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RESEARCH ARTICLE

Clinical laboratory parameters associated with severe or critical novel coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis

Jude Moutchia[1,2☯]*, **Pratik Pokharel**[2,3☯], **Aldiona Kerri**[2,3☯], **Kaodi McGaw**[2,4☯], **Shreeshti Uchai**[2,3☯], **Miriam Nji**[5☯], **Michael Goodman**[5☯]

1 Bamenda Regional Hospital, Bamenda, Cameroon, **2** EHESP–French School of Public Health, Paris, France, **3** School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom, **4** University of Cambridge, Cambridge, United Kingdom, **5** Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, United States of America

☯ These authors contributed equally to this work.
* msjude27@gmail.com

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Abstract

Background

To date, several clinical laboratory parameters associated with Coronavirus disease 2019 (COVID-19) severity have been reported. However, these parameters have not been observed consistently across studies. The aim of this review was to assess clinical laboratory parameters which may serve as markers or predictors of severe or critical COVID-19.

Methods and findings

We conducted a systematic search of MEDLINE, Embase, Web of Science, CINAHL and Google Scholar databases from 2019 through April 18, 2020, and reviewed bibliographies of eligible studies, relevant systematic reviews, and the medRxiv pre-print server. We included hospital-based observational studies reporting clinical laboratory parameters of confirmed cases of COVID-19 and excluded studies having large proportions (>10%) of children and pregnant women. Two authors independently carried out screening of articles, data extraction and quality assessment. Meta-analyses were done using random effects model. Meta-median difference (MMD) and 95% confidence interval (CI) was calculated for each laboratory parameter. Forty-five studies in 6 countries were included. Compared to non-severe COVID-19 cases, severe or critical COVID-19 was characterised by higher neutrophil count (MMD: 1.23 [95% CI: 0.58 to 1.88] $\times 10^9$ cells/L), and lower lymphocyte, CD4 and CD8 T cell counts with MMD (95% CI) of -0.39 (-0.47, -0.31) $\times 10^9$ cells/L, -204.9 (-302.6, -107.1) cells/μl and -123.6 (-170.6, -76.6) cells/μl, respectively. Other notable results were observed for C-reactive protein (MMD: 36.97 [95% CI: 27.58, 46.35] mg/L), interleukin-6 (MMD: 17.37 [95% CI: 4.74, 30.00] pg/ml), Troponin I (MMD: 0.01 [0.00, 0.02] ng/ml), and D-dimer (MMD: 0.65 [0.45, 0.85] mg/ml).

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Competing interests: The authors have declared that no competing interests exist.

Conclusions

Relative to non-severe COVID-19, severe or critical COVID-19 is characterised by increased markers of innate immune response, decreased markers of adaptive immune response, and increased markers of tissue damage and major organ failure. These markers could be used to recognise severe or critical disease and to monitor clinical course of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is an emerging zoonosis caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1, 2]. Phylogenetically, SARS-CoV-2 sufficiently differs from other zoonotic coronaviruses, such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) introduced to humans in the past two decades [1, 3]. Disease resulting from infection with SARS-CoV-2 was first reported in Wuhan, China in December 2019, and the virus rapidly spread to other regions of the world thereafter [4, 5]. Given the scale of the outbreak, COVID-19 was declared a pandemic on March 12 2020 by the World Health Organization [6]. As of April 19, 2020, there have been 2,394,291 confirmed cases in 185 countries/regions and 164,938 COVID-related deaths [7].

Clinical features of infection with SARS-CoV-2 vary widely and have been classified as mild, severe or critical, with some persons remaining asymptomatic [8, 9]. Majority of SARS--CoV-2 infected persons display mild symptoms similar to a viral upper respiratory tract infection such as dry cough, fever, sore throat, nasal congestion, and muscle pain [8–10]. Severe COVID-19 is characterised by features of severe pneumonia such as dyspnoea, respiratory frequency $\geq$30 breaths per minute and blood oxygen saturation $\leq$93%, while critical COVID-19 is characterised by respiratory failure, septic shock, and/or multiple organ failure [8, 9]. Severe or critical COVID-19 is highly associated with mortality [11]. In a single-centre observational study of critical COVID-19 patients, up to 61% of critical COVID-19 patients and 94% of critical COVID-19 patients requiring mechanical ventilation died within 28 days of admission into the intensive care unit [12].

