded at full-text assessment stage if they were not relevant to the review topic, were exact duplicates, were not in the English language, did not report results by disease severity or mortality (wrong outcomes), were not original research articles (wrong study design), were not available in full-text, or were focused on ineligible patient populations (eg pregnant women and children).

Reviewers extracted data on study characteristics (ie, authors, date of publication, study location, sample size, and study design), characteristics of the participants (ie, mean age and sex), disease status (ie, severe vs non-severe, deceased vs survived), laboratory markers at admission (ie, mean and SD, median and interquartile range (IQR), or range of minimum and maximum observations), and inclusion and exclusion criteria.

2.3 | Disease status and laboratory markers

Across all studies, COVID-19 cases were diagnosed based on clinical suspicion and all cases were ultimately confirmed via reverse transcription-polymerase chain reaction (RT-PCR). Disease status was evaluated as COVID-19-related disease severity and mortality, which were compared to non-severe and surviving categories, respectively. COVID-19 severity was classified using various criteria across studies. Most studies used the Chinese National Commission of Health Guidelines, which provide the following categories for COVID-19 severity[17]: (a) Mild—May include fever, respiratory symptoms, and signs of pneumonia on radiological imaging; (b) Severe—Respiratory distress with the respiratory rate (RR) ≥ 30, oxygen (O_2) saturation ≤ 93% at rest on room air, or P_aO_2/FiO_2 ≤ 300 mm Hg; (c) Critical – Respiratory failure, the

requirement for mechanical ventilation, shock, or ICU admission. Some studies used the American Thoracic Society (ATS) Guidelines for Community-Acquired Pneumonia (CAP) which define severe pneumonia as either the development of septic shock with vasopressor requirement, respiratory failure requiring mechanical ventilation, or at least three of the following: RR > 30, P_aO_2/FiO_2 < 250 mm Hg, multilobar infiltrates, confusion, uremia (BUN ≥ 20 mg/dL), leukopenia ($<4.0 \times 10^9$ cells/L), thrombocytopenia ($<100 \times 10^9$ cells/L), hypothermia (core temperature < 36 C), and hypotension requiring aggressive fluid resuscitation.[18] Other studies defined severity based on one of the following: admission to Intensive Care Unit (ICU), development of acute respiratory distress syndrome (ARDS), oxygen saturation at rest, the requirement of invasive mechanical ventilation (IMV), development of acute cardiac injury, or custom composite endpoints. A table reflecting the major classification schemes is presented in Supplement 2.

The following laboratory markers were considered in this study: Hemoglobin (Hb), white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), platelet count (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, interleukin-6 (IL-6), interleukin-10 (IL-10), procalcitonin (PCT), albumin, total bilirubin, prothrombin time (PT), creatinine (Cr), blood urea nitrogen (BUN), activated partial thromboplastin time (APTT), Ddimer, lactate dehydrogenase (LDH), creatine kinase (CK), high sensitivity troponin I (hsTropI), troponin I (TropI), creatine kinase myocardial band (CKMB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transferase (GGT).

2.4 | Risk of bias

This systematic review and meta-analysis follow the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[19] The quality of included studies was assessed by using the Institute of Health Economics (IHE) quality appraisal of the case series studies checklist.[20] Although the checklist includes twenty critical appraisal items for quality assessment, only fifteen criteria were relevant to those included in this review, of which both reviewers agreed that seven were especially important to the risk of bias. These seven items were: Consecutive recruitment, reporting of patient characteristics, clear eligibility criteria, similar disease point at study entry, appropriate outcome measurement, sufficient follow-up, and estimates of random variability.[20] Based on reviewers' judgment, the risk of bias was categorized as low, medium, or high, if 0, 1, or ≥ 2 checklist items were marked as no or unclear, respectively.

2.5 | Risk of duplicate data

To determine the potential of duplicate data from the studies selected for inclusion, we compared studies based on their research teams (eg, authors list), study location (ie, city and hospital), and reported study period. If two or more studies shared study sites and had overlapping study periods, one study was designated as a reference study and assigned a low duplicate risk and the others were considered a high duplicate risk. Reference studies were selected based on the length of the study period, the number of patients in the sample, and number of laboratory markers reported and had to be agreed upon by both reviewers. Furthermore, the risk of duplication was separately considered for each laboratory marker in those studies considered to be at high risk of duplicate reporting. Within a high duplicate risk study, laboratory markers not reported in the associated reference study were considered as low risk of duplication.

2.6 | Statistical analyses

Reported means and SDs for laboratory parameters in each included study were used to estimate weighted mean differences (WMD) and 95% confidence intervals (95% CI) for severe versus non-severe and deceased versus surviving patients. In the absence of mean and SD values, sample sizes, medians, and measures of precision (ie IQR or range) were used to calculate mean and SD (Supplement 3 and 4).[21] These data were then pooled to provide overall WMDs and their 95% CIs using the DerSimonian and Laird random-effects model.[22] To quantify heterogeneity, the I^2 (%) statistic was calculated as a measure of inconsistency.[23] I^2 thresholds of 25%, 50%, and 75%, indicated low, medium, and high levels of heterogeneity, respectively.[23]

To assess the potential impact of duplicate data, as a sensitivity analysis, we excluded studies categorized as high risk of duplication. Additional sensitivity analyses were performed by excluding studies with a high risk of bias and studies with confidence intervals not overlapping with the 95% CIs of the pooled estimates (ie, "outlier studies").[11]

To account for Type I error rate for multiple hypothesis testing (ie, 27 and 23 laboratory markers for disease severity and mortality, respectively), Bonferroni correction was used to declare the significance levels of P values.[24] The Bonferroni corrected P value for the disease severity tests including overall estimates, sensitivity analysis by the risk of duplicates, and sensitivity analysis by the risk of bias was .002 (ie, corrected $P = .05/27$) and for sensitivity analysis of outliers, where only 15 laboratory markers were tested, was .003 (ie, corrected $P = .05/15$). The Bonferroni corrected p-value for the mortality analyses including overall estimates, sensitivity analysis by the risk of duplicates, and sensitivity analysis by the risk of bias was .002 (ie, corrected $P = .05/23$), and for sensitivity analysis of outliers, where only 8 laboratory markers were tested, was .006 (ie, corrected $P = .05/8$).

Finally, to assess the potential impact of age and sex on WMD variation when comparing severe to non-severe or fatal to nonfatal cases, univariate random-effects meta-regression, using the method of moments, was conducted on 11 laboratory markers, including ALC, ANC, WBC, Ddimer, PT, ferritin, IL-6, IL-10, CRP, ESR, and albumin. These markers were selected because they reflect the key pathogenetic mechanisms involved and may vary by age and sex. We calculated tests

for covariates using a minimum of 10 000 Monte Carlo random permutations.[25] All statistical analyses were performed using STATA software (version 16.1; StataCorp, College Station, TX).[26]

3 | RESULTS

In total 15 314 studies were identified through systematic search and backward chaining (Figure 1). Following the removal of duplicates and title/abstract screening, 527 studies remained for full-text review. 64 studies remained for data extraction and analysis after excluding ineligible studies for the following reasons: irrelevant to study objectives (N = 292), wrong study outcomes (N = 68), ineligible study design (N = 30), wrong patient population (N = 28), not available in full-text (N = 23), duplicate of included study (N = 13), and not in English (N = 9). All included studies were case series.

The key characteristics of included studies are presented in Table 1. Forty-nine studies reported severity outcomes,[27-75] fourteen reported mortality outcomes[27-29,76-86] and one reported both mortality and severity.[87] COVID-19 severity was classified using Chinese National Commission of Health Guidelines in 31 studies, American Thoracic Society Guidelines for Community-Acquired Pneumonia in three studies, oxygen saturation at rest in two studies, ICU admission in seven studies, ARDS in one study, cardiac injury in one study, IMV in two studies, and custom composite endpoints in three studies.