Currently, there is no approved cure for infection with SARS-CoV-2 and an effective vaccine is not yet available. Approximately 18% of diagnosed COVID-19 cases have severe or critical disease, and about 5% of diagnosed COVID-19 require intensive care management with or without mechanical ventilation [8, 13]. Consequently, there is substantial pressure on healthcare systems worldwide, particularly on intensive care units. As healthcare systems become further stretched by the increasing numbers of cases, identifying clinical laboratory parameters associated with severe and critical cases is crucial in helping clinicians triage patients appropriately and optimize use of the limited healthcare resources. Furthermore, as more clinical trials are being launched to test possible treatments for COVID-19, laboratory parameters associated with COVID-19 severity can aid in monitoring the clinical evolution of cases on trial drugs and serve as composite or secondary outcomes for these trials.

To date, changes in several clinical laboratory parameters have been linked to COVID-19 severity [4, 13–16]. However, it is not clear if these changes are observed consistently across studies. With these considerations in mind, the objective of this systematic review and meta-analysis was to investigate which clinical laboratory parameters may be associated with severe or critical COVID-19 disease.

Methods

Protocol and registration

We registered our study protocol with the International Prospective Register of Systematic Reviews (PROSPERO); registration number CRD42020176651 [17]. This review and meta-analysis was conducted and has been reported according to The Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) statement and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [18, 19].

Eligibility criteria

This review and meta-analysis included observational studies reporting clinical laboratory parameters among patients with confirmed COVID-19. Cases were diagnosed using guidelines by either the World Health Organization or the China National Commission for Health [20, 21].

The exposure of interest of this review was severe or critical COVID-19 and the comparator was non-severe COVID-19. According to the criteria defined by China National Health Commission, severe COVID-19 is characterised by dyspnoea, $\geq$30 breaths/minute, blood oxygen saturation $\leq$93%, arterial partial pressure of oxygen to fraction of inspired oxygen (PaO^2/FiO^2) ratio $<$300, and/or lung infiltrates $>$50% within 24–48 hours; and critical COVID-19 is characterised by respiratory failure, septic shock, and/or multiple organ failure [22]. Non-severe COVID-19 is defined by no or mild pneumonia [22]. We also considered COVID-19 cases requiring oxygen therapy, and COVID-19 cases admitted to intensive care units as severe or critical cases.

The outcomes of interest were clinical laboratory parameters. These included hematologic indices (White blood cells, Neutrophils, Lymphocytes, Monocytes, Platelets, Haemoglobin, CD3, CD4, CD8), biochemical indices (Total bilirubin, Alanine aminotransferase, Aspartate aminotransferase, Total protein, Albumin, Globulin, Prealbumin, Urea, Creatinine, Glucose, Creatine kinase muscle-brain, Troponin I, Cholinesterase, Cystatin C, Lactate dehydrogenase, α-hydroxybutyric dehydrogenase), infection/inflammation-related indices (C-reactive protein [high sensitivity and standard], Interleukin-6, Erythrocyte sedimentation rate, Procalcitonin, Serum ferritin), coagulation indices (Prothrombin time, Activated partial thromboplastin, D-dimer) and electrolytes (Sodium, Potassium, Calcium, Chloride).

We included only hospital-based studies and excluded reviews, opinion articles, and studies that did not report clinical laboratory parameters stratified by COVID-19 disease severity. Also, as children and pregnant women have different cut-off values for most clinical laboratory parameters compared to general adults, we excluded studies that examined populations with large proportions of children under 11 years of age and pregnant women to reduce clinical heterogeneity. We considered studies that included children, pregnant women along with the general adult population as eligible only if the proportion of children or pregnant women constituted less than 10%.

Search strategy

We conducted a systematic search of Ovid MEDLINE, Ovid Embase, Clarivate Analytics Web of Science Core Collection, EBSCO CINAHL and Google Scholar databases from 2019 through April 18, 2020. The search strategy used both controlled vocabulary and free text words relevant to COVID-19 and clinical laboratory parameters (see search strategy in S1 Text in S1 File). We also reviewed bibliographies of eligible studies, relevant systematic reviews to identify additional papers that were missed by the electronic search. Further, we performed a

manual search of the medRxiv pre-print server to identify latest relevant studies that might still be undergoing peer-review. The search was limited to the years 2019–2020 and there was no limitation regarding language of publication.

Study selection

Following deduplication of records retrieved during the systematic search, we exported retained articles into Covidence review manager to facilitate the screening of titles and abstracts, which was followed by a full text review to determine eligibility [23].

Two authors (JM and PP) independently carried out title and abstract screening and full text evaluation of all articles using the eligibility criteria listed in the previous section. The discrepancies in study selection were resolved through adjudication by a third author (KM). To avoid including data on the same patient populations more than once in the meta-analysis, we matched studies based on the location of the study (hospital, town) and the period over which data was collected. For two or more studies conducted at the same location over the same or overlapping periods, we included only the largest study, unless one of the smaller studies presented relevant information not included in the larger study.

Data extraction and data items

Two authors (JM and PP) independently extracted, verified and summarized data from each study included in the meta-analysis. The information extracted from the selected studies included: study author(s), study sponsors, date of publication, study period, study location, study design, sample size, sample characteristics (age, gender, comorbidities), exposure characteristics (study definition of severity of COVID-19, timing of classification of disease severity [on admission or otherwise], number of cases with non-severe COVID-19, number of cases with severe or critical COVID-19), timing of blood sample collection (on admission or otherwise), clinical laboratory parameters stratified by COVID-19 severity, mean (standard deviation [SD]) and/or median (interquartile range [IQR] or minimum-maximum [total] range) of clinical laboratory parameters when reported on continuous scales, and numbers (percentages) of cases above and below cut-off values when reported on categorical scales. Discrepancies in collected data were resolved by re-checking the primary studies until consensus was reached. For the studies which had unclear severity classification, the authors were contacted to seek additional clarification. Studies in the Chinese language were translated into English language by a Chinese native speaker. The extracted data were exported into R programming software.

Quality assessment

Two authors (AK and MN) independently carried out quality assessment of each article using National Institutes of Health (NIH) study quality assessment tools for observational cohort and cross-sectional studies, and for case series studies [24]. These tools were used to evaluate the risk of bias and to assess the overall validity of reported results. Each study was assessed using all elements of the relevant tool, and an overall judgement was made by considering the responses to the various elements. An overall rating of poor quality translates to a high risk of bias, and an overall rating of good quality translates to a low risk of bias [24]. The final decision for each study was made through professional judgement and by consensus among the authors. We evaluated the impact of studies with a high risk of bias by doing sensitivity analysis using the Leave-One-Out method [25].

Summary measures and data synthesis

Where clinical laboratory parameters were measured on a continuous scale, we pooled median differences from each study using the quantile estimation method [26]. The result of this analysis was expressed as a meta-median difference (MMD) accompanied by a corresponding 95% confidence interval (CI). We preferred median differences over mean differences because clinical laboratory indices are usually skewed, and mean values could be influenced by outlier values, particularly in small samples. We performed a sensitivity analysis by pooling mean differences from each study using inverse variance weighting. Where the studies reported only median (IQR or total range) values, we computed mean (SD) using methods previously described [27, 28].

Where clinical laboratory parameters were measured on a categorical scale, we computed prevalence ratios for each study using counts of events in the exposure and comparator group and calculated meta-prevalence ratios (MPR) and the 95% CIs using the Mantel-Haenszel method.