The 50 severity studies contributed a total of 11 173 patients, of which 7845 were from at least 522 hospitals across China, 85 were from at least 4 hospitals in Singapore, 3315 were from at least 7 hospitals in the United States, and 40 were from one hospital in Germany. The 15 mortality studies contributed a total of 2525 patients from 6 hospitals in Wuhan, Hubei, China. Blood samples were collected within 2 days of hospital admission in all but two studies.[48,81] 15 severity studies[34,40,45,47-50,58-60,64,66,67,88,89] and two mortality studies[29,83] reported median time from symptom onset to hospital admission, which ranged from 3.5[40] to 12[83] days. There were significant differences in time to admission for three severity studies[48,58,89] and one mortality study (Table 1).[29]

3.1 | Meta-analysis of laboratory tests and severity

A summary of meta-analysis results for severity is presented in Table 2. In total, 27 laboratory markers were analyzed for associations with disease severity. Only Hb, PLT, Cr, APTT, TropI, CKMB, ALP, and GGT did not achieve statistical significance. Among markers involved in a complete blood count (CBC), the WMDs of WBC and ANC in patients with severe vs those with the non-severe disease were 1.23×10^9

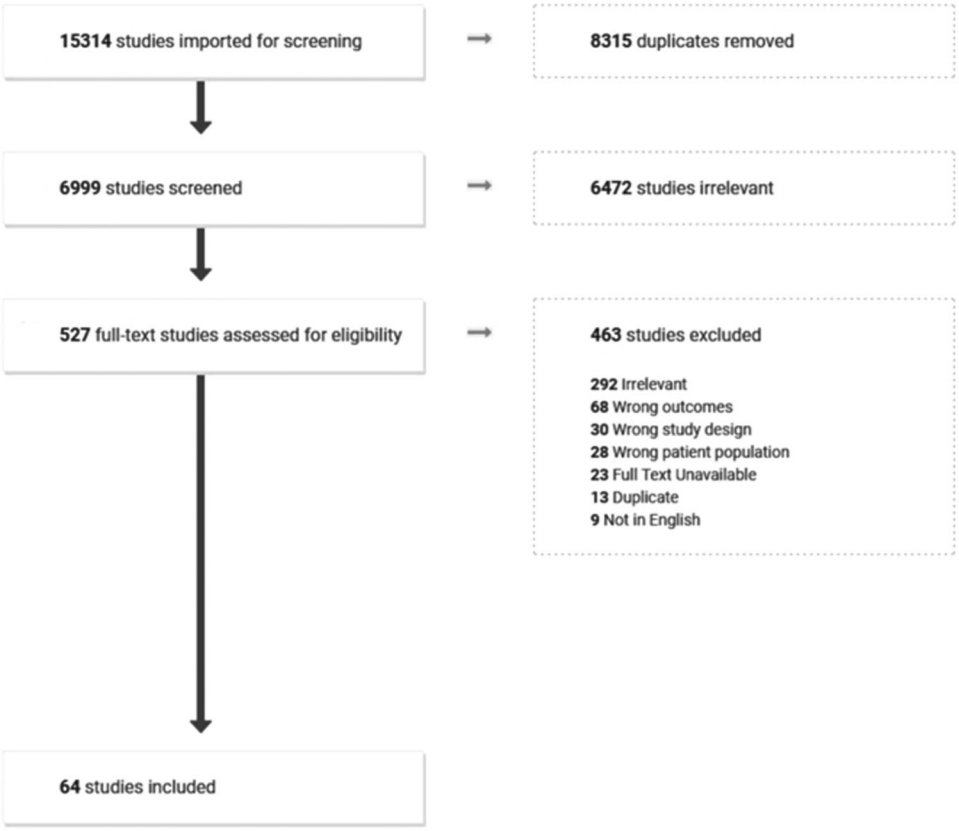

FIGURE 1 PRISMA flow diagram outlining study selection

TABLE 1 Main characteristics of included studies

Study (ID)	Outcomes	Study characteristics	Patient characteristics	Risk of bias	Duplicate risk
Xu et al (54)[76]	ALC, ALT, ANC, AST, BUN, CK, Cr, CRP, Ddimer, IL-6, IL-10, PCT, PT, WBC	Setting: Hubei Provincial Hospital of Chinese and Western Medicine, Wuhan, China Study period: Dec 26-Mar 1 Follow-up: Unclear Sample size: 145 Exposure: Mortality	Survivors: 117 Male, n: 59 Age, y: 72.75 ± 7.26 Deceased: 28 Male, n: 17 Age, y: 55 ± 17.25	Low	Low
Zhou et al (13)[77]	Alb, ALC, ALT, Ddimer, Ferr, Hb, IL-6, LDH, PLT, PCT, PT, hsTropI, WBC	Setting: Jin Yintan Hospital, Wuhan Pulmonary Hospital, Wuhan, China Study period: Dec 29-Jan 31 Follow-up: Jan 31 (complete) Sample size: 191 Exposure: Mortality (death or discharge by study end)	Survivors: 137 Male, n: 81 Age, y: 51.7 ± 9.7 Deceased: 54 Male, n: 38 Age, y: 69.3 ± 9.9	Low	Low (reference study)
Yang et al (15)[78]	ALC, Bili, Cr, Hb, PLT	Setting: Jin Yintan Hospital, Wuhan, China Study period: Dec 24-Jan 26 Follow-up: Feb 9 (28 d for mortality) Sample size: 52 Exposure: Mortality (28-d mortality)	Survivors: 20 Male, n: 14 Age, y: 51.9 ± 12.9 Deceased: 32 Male, n: 21 Age, y: 64.6 ± 11.2	Low	High Reasons: Setting and period shared with Zhou (13), Wu (6)
Ruan et al (11)[79]	Alb, ALC, ALT, AST, Bili, Cr, CRP, Ferritin, Hb, IL-6, LDH, PLT, hsTropI, WBC	Setting: Jin Yintan Hospital, Tongji Hospital, Wuhan, China Study period: Unclear (before Mar 3) Follow-up: Unclear Sample size: 150 Exposure: Mortality	Survivors: 82 Male, n: 53 Age, y: 58.33 ± 27.9 Deceased: 68 Male, n: 49 Age, y: 54.33 ± 50	High	HighReasons: Setting – Zhou (13), Wu (6), Yang (15) Study period – Unclear
Wu et al (6)[87]	Alb, ALC, ALT, ANC, AST, Bili, BUN, Cr, CRP, Ddimer, ESR, Ferritin, IL-6, LDH, PLT, PT, WBC	Setting: Jin Yintan Hospital, Wuhan, China Study period: Dec 25-Jan 26 Follow-up: Feb 13 (incomplete) Sample size: 84 Exposure: Mortality (Acute Respiratory Distress Syndrome (ARDS) patients only)	Survivors: 40 Male, n: 31 Age, y: 49.03 ± 12.7 Deceased: 44 Male, n: 29 Age, y: 67.6 ± 12.1	Low	High Reasons: Setting and period shared with Zhou (13), Yang (15)
Zhang et al (59)[80]	Alb, CRP, Ddimer	Setting: Liyuan Hospital, Wuhan, China Study period: Jan 16-20 Feb Follow-up: Unclear Sample size: 19 Exposure: Mortality (ICU patients only)	Survivors: 11 Male, n: 6 Age, y: 64.33 ± 42.8 Deceased: 8 Male, n: 5 Age, y: 78 ± 25.3	Med	Low
Wang et al (47)[81]	ALC, ALT, ANC, APTT, AST, BUN, CK, Cr, CRP, Ddimer, Hb, IL-6, LDH, PLT, PCT, PT, hsTropI, WBC	Setting: Renmin Hospital, Wuhan, China Study period: Jan 1-Feb 6 Follow-up: 5 Mar (complete) Sample size: 339 Exposure: Mortality (Patients over 60 only)	Survivors: 274 Male, n: 127 Age, y: 68.67 ± 7.6 Deceased: 65 Male, n: 39 Age, y: 76.33 ± 9.6	Low	Low
Wang et al (49)[82]	Alb, ALC, ALT, ANC, AST, Bili, BUN, CK, Cr, CRP, Ddimer, IL-6, IL-10,	Setting: Tongji Hospital, Wuhan, China Study period: Jan 25-Feb 25 Follow-up: Mar 24 (complete)	Survivors: 211 Male, n: 105 Age, y: 57.7 ± 16.3	Low	Low (reference study)

TABLE 1 (Continued)