Meta-analysis was conducted using random effect models. We assessed clinical heterogeneity (age distribution, comorbidities criteria of severity) and study methodological heterogeneity (timing of blood sample collection) and considered the potential impact of these factors on the meta-analysis results. We assessed statistical heterogeneity using Cochran's Q test and calculated the I^2 statistic, which was interpreted using cut-offs of 25%, 50%, and 75% for low, moderate, and substantial heterogeneity, respectively. We performed influence analysis using the Leave-One-Out-method to identify studies that have a high influence on our results [25]. Additional sensitivity analyses were performed by excluding 'outlier' studies. A study-specific estimate was considered an outlier if its confidence interval did not overlap with the confidence interval of the meta-estimate [25].

To detect possible publication bias, funnel plots were constructed for the 4 laboratory parameters with the highest number of individual studies. Egger's test was carried out to assess statistical symmetry of the plots.

Statistical analyses were done using R programming software and in the 'meta', 'metafor', 'dmetar' and 'metadian' packages [29].

Results

Study selection

We identified 3,779 studies through database searching and from other sources (Fig 1). After removing duplicates, 1722 unique records were screened, and of those, 1398 were removed after title and abstract review. Additional 257 records were excluded due to lack of COVID-19 severity classification, lack of laboratory parameter records or ineligible study design. Of the 67 remaining studies, another 22 were excluded because they used data from the same locations or covered overlapping periods (see S2 Text in S1 File). A total of 45 studies were retained for meta-analyses.

Study characteristics

The characteristics of included studies are detailed in Table 1 and S3 Table in S1 File. All studies included in the meta-analyses were observational and hospital based. The majority of 45 studies (87%) were from China; and of those, 14 were from Wuhan and 25 from other locations in China. Two studies were from the USA, and the remaining 4 studies were from France, Germany, Japan and Singapore. All studies were published in 2020 and the data collection covered the period from December 25th, 2019 to April 2nd, 2020. The median population

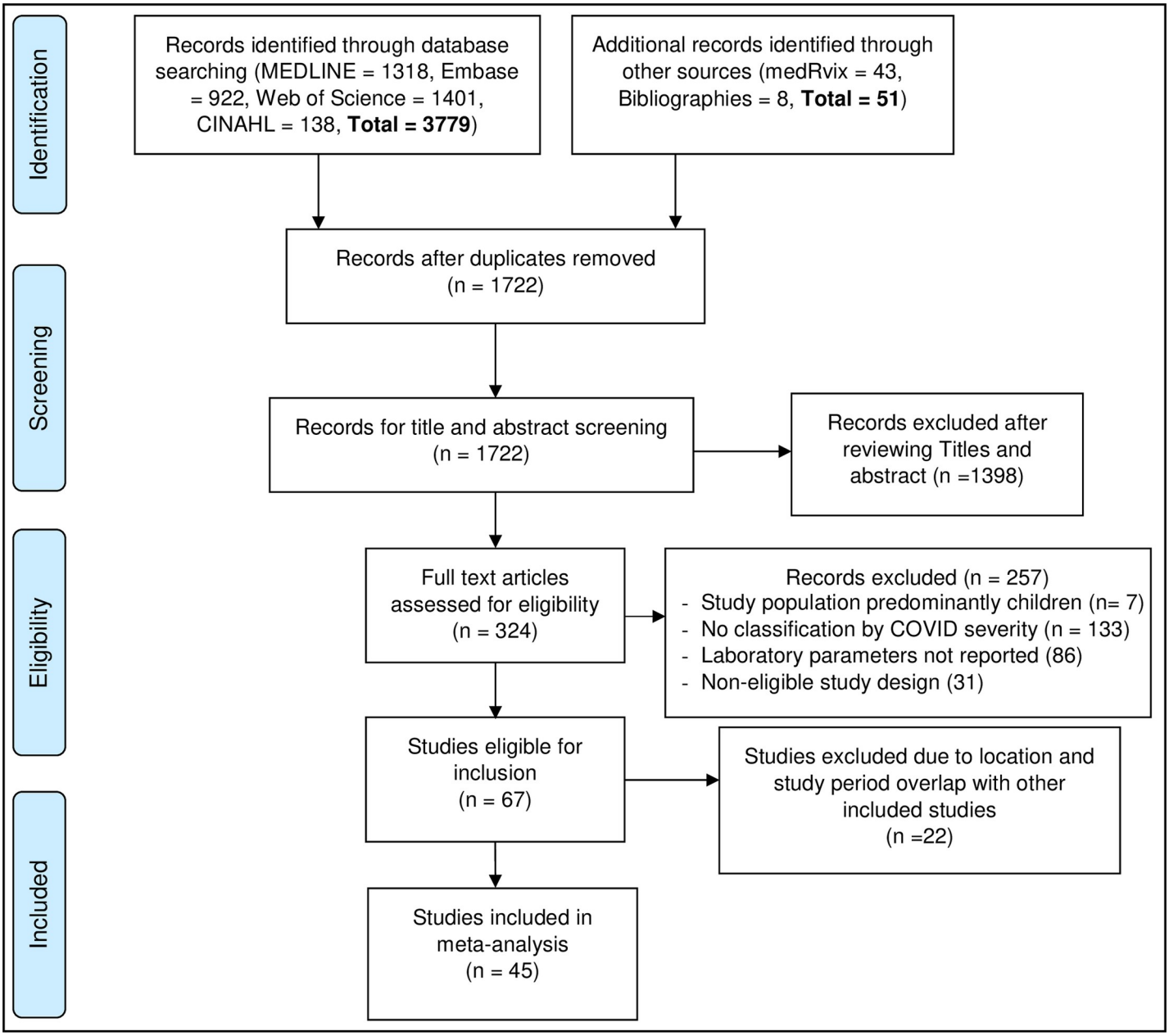


Fig 1. PRISMA flowchart of study selection.

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size of the included studies was 97 (IQR: 49–221). Data were collected retrospectively in all but one study [30]. COVID-19 severity was classified using China National Health Commission guidelines (20 studies), WHO guidelines (4 studies), American Thoracic Society guidelines (2 studies), Berlin criteria (1 study), Complementary and Natural Healthcare council (1 study), or unspecified guidelines (17 studies). Studies classified severity on admission (22 studies, 49%), on the ward (11 studies, 24%), or during unspecified periods (12 studies, 27%). Clinical laboratory tests were done on admission (33 studies, 73%), post-admission (5 studies, 11%) and at unspecified periods (7 studies, 16%). The highest number of laboratory parameters

Table 1. Characteristics of included studies.