Study (ID)	Outcomes	Study characteristics	Patient characteristics	Risk of bias	Duplicate risk
	LDH, PLT, PCT, PT, hsTropI, WBC	Sample size: 344 Exposure: Mortality (ICU patients only)	Deceased: 133 Male, n: 74 Age, y: 69.7 ± 11.2		
Chen et al (24)[83]	Alb, ALC, ALT, ANC, APTT, AST, Bili, BUN, CK, Cr, CRP, Ddimer, ESR, Ferritin, Hb, IL-6, IL-10, LDH, PLT, PCT, PT, hsTropI, WBC	Setting: Tongji Hospital, Wuhan, China Study period: Jan 13-Feb 12 Follow-up: Feb 18 (complete) Sample size: 339 Exposure: Mortality	Survivors: 161 Male, n: 88 Age, y: 51.33 ± 21.7 Deceased: 113 Male, n: 83 Age, y: 69 ± 11.3	Low	High Reasons: Setting and period shared with Wang (49)
Tang et al (12)[84]	Ddimer, PT	Setting: Tongji Hospital, Wuhan, China Study period: Jan 1-Feb 3 Follow-up: Feb 13 (incomplete) Sample size: 183 Exposure: Mortality	Survivors: 162 Male, n: 82 Age, y: 52.4 ± 15.6 Deceased: 21 Male, n: 16 Age, y: 64 ± 20.7	Med	High Reasons: Setting and period shared with Tang (43), Fibrinogen OK
Tang et al (43)[85]	Ddimer, PLT, PT	Setting: Tongji Hospital, Wuhan, China Study period: Jan 1-Feb 13 Follow-up: Mar 13 (complete) Sample size: 449 Exposure: Mortality (Severely ill patients only)	Survivors: 315 Male, n: 178 Age, y: 63.7 ± 12.2 Deceased: 134 Male, n: 90 Age, y: 68.7 ± 11.4	Low	Low
Yan et al (55)[86]	Alb, ALC, ALT, ANC, APTT, AST, Bili, BUN, CK, Cr, CRP, Ddimer, ESR, Ferritin, Hb, IL-6, LDH, PLT, PCT, PT, hsTropI, WBC	Setting: Tongji Hospital, Wuhan, China Study period: Jan 10-Feb 24 Follow-up: Unclear Sample size: 48 Exposure: Mortality (Diabetic patients only)	Survivors: 9 Male, n: 3 Age, y: 64.7 ± 7.3 Deceased: 39 Male, n: 30 Age, y: 70.5 ± 10.1	Med	High Reasons: Setting and period shared with Wang (49), Ferritin, Hemoglobin, Thromboplastin time OK
Du et al (27)[27]	Alb, ALC, ALT, ANC, APTT, AST, Bili, Cr, CRP, Ddimer, PCT, PT, WBC	Setting: Wuhan Pulmonary Hospital, Wuhan, China Study period: Dec 25-Feb 7 Follow-up: Complete Sample size: 179 Exposure: Mortality	Survivors: 158 Male, n: 87 Age, y: 56 ± 13.5 Deceased: 21 Male, n: 10 Age, y: 70.2 ± 7.7	Low	Low (reference study)
Gao et al (14)[28]	ALC, ALT, AST, Bili, Cr, Ddimer, Hb, PLT, PCT, PT, hsTropI, WBC	Setting: Wuhan Pulmonary Hospital, Wuhan, China Study period: Jan 1-Jan 29 Follow-up: Feb 9 (incomplete) Sample size: 15 Exposure: Mortality	Survivors: 8 Male, n: 6 Age, y: 56.3 ± 10 Deceased: 7 Male, n: 4 Age, y: 68 ± 3.3	Med	High Reasons: Setting and period shared with Du (27)

(Continues)

TABLE 1 (Continued)

Study (ID)	Outcomes	Study characteristics	Patient characteristics	Risk of bias	Duplicate risk
Chen et al (23)[29]	Alb, ALC, ALT, ANC, AST, CK, Cr, CRP, Ddimer, ESR, IL-6, LDH, PLT, PCT, WBC	Setting: Zhongnan Hospital, Wuhan, China Study period: Jan 1- Feb 10 Follow-up: Feb 20 (incomplete) Sample size: 55 Exposure: Mortality (Patients over 65 only)	Survivors: 36 Male, n: 18 Age, y: 72 ± ? Deceased: 19 Male, n: 16 Age, y: 77 ± ?	High	Low
Myers et al (37)[30]	ALC, ALT, ANC, AST, Bili, Cr, LDH, WBC	Setting: Multicenter, Northern California, USA Study period: Mar 1-Mar 31 Follow-up: Apr 9 (incomplete) Sample size: 277 Exposure: Severity (ICU or non-ICU)	Non-severe: 264 Male, n: 138 Age, y: 60.33 ± 17.04 Severe: 113 Male, n: 74 Age, y: 63 ± 15.02	Med	Low
Lu et al (35)[31]	BUN, Cr	Setting: Multicenter, 42 hospitals in Hubei, Sichuan, and Chongqing, China Study period: Jan 13-Feb 18 Follow-up: Complete Sample size: 304 Exposure: Severity (severe or mild, Chinese classification)	Non-severe: 196 Male, n: 116 Age, y: 39.7 ± 13.4 Severe: 108 Male, n: 66 Age, y: 60.6 ± 19.7	Low	High Reasons: Multicenter study across 3 provinces in China
Guan et al (5)[32]	ALC, Hb, PLT, WBC	Setting: Multicenter, 522 hospitals in China Study period: Dec 11-Jan 29 Follow-up: Jan 31 (incomplete) Sample size: 1099 Exposure: Severity (ICU/IMV/Death or not)	Non-severe: 1032 Male, n: 595 Age, y: 46 ± 16.3 Severe: 67 Male, n: 45 Age, y: 62.3 ± 13.6	High	High Reasons: Multicenter study across many hospitals in China
Zheng et al (63)[33]	ALC, ALT, ANC, AST, CRP, Ddimer, PT, WBC	Setting: Chengdu Public Health Clinical Medical Center, Chengdu, China Study period: Jan 11-Feb 20 Follow-up: Feb 23 (incomplete) Sample size: 99 Exposure: Severity (Critical or noncritical, Chinese classification)	Non-severe: 67 Male, n: 32 Age, y: 42.5 ± 15.1 Severe: 32 Male, n: 19 Age, y: 63.8 ± 16.5	Med	Low
Yao et al (57)[34]	Alb, ALC, ALT, ANC, Cr, CRP, Ddimer, Hb, PCT, WBC	Setting: Dabieshan Medical Center, Huanggang City, China Study period: Jan 30-Feb 11 Follow-up: Mar 3 (complete) Sample size: 108 Exposure: Severity (Severe or non-severe, ATS classification)	Non-severe: 83 Male, n: 30 Age, y: 46.7 ± 16.6 Severe: 25 Male, n: 13 Age, y: 60 ± 16.5	Low	Low
Liu et al (34)[35]	ALC, APTT, CK, CKMB, Ddimer, IL-6, IL-10, LDH, PT	Setting: First Affiliated Hospital of Nanchang University, China Study period: Jan 22-Feb 15 Follow-up: Unclear Sample size: 76 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 30 Male, n: NR Age, y: NR Severe: 46 Male, n: NR Age, y: NR	High	Low

TABLE 1 (Continued)

Study (ID)	Outcomes	Study characteristics	Patient characteristics	Risk of bias	Duplicate risk
Wu et al (52)[36]	Alb, ALC, ALT, ANC, APTT, AST, Bili, BUN, CK, CKMB, Cr, CRP, Ddimer, ESR, Hb, LDH, PLT, PCT, PT, WBC	Setting: First People's Hospital of Yancheng City, Second People's Hospital of Yancheng City, Second People's Hospital of Fuyang City, Fifth People's Hospital of Wuxi, China Study period: Jan 20-Feb 19 Follow-up: Feb 19 (incomplete) Sample size: 280 Exposure: Severity (Critical/severe or mild, Chinese classification)	Non-severe: 197 Male, n: 106 Age, y: 37.6 ± 17.1 Severe: 83 Male, n: 45 Age, y: 63 ± 10.2	High	Low
Qian et al (39)[37]	Alb, ALC, ALT, ANC, AST, BUN, Cr, CRP, Ddimer, Hb, PLT, PCT, WBC	Setting: Five hospitals in Zheijang, China Study period: Jan 20-Feb 11 Follow-up: Feb 16 (incomplete) Sample size: 91 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 82 Male, n: NR Age, y: 46.8 ± 15.6 Severe: 9 Male, n: NR Age, y: 66.7 ± 22.7	High	Low (reference study)
Sun et al (42)[38]	ALC, ANC, Hb, PLT, WBC	Setting: Hospitals in Wenzhou, Zheijang, China Study period: Jan 19-Feb 20 Follow-up: Unclear Sample size: 116 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 89 Male, n: 42 Age, y: 57.7 ± 11.5 Severe: 18 Male, n: 66 Age, y: 69.2 ± 10.2	Med	High Reasons: Setting and period shared with Qian (39)
Gao et al (30)[39]	ALC, ALT, ANC, APTT, AST, BUN, Cr, CRP, Ddimer, IL-6, PCT, PT, WBC	Setting: Second People's Hospital of Fuyang, China Study period: Jan 23-Feb 2 Follow-up: Unclear Sample size: 43 Exposure: Severity (ARDS/ICU or not)	Non-severe: 28 Male, n: 17 Age, y: 43 ± 14 Severe: 15 Male, n: 9 Age, y: 45.2 ± 7.7	High	High Reasons: Setting and period shared with Wu (52), Interleukin-6 OK
Wang et al (48)[40]	ALC, ALT, ANC, AST, Bili, BUN, Cr, CRP, Hb, IL-6, PLT, PCT, WBC	Setting: Second People's Hospital of Fuyang, China Study period: Jan 20-Feb 9 Follow-up: Feb 18 (incomplete) Sample size: 125 Exposure: Severity (Critical or noncritical, Chinese classification)	Non-severe: 100 Male, n: 55 Age, y: 39.5 ± 14.8 Severe: 16 Male, n: 19 Age, y: 49.4 ± 13.6	Med	High Reasons: Setting and period shared with Wu (52), Gao (30)
Fan et al (2)[41]	ALC, ANC, Hb, LDH, PLT, WBC	Setting: National Center for Infectious Diseases, Singapore Study period: Jan 23-Feb 28 Follow-up: Unclear (incomplete) Sample size: 67 Exposure: Severity (ICU or non-ICU)	Non-severe: 58 Male, n: 31 Age, y: 42 ± 16 Severe: 9 Male, n: 6 Age, y: 54.3 ± 13.1	Med	Low (reference study)
Young et al (9)[42]	ALC, ANC, CRP, Hb, LDH, PLT, WBC	Setting: Four hospitals in Singapore Study period: Jan 23-Feb 3 Follow-up: Unclear (incomplete) Sample size: 18	Non-severe: 12 Male, n: 7 Age, y: 41.3 ± 21.9 Severe: 2	Low	High Reasons: Setting and period shared with Fan (2)