Study	Study characteristics	Patient characteristics	[a]Risk of Bias
[e]Cai *et al.* [44]	**Hospital(s):** Third people's Hospital of Shenzhen	**Number of non-severe COVID-19 cases:** 240	**Low**
		Number of severe/critical COVID-19 cases: 58	
	Location(s): Shenzhen, China	[b]**Age:** 47 (33–61) years, **Males:** 149/298 (50.0%), **Hypertension:** 38/298 (12.8%), **Diabetes:** 19/298 (6.4%), **Cancer:** 4/298 (1.4%)	
	Study period: 11 Jan 2020–6 Feb 2020		
	Sample size: 298		
Cao Min *et al.* [45]	**Hospital(s):** Shanghai Public Health Clinical Centre	**Number of non-severe COVID-19 cases:** 179	**Low**
		Number of severe/critical COVID-19 cases: 19	
	Location(s): Shanghai, China	[d]**Age:** 50.1 (16.3) years, **Males:** 101/198 (51.0%), **Hypertension:** 42/198 (21.2%), **Diabetes:** 15/198 (7.6%), **Cancer:** 4/198 (2.0%)	
	Study period: x Jan 2020—x Feb 2020		
	Sample size: 198		
Cao Weiliang *et al.* [46]	**Hospital(s):** Xiangyang No.1 Hospital	**Number of non-severe COVID-19 cases:** 107	**High**
	Location(s): Xiangyang, China	**Number of severe/critical COVID-19 cases:** 21	
	Study period: 1 Jan 2020–16 Feb 2020	**Age:** >65 years = 24 (18.8%), **Males:** 60/128 (46.9%), **Hypertension:** NR, **Diabetes:** NR, **Cancer:** NR	
	Sample size: 128		
Chen Dong *et al.* [47]	**Hospital(s):** Wenzhou Central Hospital, 6th People's Hospital of Wenzhou	**Number of moderate/non-severe COVID-19 cases:** 135	**Low**
		Number of severe/critical COVID-19 cases: 40	
	Location(s): Wenzhou, Zhejiang Province, China	[b]**Age:** 46 (34–54) years, **Males:** 83/175 (47.4%), **Hypertension:** 28/175 (16.0%), **Diabetes:** 12/175 (6.8%), **Cancer:** NR	
	Study period: 11 Jan 2020–15 Feb 2020		
	Sample size: 175		
[f]Chen Guang *et al.* [48]	**Hospital(s):** Tongji Hospital	**Number of non-severe COVID-19 cases:** 10	**Medium**
	Location(s): Wuhan, China	**Number of severe/critical COVID-19 cases:** 11	
	Study period: late Dec 2019–27 Jan 2020	[b]**Age:** 56 (50–65) years, **Males:** 17/21 (81.0%), **Hypertension:** 5/21 (23.8%), **Diabetes:** 3/21 (14.3%), **Cancer:** NR	
	Sample size: 21		
Chen Meizhu *et al.* [49]	**Hospital(s):** Fifth Affiliated Hospital of Sun Yat-sen University	**Number of moderate/non-severe COVID-19 cases:** 71	**Low**
		Number of severe/critical COVID-19 cases: 26	
	Location(s): Zhuhai, China	[d]**Age:** 47.5(15–80) years, **Males:** 42/97 (43.3%), **Hypertension:** 16/97 (16.5%), **Diabetes:** 6/97 (6.2%), **Cancer:** 6/97 (6.2%)	
	Study period: 17 Jan 2020–10 March 2020		
	Sample size: 97		
Dai *et al.* [32]	**Hospital(s):** Hospitals in Hunan Province	**Number of non-severe COVID-19 cases:** 77	**High**
	Location(s): Hunan province	**Number of severe/critical COVID-19 cases:** 841	
	Study period: 21 Jan 2020 to 13 Feb 2020	[c]**Age:** 44.73 (16.0) years, **Males:** 479/918 (52.18%), **Hypertension:** NR, **Diabetes:** NR, **Cancer:** NR	
	Sample size: 918		
Fang *et al.* [50]	**Hospital(s):** Anhui Provincial Hospital	**Number of non-severe COVID-19 cases:** 55	**Low**
	Location(s): Anhui province	**Number of severe/critical COVID-19 cases:** 24	
	Study period: 22 Jan 2020–18 Feb 2020	[c]**Age:** 45.1 (16.6) years, **Males:** 45/79 (57.0%)	
	Sample size: 79	**Hypertension:** 16/79 (20.3%), **Diabetes:** 8/79 (14.5%), **Cancer:** 1/79 (1.3%)	
Gong *et al.* [51]	**Hospital(s):** Guangzhou Eighth People's Hospital, Zhongnan Hospital of Wuhan University and the Third Affiliated Hospital of Sun Yat-sen University, but 189 used in the analysis come only from Guangzhou Eighth People's Hospital	**Number of non-severe COVID-19 cases:** 161	**Low**
		Number of severe/critical COVID-19 cases: 28	
		[b]**Age:** 49.0 (35.0–63.0) years	
		Males: 88/189 (46.6%)	
	Location(s): Ghaungzhou and Wuhan, but 189 only from Ghaungzhou	**Proportion with at least one severe disease (Hypertension, Diabetes, Cardiovascular disease, Chronic Respiratory Disease, Tuberculosis):** 55/189 (29.1%)	
	Study period: 20 Jan 2020–2 Mar 2020		
	Sample size: 189		

(*Continued*)

Table 1. (Continued)

Study	Study characteristics	Patient characteristics	[a]Risk of Bias
Goyal *et al.* [52]	**Hospital(s):** New York-Presbyterian Hospital's Weill Cornell Medical Center and Lower Manhattan Hospitals	**Number of non-severe COVID-19 cases:** 263	**Low**
		Number of severe/critical COVID-19 cases: 130	
	Location(s): New York, USA	[b]**Age:** 62.2 (48.6–73.7) years, **Males:** 238/393 (60.6%), **Hypertension:** 197/393 (50.1%), **Diabetes:** 99/393 (25.2%), **Cancer:** 23/393 (5.9%).	
	Study period: 5 March 2020–27 March 2020		
	Sample size: 393		
[g]Guan *et al.* [13]	**Hospital(s):** 552 sites across china with largest number from Wuhan Jinyintan Hospital (132)	**Number of non-severe COVID-19 cases:** 926	**Medium**
		Number of severe/critical COVID-19 cases: 173	
		[b]**Age:** 47 (35–58) years	
		Males: 637/1096 (58.1%)	
	Location(s): Multiple cities, China	**Hypertension:** 165/1099 (15%), **Diabetes:** 81/1099 (7.4%)	
	Study period: 11 Dec 2020–29 Jan 2020	**Cancer:** 10/1099 (0.9%)	
	Sample size: 1099		
[h]Han *et al.* [53]	**Hospital(s):** Renmin Hospital of Wuhan University	**Number of non-severe COVID-19 cases:** 23	**Low**
		Number of severe/critical COVID-19 cases: 24	
	Location(s): Wuhan, China	[b]**Age:** 64.91 (31–87) years, **Males:** 26/47 (55.31%), **Hypertension:** 18/47 (38.30%), **Diabetes:** 7/47 (14.89%), **Cancer:** NR	
	Study period: 1 Feb 2020–18 Feb 2020		
	Sample size: 47		
Herold *et al.* [14]	**Hospital(s):** University Hospital, Ludwig Maximilian University of Munich	**Number of non-severe COVID-19 cases:** 27	**Low**
		Number of severe/critical COVID-19 cases: 13	
	Location(s): Munich, Germany	[b]**Age:** 57 (19–81) years, **Males:** 29/40 (72%), **Hypertension:** 19/36 (53%), **Diabetes:** 3/37 (8%), **Cancer:** NR	
	Study period: 29 Feb 2020–27 Mar 2020		
	Sample size: 40		
Hu *et al.* [54]	**Hospital(s):** Tianyou Hospital	**Number of non-severe COVID-19 cases:** 151	**Medium**
		Number of severe/critical COVID-19 cases: 172	
	Location(s): Wuhan	[d]**Age:** 61 (23–91) years, **Males:** 166/323 (51.4%), **Hypertension:** 105/323 (32.5%), **Diabetes:** 47/323 (14.6%), **Cancer:** 5/323 (1.5%)	
	Study period: 8 Jan 2020–20 Feb 2020		
	Sample size: 323		
Lescure *et al.* [55]	**Hospital(s):** Bichat-Claude Bernard University Hospital and Pellegrin University Hospital	**Number of non-severe COVID-19 cases:** 2	**Low**
		Number of severe/critical COVID-19 cases: 3	
		[b]**Age:** 46 (30–80) years	
		Males: 3/5 (60.0%), **Hypertension:** 1/5 (20%)	
	Location(s): Paris and Bordeaux, France	**Diabetes:** 0 (0%), **Cancer:** 1/5 (20%)	
	Study period: 23 Jan 2020–14 Feb 2020		
	Sample size: 5		
Liu Chuan *et al.* [56]	**Hospital(s):** Lanzhou University First Hospital, Shenyang Sixth People's Hospital, Ankang Central Hospital, Lishui Central Hospital, Zhenjiang Third People's Hospital, Baoding People's Hospital, Linxiazhou People's Hospital	**Number of non-severe COVID-19 cases:** 28	**High**
		Number of severe/critical COVID-19 cases: 4	
		[b]**Age:** 38.5 (26.25–45.75) years	
		Males: 20/32 (62.5%)	
		Hypertension: 1/32 (3.1%)	
		Diabetes: NR	
	Location(s): Lanzhou, Shanghai, Ankang, Lishui, Zhenjiang, Baoding and Linxia. China	**Cancer:** 2/32 (6.25%)	
	Study period: 23 Jan 2020–8 Feb 2020		
	Sample size: 32		