(Continues)

TABLE 1 (Continued)

Study (ID)	Outcomes	Study characteristics	Patient characteristics	Risk of bias	Duplicate risk
		Exposure: Severity (O_2 saturation < 92% on room air or not)	Male, n: 6 Age, y: 55.3 ± 16.1		
Zhou et al (65)[43]	Alb, ALC, ALP, ALT, ANC, APTT, AST, Bili, BUN, Cr, CRP, Ddimer, GGT, Hb, IL-6, PLT, PCT, PT, WBC	Setting: Huangshi Central Hospital, Huangshi, Hubei, China Study period: Jan 28-Mar 2 Follow-up: Unclear Sample size: 21 Exposure: Severity (Critical or severe, Chinese classification)	Non-severe: 8 Male, n: 3 Age, y: 64 ± 15.5 Severe: 13 Male, n: 10 Age, y: 67.4 ± 13.4	Med	Low
Qu et al (40)[44]	ALC, ALT, AST, LDH, PLT	Setting: Huizhou Municipal Central Hospital, Guangdong, China Study period: Jan-Feb Follow-up: Feb 21 (complete) Sample size: 30 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 27 Male, n: NR Age, y: 49.4 ± 14.9 Severe: 3 Male, n: NR Age, y: 60 ± 5.3	Med	Low
Zhu et al (66)[45]	ALC, ANC, CRP, Ddimer, ESR, IL-6, IL-10, PLT, TropI, WBC	Setting: Hwa Mei Hospital, Ningbo, Zheijang, China Study period: Jan 23-Feb 20 Follow-up: Unclear Sample size: 127 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 111 Male, n: 73 Age, y: 50 ± 15.5 Severe: 16 Male, n: 9 Age, y: 57.5 ± 11.7	Med	Low
Huang et al (3)[46]	Alb, ALC, ALT, ANC, AST, Bili, Cr, Ddimer, Hb, LDH, PLT, PT, hsTropI, WBC	Setting: Jin Yintan Hospital, Wuhan, Hubei, China Study period: Dec 16-Jan 2 Follow-up: Unclear Sample size: 41 Exposure: Severity (ICU or non-ICU)	Non-severe: 28 Male, n: 19 Age, y: 49.2 ± 13 Severe: 13 Male, n: 11 Age, y: 50.3 ± 16.6	Med	Low
Xie et al (53)[47]	ALC, ALP, ALT, ANC, AST, Bili, Cr, CRP, Ddimer, ESR, GGT, WBC	Setting: Jin Yintan Hospital, Wuhan, Hubei, China Study period: Feb 2-Feb 23 Follow-up: Unclear Sample size: 79 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 51 Male, n: 26 Age, y: 57 ± 15.3 Severe: 28 Male, n: 18 Age, y: 60.3 ± 13.6	Med	Low
Feng et al (29)[48]	Alb, ALC, ANC, Bili, BUN, CK, CKMB, Cr, CRP, Ddimer, ESR, Hb, LDH, PLT, PCT, WBC	Setting: Jin Yintan Hospital, Wuhan, Hubei, Shanghai Public Health Center, Shanghai, Tongling People's Hospital, China Study period: Jan 1-Feb 15 Follow-up: Mar 21 Sample size: 476 Exposure: Severity (Critical/severe or mild, Chinese classification)	Non-severe: 352 Male, n: 190 Age, y: 50.3 ± 19.3 Severe: 124 Male, n: 81 Age, y: 58.6 ± 14.4	High	Low (reference study)
Zou et al (67)[49]	APTT, Ddimer, PT	Setting: Shanghai Public Health Center, Shanghai, China Study period: Jan 20-Feb 24	Non-severe: 277 Male, n: 138 Age, y: 49.7 ± 20	High	High Reasons:

TABLE 1 (Continued)

Study (ID)	Outcomes	Study characteristics	Patient characteristics	Risk of bias	Duplicate risk
		Follow-up: Unclear (incomplete) Sample size: 303 Exposure: Severity (Severe or mild, Chinese classification)	Severe: 26 Male, n: 20 Age, y: 68 ± 10.2		Setting and period shared with Feng (29), Thromboplastin time and fibrinogen OK
Wu et al (6)[87]	Alb, ALC, ALT, ANC, AST, Bili, BUN, Cr, CRP, Ddimer, ESR, Ferritin, IL-6, LDH, PLT, PT, WBC	Setting: Jin Yintan Hospital, Wuhan, Hubei, China Study period: Dec 25-Jan 26 Follow-up: Feb 13 Sample size: 201 Exposure: Severity (ARDS or not)	Non-severe: 117 Male, n: 68 Age, y: 49 ± 12.7 Severe: 84 Male, n: 60 Age, y: 67.6 ± 12	Low	High Reasons: Setting and period shared with Feng (29), ALT, AST, Interleukin-6, Ferritin, Prothrombin Time OK
Zhang et al (7)[50]	ALC, CRP, Ddimer, PCT, WBC	Setting: No. 7 Hospital, Wuhan, Hubei, China Study period: Jan 16-Feb 3 Follow-up: Unclear Sample size: 140 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 82 Male, n: 38 Age, y: 51.8 ± 39.2 Severe: 58 Male, n: 33 Age, y: 58.7 ± 47.1	Med	Low
Zheng et al (62)[51]	ALC, ALT, AST, Bili, CK, Cr, CRP, Hb, LDH, PLT, WBC	Setting: North Hospital of Changsha First Hospital, Changsha, Hunan, China Study period: Jan 17-Feb 7 Follow-up: Unclear Sample size: 161 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 131 Male, n: 66 Age, y: 40.7 ± 15 Severe: 30 Male, n: 14 Age, y: 56.5 ± 15.2	Med	Low
Petrilli et al (69)[52]	ALC, ALT, AST, Cr, CRP, Ddimer, Ferritin, PCT, TropI	Setting: New York University Langone Health, New York, USA Study period: Mar 1-Apr 8 Follow-up: May 5 (complete) Sample size: 2729 Exposure: Severity (ICU/IMV/Hospice/Death or not)	Non-severe: 1739 Male, n: 1016 Age, y: 59.7 ± 17.0 Severe: 990 Male, n: 656 Age, y: 68 ± 14.8	Low	Low
He et al (32)[53]	ALC, ALT, ANC, AST, BUN, CK, Cr, CRP, Ddimer, IL-6, IL-10, LDH, PLT, PCT, PT, hsTropI, WBC	Setting: Renmin Hospital, Wuhan, Hubei, China Study period: Jan 10-Feb 13 Follow-up: Feb 13 (incomplete) Sample size: 204 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 135 Male, n: 42 Age, y: 42.3 ± 16.5 Severe: 69 Male, n: 37 Age, y: 62.3 ± 16.6	Med	Low (reference study)
Deng et al (26)[54]	CK, CKMB, CRP, Ddimer, Hb, LDH, PCT, TropI	Setting: Renmin Hospital, Wuhan, Hubei, China Study period: Jan 6-Feb 20 Follow-up: Mar 11 (incomplete) Sample size: 112	Non-severe: 45 Male, n: 19 Age, y: 67.3 ± 15.2 Severe: 67 Male, n: 38	Med	High Reasons: Setting and period shared with He (32), Shi (41)

(Continues)

TABLE 1 (Continued)

Study (ID)	Outcomes	Study characteristics	Patient characteristics	Risk of bias	Duplicate risk
		Exposure: Severity (Severe or mild, Chinese classification)	Age, y: 54 ± 21.4		
Han et al (31)[55]	hsTropI	Setting: Renmin Hospital, Wuhan, Hubei, China Study period: Jan 1-Feb 18 Follow-up: Unclear Sample size: 173 Exposure: Severity (Critical/severe or mild, Chinese classification)	Non-severe: 198 Male, n: 71 Age, y: 59 ± 10.8 Severe: 75 Male, n: 26 Age, y: 58.6 ± 14.9	High	High Reasons: Setting and period shared with He (32), Shi (41), Deng (26)
Shi et al (41)[56]	Alb, ALC, ALT, AST, Cr, CRP, Hb, PLT, PCT, WBC	Setting: Renmin Hospital, Wuhan, Hubei, China Study period: Jan 20-Feb 10 Follow-up: Feb 15 (incomplete) Sample size: 416 Exposure: Severity (Cardiac injury or not)	Non-severe: 334 Male, n: 161 Age, y: 57.7 ± 11.5 Severe: 82 Male, n: 44 Age, y: 69.2 ± 10.2	Med	High Reasons: Setting and period shared with He (32)
Lei et al (33)[57]	ALC, ALT, ANC, APTT, AST, Bili, BUN, CK, Cr, CRP, Ddimer, LDH, PLT, PT, WBC	Setting: Renmin Hospital, Zhongnan Hospital, Tongji Hospital, Central Hospital, Wuhan, Hubei, China Study period: Jan 1-Feb 5 Follow-up: Mar 10 (complete) Sample size: 34 Exposure: Severity (ICU or non-ICU)	Non-severe: 19 Male, n: 9 Age, y: 44.7 ± 23.4 Severe: 5 Male, n: 44 Age, y: 57.7 ± 24.9	Low	High Reasons: Multicenter from three major COVID-19 Hospitals in China
Li et al (1)[58]	ALC, ANC, CRP, PCT, WBC	Setting: Second Affiliated Hospital of Chongqing Medical University, Chongqing Three Gorges Central Hospital, Yanzhuang Central Hospital of Gancheng District, China Study period: Jan-Feb Follow-up: Unclear (incomplete) Sample size: 83 Exposure: Severity (Critical/severe or mild, Chinese classification)	Non-severe: 58 Male, n: 29 Age, y: 41.9 ± 10.6 Severe: 25 Male, n: 15 Age, y: 53.7 ± 12.3	Med	High Reasons: Multicenter study from China
Chen et al (22)[59]	Alb, ALC, ALP, ALT, ANC, APTT, AST, Bili, BUN, Cr, CRP, Ddimer, ESR, GGT, Hb, LDH, PLT, PCT, PT, TropI, WBC	Setting: Taizhou Public Health Center, Enze Hospital, Zheijang, China Study Period: Jan 1-Mar 11 Follow-up: Mar 11 Sample size: 145 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 102 Male, n: 56 Age, y: 45.3 ± 13.6 Severe: 43 Male, n: 23 Age, y: 52.8 ± 15.5	Med	Low
Cai et al (18)[60]	ALC, ALP, ALT, ANC, AST, Bili, BUN, CK, CKMB, Cr, CRP, Ddimer, ESR, GGT, IL-6, LDH, PCT, WBC	Setting: Third People's Hospital of Shenzhen, Shenzhen, China Study Period: Jan 11-Feb 6 Follow-up: Mar 6 (complete) Sample size: 298 Exposure: Severity (Severe or non-severe, ATS classification)	Non-severe: 240 Male, n: 106 Age, y: 42.7 ± 18.5 Severe: 58 Male, n: 39 Age, y: 61.5 ± 7.6	Low	Low

TABLE 1 (Continued)

Study (ID)	Outcomes	Study characteristics	Patient characteristics	Risk of bias	Duplicate risk
Wan et al (44)[61]	Alb, ALC, ALT, ANC, APTT, AST, Bili, CK, Cr, CRP, Ddimer, Hb, LDH, PLT, PCT, PT, WBC	Setting: Three Gorges Hospital, Chongqing, China Study period: Jan 23-Feb 8 Follow-up: Feb 8 (incomplete) Sample size: 135 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 95 Male, n: 52 Age, y: 42 ± 12 Severe: 40 Male, n: 21 Age, y: 60.3 ± 16.2	High	Low (reference study)
Wan et al (45)[62]	ALC, ANC, IL-6, IL-10, WBC	Setting: Three Gorges Hospital, Chongqing, China Study period: Jan 26-Feb 4 Follow-up: Unclear Sample size: 123 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 102 Male, n: NR Age, y: 43 ± 13.1 Severe: 21 Male, n: NR Age, y: 61.3 ± 15.6	High	High Reasons: Setting and period shared with Wan (44), Interleukin-6 and 10 OK
Chuan et al (8)[63]	ALC, ANC, CRP, ESR, Ferritin, IL-6, PCT, WBC	Setting: Tongji Hospital, Wuhan, Hubei China Study period: Jan 10-Feb 12 Follow-up: Unclear Sample size: 452 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 166 Male, n: 80 Age, y: 52 ± 15.5 Severe: 286 Male, n: 155 Age, y, y: 60.3 ± 13.3	Med	Low (reference study)
Pei et al (38)[64]	Alb, ALC, ALT, ANC, AST, BUN, Cr, CRP, Ddimer, ESR, IL-6, IL-10, PT, hsTropI	Setting: Tongji Hospital, Wuhan, Hubei China Study period: Jan 28-Feb 9 Follow-up: Feb 23 (incomplete) Sample size: 333 Exposure: Severity (Critical/severe or mild, Chinese classification)	Non-severe: 144 Male, n: 67 Age, y: 50.9 ± 12.5 Severe: 189 Male, n: 115 Age, y: 59.8 ± 12.1	High	High Reasons: Setting and period shared with Chuan (8), ALT, AST, Trop, Alb, BUN, Cr, PT, Ddimer, IL-10 OK
Wang et al (46)[65]	Alb, ALC, ALP, ANC, Bili, BUN, Cr, CRP, Ddimer, Ferritin, GGT, LDH, PCT, WBC	Setting: Tongji Hospital, Wuhan, Hubei China Study period: Jan Follow-up: Unclear Sample size: 65 Exposure: Severity (Critical/severe or mild, Chinese classification)	Non-severe: 30 Male, n: NR Age, y: 55.2 ± 12.4 Severe: 35 Male, n: NR Age, y: 61.3 ± 12.2	High	High Reasons: Setting and period shared with Chuan (8), Chen (21)
Chen et al (21)[66]	Alb, ALC, ALT, ANC, APTT, AST, Bili, BUN, CK, Cr, CRP, Ddimer, Ferritin, Hb, IL-6, IL-10, LDH, PLT, PCT, PT, WBC	Setting: Tongji Hospital, Wuhan, Hubei China Study period: Dec-Jan 27 Follow-up: Unclear Sample size: 21 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 10 Male, n: 7 Age, y: 55.2 ± 12.4 Severe: 11 Male, n: 10 Age, y: 61.3 ± 12.2	Med	High Reasons: Setting and period shared with Chuan (8), Wang (46), IL-10 OK
Goyal et al (68)[67]	Alb, BUN, ESR, Hb	Setting: Two Hospitals in Manhattan, USA Study period: Mar 3-Mar 27 Follow-up: Apr 10 (incomplete) Sample size: 393	Non-severe: 263 Male, n: 146 Age, y: 61.2 ± 20.7 Severe: 130	Med	Low

(Continues)

TABLE 1 (Continued)

Study (ID)	Outcomes	Study characteristics	Patient characteristics	Risk of bias	Duplicate risk
		Exposure: Severity (Invasive mechanical ventilation or not)	Male, n: 92 Age, y: 63.3 ± 16.4		
Wang et al (10)[68]	ALC, ALT, ANC, AST, Cr, CRP, ESR, Hb, IL-6, LDH, PLT, PCT, WBC	Setting: Union Hospital Tongji Medical College, Wuhan, Hubei, China Study period: Jan 16-Jan 29 Follow-up: Feb 4 (incomplete) Sample size: 69 Exposure: Severity (O_2 saturation < 90% on room air or not)	Non-severe: 55 Male, n: 25 Age, y: 40 ± 14.5 Severe: 14 Male, n: 7 Age, y: 69.8 ± 12.4	Low	Low
Mao et al (36)[69]	ALC, ALT, ANC, AST, BUN, CK, Cr, CRP, Ddimer, LDH, PLT, WBC	Setting: Union Hospital Tongji Medical College, Wuhan, Hubei, China Study period: Jan 16-Feb 19 Follow-up: Unclear Sample size: 214 Exposure: Severity (Severe or non-severe, ATS classification)	Non-severe: 88 Male, n: 43 Age, y: 48.9 ± 14.7 Severe: 126 Male, n: 44 Age, y: 58.2 ± 15	Med	High Reasons: Setting and period shared with Wang (10)
Wei et al (50)[70]	Alb, ALC, Bili, BUN, CK, Cr, IL-6, IL-10, LDH, PCT, hsTropI, WBC	Setting: Union Hospital Tongji Medical College, Wuhan, Hubei, China Study period: Feb 13-Mar 3 Follow-up: Unclear Sample size: 252 Exposure: Severity (Critical/severe or mild, Chinese classification)	Non-severe: 131 Male, n: 59 Age, y: 60.1 ± 12.4 Severe: 121 Male, n: 71 Age, y: 69.8 ± 12.4	High	Low
Zhou et al (64)[71]	ALC, ALT, ANC, AST, CK, Cr, CRP, LDH, hsTropI, WBC	Setting: Union Hospital Tongji Medical College, Wuhan, Hubei, China Study period: Feb 5-Feb 13 Follow-up: Unclear Sample size: 34 Exposure: Severity (Critical or severe, Chinese classification)	Non-severe: 26 Male, n: 12 Age, y: 63.3 ± 8.6 Severe: 8 Male, n: 5 Age, y: 69.3 ± 9	Med	High Reasons: Setting and period shared with Wang (10), Trop, CK, CKMB OK
Herold et al (70)[72]	ALC, Bili, Cr, CRP, Ddimer, Ferritin, IL-6, LDH, PLT, PCT, WBC	Setting: University Hospital, Munich, Germany Study period: Feb 29-Mar 27 Follow-up: Unclear Sample size: 34 Exposure: Severity (invasive mechanical ventilation or not)	Non-severe: 27 Male, n: 16 Age, y: 51.7 ± 15.3 Severe: 13 Male, n: 13 Age, y: 63.5 ± 10.8	Med	Low
Wei et al (51)[73]	Alb, ALC, ALT, ANC, AST, BUN, CK, CKMB, CRP, Ddimer, IL-6, LDH, PCT, WBC	Setting: Unknown Hospital(s) in Anhui, China Study period: Unclear Follow-up: Unclear Sample size: 167 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 137 Male, n: 75 Age, y: 40.8 ± 15.5 Severe: 30 Male, n: 20 Age, y: 49 ± 12.6	High	High Reasons: Unknown hospital (s), Unclear study period
Aggarwal et al (16)[74]	ALC, ALT, ANC, AST, Cr, CRP, Hb, PLT, WBC	Setting: Unspecified hospital in Midwestern USA Study period: Through Apr 4 Follow-up: Unclear Sample size: 16	Non-severe: 8 Male, n: 7 Age, y: 68.2 ± 19 Severe: 8	Med	Low

TABLE 1 (Continued)

Study (ID)	Outcomes	Study characteristics	Patient characteristics	Risk of bias	Duplicate risk
		Exposure: Severity (ICU/IMV/Death/ Inotropes or not)	Male, n: 5 Age, y: 59.7 ± 11.2		
Du et al (28)[75]	Alb, ALC, ALT, ANC, APTT, AST, BUN, CKMB, Cr, CRP, Ddimer, Hb, PLT, PCT, PT, TropI, WBC	Setting: Wuhan Pulmonary Hospital, Tianyou Hospital, Shanghai, Central Hospital of Wuhan, China Study period: Dec 25-Feb 24 Follow-up: Complete Sample size: 109 Exposure: Severity (ICU or non-ICU)	Non-severe: 58 Male, n: 38 Age, y: 72.7 ± 11.6 Severe: 51 Male, n: 36 Age, y: 68.4 ± 9.7	High	Low
Zhang et al (58)[88]	ALC, ALT, ANC, APTT, AST, Bili, BUN, CK, CKMB, Cr, Ddimer, LDH, PLT, PT, hsTropI, WBC	Setting: Zhongnan Hospital, Wuhan, Hubei, China Study period: Jan 2-Feb 10 Follow-up: Feb 15 (incomplete) Sample size: 221 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 166 Male, n: 73 Age, y: 50.4 ± 21.2 Severe: 55 Male, n: 35 Age, y: 62.7 ± 16.8	Med	Low (reference study)
Wang et al (4)[89]	ALC, ALT, ANC, AST, Bili, Cr, Ddimer, LDH, PLT, PT, hsTropI, WBC	Setting: Zhongnan Hospital, Wuhan, Hubei, China Study period: Jan 1-Jan 28 Follow-up: Feb 3 (incomplete) Sample size: 138 Exposure: Severity (ICU or non-ICU)	Non-severe: 102 Male, n: 53 Age, y: 50 ± 18.8 Severe: 36 Male, n: 22 Age, y: 67 ± 16.3	Med	High Reasons: Setting and period shared with Zhang (58), Trop, Procalcitonin OK
Zhang et al (60)[115]	Alb, ALP, ALT, AST, Bili, CRP, GGT, LDH	Setting: Zhongnan Hospital, Wuhan, Hubei, China Study period: Jan 22-Feb 22 Follow-up: Mar 9 (incomplete) Sample size: 115 Exposure: Severity (Severe or mild, Chinese classification)	Non-severe: 84 Male, n: 29 Age, y: 44 ± 14.8 Severe: 20 Male, n: 35 Age, y: 64.6 ± 13.3	Med	Low

(0.85, 1.60) and 1.49×10^9 (0.96, 2.01) cells/L, respectively. ALC and PLT showed associations in the opposite direction, with WMDs of -0.30×10^9 (−0.37, −0.24) and -16.69×10^9 (−35.35, 1.96) cells/L, respectively. Among inflammatory markers, the most pronounced difference was for ferritin at 423.13 ng/mL (281.41, 582.85). Other inflammatory markers including IL-6 and IL-10 also showed statistically significant associations. Among markers for tissue damage the most marked differences were for LDH, CK, and hsTropI at 120.31 U/L (93.50, 147.12), 45.33 U/L (18.60, 72.07), and 11.07 pg/mL (3.64, 18.50), respectively. TropI did not reach statistical significance at a WMD of 0.04 ng/mL (−0.01, 0.09), but was only reported in three studies (Table 2).

3.2 | Meta-analysis of laboratory tests and mortality

A summary of meta-analysis results for mortality is presented in Table 3. In general, the trends in WMDs were the same as for severity, but with larger absolute differences. Of the 22 laboratory markers that were analyzed for associations with mortality, only Hb, ESR, and APTT did not achieve statistical significance. Among the CBC markers, the WMDs of WBC, ANC, and PLT in patients who died vs those that survived were 3.49×10^9 (2.71, 4.27), 3.82×10^9 (2.76, 4.87), and -43.41×10^9 (−54.55, −32.27) cells/L, respectively. The WMD for ALC was -0.34×10^9 (−0.45, −0.23) cells/L, which is similar to the value seen for severity. Among the inflammatory markers and acute phase reactants, ferritin showed the most marked elevation at 814.14 ng/mL (551.48, 1076.81). CRP, ESR, IL-6, IL-10, and PCT also showed positive associations. Of the liver, coagulation, and renal function tests, D-dimer was the most markedly elevated at 5.74 mg/L (3.91, 7.58). Among markers of tissue damage, LDH, CK, and hsTropI all showed marked elevations at 232.41 U/L (178.31, 286.52), 97.18 U/L (60.01, 134.25), and 90.47 pg/mL (47.79, 133.14), respectively.

TABLE 2 Weighted mean differences in admission laboratory values comparing patients with severe disease to those with non-severe disease

Laboratory marker	Studies, n	Patients, n	Weighted mean difference (95% CI)	I^2 (%)	*P* value
Complete blood count					
Hemoglobin (Hb, g/L)	21	3819	−3.91 (−6.47, −1.35)	62.4	.003[NS]
White blood cell count (WBC, 10^9/L)	40	6705	1.23 (0.85, 1.60)	77.7	.000
Absolute neutrophil count (ANC, 10^9/L)	35	4930	1.49 (0.96, 2.01)	92.3	.000
Absolute lymphocyte count (ALC, 10^9/L)	44	9873	−0.30 (−0.37, −0.24)	89	.000
Platelet count (PLT, 10^9/L)	27	4515	−16.69 (−35.35, 1.96)	92.6	.080[NS]
Inflammatory markers					
C-reactive protein (CRP, mg/L)	35	7660	39.91 (33.17, 46.64)	84.5	.000
Erythrocyte sedimentation rate (ESR, mm/h)	11	2653	6.84 (3.37, 10.31)	69.4	.000
Ferritin (ng/mL)	6	3508	432.13 (281.41, 582.85)	72.0	.000
Interleukin-6 (IL-6, pg/mL)	16	2526	12.25 (7.00, 17.50)	95.8	.000
Interleukin-10 (IL-10, pg/mL)	7	1136	1.86 (1.07, 2.64)	91.3	.000
Procalcitonin (ng/mL)	22	6481	0.08 (0.05, 0.11)	94.2	.000
Liver function tests					
Albumin (g/L)	18	3169	−4.36 (−5.08, −3.64)	75.1	.000
Bilirubin (Bili, μM)	20	3025	1.93 (1.28, 2.57)	42.9	.000
Prothrombin time (PT, s)	17	2304	0.44 (0.24, 0.64)	78.0	.000
Renal function tests					
Creatinine (Cr, μM)	32	7580	7.34 (2.59, 12.10)	91.7	.002[NS]
Blood urea nitrogen (BUN, mM)	21	3797	1.28 (0.82, 1.74)	88.2	.000
Coagulation markers					
Activated partial thromboplastin time (APTT, s)	11	1288	0.59 (−1.22, 2.39)	83.9	.523[NS]
D-dimer (mg/L)	30	6950	0.67 (0.52, 0.82)	92.7	.000
Markers of tissue damage					
Lactate dehydrogenase (LDH, U/L)	27	3791	120.31 (93.50, 147.12)	89.3	.000
Creatine kinase (CK, U/L)	15	2585	45.33 (18.60, 72.07)	93.5	.001
High sensitivity troponin I (hsTropI, pg/mL)	6	1223	11.07 (3.64, 18.50)	73.7	.004[NS]
Troponin I (TropI, ng/mL)	3	3222	0.04 (−0.01, 0.09)	87.8	.134[NS]
Creatine kinase myocardial band (CKMB, U/L)	8	1639	2.44 (0.78, 4.11)	90.9	.004[NS]
Alanine aminotransferase (ALT, U/L)	31	6854	6.25 (3.09, 9.42)	86.6	.000
Aspartate aminotransferase (AST, U/L)	30	6746	8.52 (4.98, 12.06)	91.1	.000
Alkaline phosphatase (ALP, U/L)	6	723	−1.50 (−6.41, 3.41)	28.7	.549[NS]
Gamma glutamyl transferase (GGT, U/L)	6	723	5.01 (−3.16, 13.17)	48.0	.230[NS]

I^2 statistic – Describes the percentage of variation across studies estimated to be due to heterogeneity.
[NS]Denotes nonsignificant *P* values. Bonferroni corrected significance levels is .002.

3.3 | Meta-regression analyses for age and sex

Meta-regressions were conducted for age and sex as described in the Methods section. All associations were nonsignificant when compared to Bonferroni corrected significance levels (data not provided).

3.4 | Sensitivity analyses for bias risk, duplicate risk, and outlier studies

Of the 64 included studies, 17, 31, and 16 were assigned high, medium, and low risks of bias, respectively (Table 1). Insufficient or unclear follow-up durations and nonconsecutive recruitment were the most common shortcomings among high-risk studies. When studies at high risk of bias were excluded for sensitivity analysis, final estimates and statistical significance were unchanged, except for IL-6 in association with disease severity; the WMD dropped from 12.25 pg/mL (7.00, 17.50) to 2.58 pg/mL (−1.53, 6.69) (Supplement 5). A total of 27 studies were assessed to be at high risk of duplication (Table 1). Excluding these studies resulted in loss of statistical significance for IL-6 (WMD = 8.37 pg/mL; 2.76, 13.99) and CK (WMD = 27.65 U/L; 10.19, 45.11) in association with severity, and for IL-6 (WMD = 46.34 pg/mL; 4.35, 88.33) and ALT (WMD = 4.60 U/L; 1.03, 8.17) in association with mortality (Supplement 5 and 6). Excluding outlier studies (8 among studies of mortality and 15 among studies of severity) reduced heterogeneity but had minimal impact on

TABLE 3 Weighted mean differences in admission laboratory values comparing patients that died to those that survived

Laboratory marker	Studies (n)	Patients (n)	Weighted mean difference (95% CI)	I^2 (%)	*P* value
Complete blood count					
Hemoglobin (Hb, g/L)	7	1069	−0.15 (−2.49, 2.19)	0.0	.901[NS]
White blood cell count (WBC, 10^9/L)	10	1824	3.49 (2.71, 4.27)	59.8	.000
Absolute neutrophil count (ANC, 10^9/L)	8	1468	3.82 (2.76, 4.87)	72.4	.000
Absolute lymphocyte count (ALC, 10^9/L)	12	1876	−0.34 (−0.45, −0.23)	81.7	.000
Platelet count (PLT, 10^9/L)	11	2001	−43.41 (−54.55, −32.27)	40.5	.000
Inflammatory markers					
C-reactive protein (CRP, mg/L)	10	1635	66.11 (52.16, 80.06)	68.1	.000
Erythrocyte sedimentation rate (ESR, mm/h)	4	461	8.73 (3.23, 14.24)	0.0	.002[NS]
Ferritin (ng/mL)	5	747	814.14 (551.48, 1076.81)	70.1	.000
Interleukin-6 (IL-6, pg/mL)	9	1630	32.59 (23.99, 41.19)	97.4	.000
Interleukin-10 (IL-10, pg/mL)	3	763	7.55 (6.44, 8.65)	0.0	.000
Procalcitonin (ng/mL)	8	1399	0.29 (0.20, 0.38)	69.1	.000
Liver function tests					
Albumin (g/L)	9	1342	−3.98 (−5.23, −2.72)	81.0	.000
Bilirubin (bili, μM)	8	1146	4.49 (3.56, 5.43)	20.5	.000
Prothrombin time (PT, s)	11	2251	1.21 (0.77, 1.64)	81.0	.000
Renal function tests					
Creatinine (Cr, μM)	11	1630	16.50 (10.74, 22.25)	61.2	.000
Blood urea nitrogen (BUN, mM)	6	1234	3.99 (2.93, 5.04)	81.5	.000
Coagulation markers					
Activated partial thromboplastin time (APTT, s)	4	840	0.97 (0.07, 1.86)	0.0	.034[NS]
D-dimer (mg/L)	12	2323	5.74 (3.91, 7.58)	74.6	.000
Markers of tissue damage					
Lactate dehydrogenase (LDH, U/L)	8	1435	232.41 (178.31, 286.52)	82.5	.000
Creatine kinase (CK, U/L)	6	1205	97.18 (60.01, 134.35)	80.9	.000
High sensitivity troponin I (hsTropI, pg/mL)	6	1346	90.47 (47.79, 133.14)	91.9	.000
Alanine aminotransferase (ALT, U/L)	11	1842	5.45 (2.64, 8.26)	28.4	.000
Aspartate aminotransferase (AST, U/L)	10	1633	13.89 (8.16, 19.63)	69.3	.000

I^2 statistic—Describes the percentage of variation across studies estimated to be due to heterogeneity.
[NS] Denotes nonsignificant *P* values. Bonferroni corrected significance level is .002.

overall estimates, except for Cr and CKMB in association with disease severity, which achieved statistical significance at 6.69uM (3.31, 10.06) and 2.31 U/L (0.61, 4.02), respectively (Supplement 5).

4 | DISCUSSION

In this systematic review and meta-analysis, we observed significant differences in many admission laboratory values between severe and non-severe, and fatal and nonfatal cases of COVID-19. Although the WMDs for most parameters were statistically significant, those that were most pronounced, and thus those would be most clinically useful, are markers of overactive inflammatory response, blunted adaptive response, intravascular coagulation, and cell death, reflecting the pathophysiology of severe and fatal COVID-19.[7-9]

In support of the role that hyper inflammation plays in COVID-19, the levels of all included acute phase reactants were significantly altered at admission when comparing severe to non-severe and fatal to nonfatal cases. Among the acute phase proteins, the largest difference was observed for ferritin, which is driven by IL-18.[90] Although IL-18 was not reported in any of the included studies, we expect elevated levels. CRP was also markedly elevated, and albumin was decreased, both of which are acute phase reactions driven by IL-6, a major pro-inflammatory cytokine.[91] As expected by the derangements in acute phase reactants, IL-6 levels were increased and were more prominent for fatal than for severe cases.

Inflammation is a major component of innate immunity and is typically a transient initial response to any pathogen or injury, eventually subsiding and being replaced by a focused immune response when the trigger is infectious.[92] The inflammatory response is driven and sustained by numerous pro-inflammatory cytokines and chemokines including IL-6, TNF-α, and CXCL10, which are not only elevated in COVID-19 but have also been implicated in the pathogenesis of disease caused by the related respiratory coronaviruses SARS-CoV

and MERS-CoV.[9,92] As such, a prolonged hyper inflammatory state caused by dysregulated release of pro-inflammatory cytokines, known as cytokine storm syndrome, is thought to be central to the pathogenesis of severe and fatal COVID-19.[93]

Although T-lymphocytes are usually the major producers of many cytokines including IL-6,[94] ALC was decreased for both severe and fatal disease, consistent with hypotheses proposing alternate major sources of cytokines in COVID-19.[95] In fact, even in patients with relatively mild illness, lymphopenia is a common and characteristic feature of COVID-19, suggesting that the adaptive immune response is blunted and may be delayed or insufficient.[27,29,30,32,43,44,52,87,88] One possible explanation is that, like a number of other viruses,[96] SARS-CoV2 may directly infect lymphocytes. SARS-CoV2 relies on angiotensin-converting enzyme 2 (ACE2) for cellular entry,[97] and it has been reported that a small proportion of lymphocytes are ACE2 positive.[98] Another possibility is that inflammatory cytokines such as IL-6 induce chemotaxis of lymphocytes to lymphoid organs, thus reducing circulating concentrations.[99] Functional exhaustion of lymphocytes due to SARS-CoV2-induced inhibitory cytokines such as IL-10, which was significantly elevated in our analysis, has also been suggested.[95,100] However, IL-10 is an important anti-inflammatory cytokine that may in fact not be elevated enough to combat inflammation in fatal COVID-19.[101]

In contrast to ALC, ANC was elevated with a more pronounced difference observed for fatal than for severe illness. Neutrophils play a major role in inflammation and are not typically elevated in viral infections. However, in COVID-19, not only are their concentrations increased, but they have been suggested to be major producers of pro-inflammatory cytokines[102,103] and to contribute to the development of acute respiratory distress syndrome (ARDS) through the formation of neutrophil extracellular traps (NETs)[102,104] and direct tissue infiltration causing vascular leakage.[105] On the other hand, neutrophilia is classically a marker of bacterial infection; thus, it is possible that the observed elevations in ANC seen in severe/fatal COVID-19 reflect bacterial super-infection contributing to severe illness. However, procalcitonin, which is a more specific marker of bacterial infection,[106] has been reported to fall within normal reference ranges even in patients with fatal illness,[27-29,76,77,81-83,86] suggesting that this explanation may not be sufficient. In SARS-CoV, neutrophilia is an independent predictor of severe illness and is associated with hypersensitivity pneumonitis.[107] Hence, a similar mechanism might be plausible for the neutrophilia seen in severe/fatal COVID-19.

In addition to causing localized damage at sites of inflammation, prolonged activation of neutrophils may also contribute to systemic damage in other ways. There were significant abnormalities in Ddimer, PLT, and PT, three of the analyzed coagulation parameters. The largest difference was for Ddimer, which is a fibrin degradation product indicative of intravascular thrombosis. The significant elevation in PT and decrease in PLT is likely due to the development of consumptive coagulopathy, as clotting factors and platelets are used up in forming microthrombi. Elevated Ddimer in severe and fatal COVID-19 may be explained by NETs, which can play a major role in the formation of intravascular thrombi.[102,108] In addition, inflammatory cytokines such as IL-6 have procoagulant effects that contribute to an inflammation-induced hypercoagulable state known as thromboinflammation,[7] reinforcing the connection between the innate immune system and thrombosis. Once ARDS has developed and a patient becomes hypoxemic, thrombosis may also be promoted via a hypoxia-inducible factor-mediated pathway.[85,109]

Tissue damage is an inevitable and unsurprising result of the disease processes described, as evidenced by significant increases in most markers of tissue damage that were analyzed. LDH is a ubiquitous intracellular enzyme that was markedly elevated in both severe and fatal cases. CK, which is highly expressed in skeletal muscle and the aminotransferases, which are expressed in hepatocytes, were also significantly elevated, but to a lesser degree than LDH. Cardiac troponin I, a marker of heart muscle damage, was also markedly increased, especially in fatal illness. Although hypoxemia and shock are the most likely causes of myocardial damage, it is possible that direct infection of cardiomyocytes by SARS-CoV2[110] plays a role in some cases. This hypothesis is given plausibility by the presence of ACE2 on cardiomyocytes[111] and case reports of COVID-19 associated myocarditis.[112]

Meta-regression analyses conducted for age and sex on key markers involved in inflammation, poor adaptive response and intravascular coagulation did not show any significant associations between age or sex and observed marker levels. This is an important result reinforcing the utility of these markers for predicting disease severity among all adults, as males and the elderly have been overrepresented among severe cases.[2]

4.1 | Study strengths and limitations

To our knowledge, this is the first meta-analysis that assessed COVID-19 disease severity and mortality in association with laboratory markers and included a meta-regression for age and sex. In addition, the potential impacts of duplicate reporting and important sources of bias were considered. Rather than simply exclude duplicate studies, as was done in a previous systematic review,[11] we conducted a sensitivity analysis showing that exclusion had little impact on overall results. Despite these strengths, there are multiple limitations to our study. When not available, we estimated means and standard deviations from reported medians, IQRs, and ranges. Estimates from studies with small sample sizes can be imprecise, contributing to greater heterogeneity. Furthermore, we did not assess the risk of publication bias in this study. Due to the pandemic nature of COVID-19, most published studies on clinical outcomes, especially during the first months, were small case-reports and case-series. Hence, it is unlikely that small studies reporting on COVID-19 disease severity and mortality remained unpublished because of null and/or nonsignificant results. There are also limitations to the data set. For example, our entire mortality data set and 70% of the severity data set is from China, potentially limiting the generalizability of the results. Additionally, 42 of 64 studies had unreported or insufficient follow-up, which could bias the results by incorrectly classifying a patient as non-severe or living, only to develop the more

severe disease after the follow-up period. This requires updating analyses once more data becomes available outside of China. Diverse classification schemes for disease severity among different studies potentially contributed to high levels of the observed heterogeneity. Another potential contributor to heterogeneity is that time to hospitalization was unreported in all but 17 studies, however, we assume most patients were hospitalized shortly after developing severe respiratory symptoms such as dyspnea.

5 | CONCLUSIONS

The associations between markers of inflammation (ANC, IL-6, ferritin, CRP, albumin), poor adaptive immune response (ALC), intravascular coagulation (Ddimer), and tissue damage (LDH, hsTropI) observed with a severe and fatal disease in this meta-analysis not only support the key roles of these processes in COVID-19 but also provide evidence that there are identifiable biochemical and hematologic differences that exist between severe and non-severe, and fatal and nonfatal cases before the development of potentially lethal complications such as ARDS. Although these disease processes are certainly not unique to COVID-19, they appear to be key pathways involved in the development of severe/fatal disease and can all be connected to hyper inflammation and cytokine storm. Importantly, the results of the meta-regression suggest that these markers are likely reliable regardless of age or sex in adult patients. Assessment of these markers at admission contributes both to an understanding of the disease mechanisms involved, as well as guiding attempts at predicting severe illness, thus allowing for identification of patients likely to benefit from early interventions. There are no widely accepted disease prediction models yet for COVID-19,[113] but accurate tools will likely need to incorporate markers of the main pathogenetic pathways involved: inflammation, blunted adaptive response, and thrombosis. These pathways are likely also ideal targets for therapy, such as the IL-6 inhibitor tocilizumab to target inflammation,[114] or heparin to target coagulation.[85] The results also indicate that further research is warranted in the utility of different immunomodulators and anticoagulants in the treatment of COVID-19.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

MD and JK conceived and designed the study. MD and ERH analyzed the data. JK, NZJ, SC, ERH, PB, and MD interpreted the data. JK drafted the manuscript. N.Z.J, SC, ERH, PB, and MD critically revised the manuscript. MD supervised the study. All authors approved the final version of the manuscript for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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