(*Continued*)

Table 1. (Continued)

Study	Study characteristics	Patient characteristics	[a]Risk of Bias
Liu Jingyuan *et al.* [30]	**Hospital(s):** Beijing Ditan Hospital	**Number of non-severe COVID-19 cases:** 44	**Low**
	Location(s): Beijing, China	**Number of severe/critical COVID-19 cases:** 17	
	Study period: 13 Jan 2020–31 Jan 2020	[d]**Age:** [non-severe: 41.00 (1.0–76.0) years, severe: 56.00 (34.0–73.0)] years	
	Sample size: 61	**Males:** 31/61 (50.8%), **Hypertension:** 12/61 (19.7%), **Diabetes:** 5/61 (8.2%), **Cancer:** NR	
Liu Min *et al.* [57]	**Hospital(s):** Affiliated hospital of Jianghan University	**Number of non-severe COVID-19 cases:** 26	**Medium**
		Number of severe/critical COVID-19 cases: 4	
	Location(s): Wuhan, China	[c]**Age:** 35.0 (8) years	
	Study period: Jan 2020	**Males:** 10/30 (33.3%), **Hypertension:** NR, **Diabetes:** NR, **Cancer:** NR	
	Sample size: 30		
[i]Liu Tao *et al.* [58]	**Hospital(s):** Union Hospital	**Number of non-severe COVID-19 cases:** 11	**Medium**
	Location(s): Wuhan, China	**Number of severe/critical COVID-19 cases:** 69	
	Study period: 21 Jan 2020–16 Feb 2020	[b]**Age:** 53.00 (26.0–86.0) years, **Males:** 34/80 (42.50%), **Hypertension:** 14/80 (17.50%), **Diabetes:** 11/80 (13.75%), **Cancer:** 7/80 (8.75%)	
	Sample size: 80		
[j]Liu Yanli *et al.* [59]	**Hospital(s):** Central Hospital of Wuhan	**Number of non-severe COVID-19 cases:** 56	**Medium**
	Location(s): Wuhan, China	**Number of severe/critical COVID-19 cases:** 53	
	Study period: 2 Jan 2020–1 Feb 2020	[b]**Age:** 55.0 (43.0–66.0) years	
	Sample size: 109	**Males:** 59/109 (54.1%)	
		Hypertension: 37/109 (33.9%)	
		Diabetes: 12/109 (11.0%)	
		Cancer: NR	
Liu Min *et al.* [57]	**Hospital(s):** Affiliated hospital of Jianghan University	**Number of non-severe COVID-19 cases:** 26	**Medium**
		Number of severe/critical COVID-19 cases: 4	
	Location(s): Wuhan, China	[c]**Age:** 35.0 (8) years	
	Study period: Jan 2020	**Males:** 10/30 (33.3%), **Hypertension:** NR, **Diabetes:** NR, **Cancer:** NR	
	Sample size: 30		
[h]Luo *et al.* [60]	**Hospital(s):** Renmin Hospital of Wuhan University	**Number of non-severe COVID-19 cases:** 141	**Low**
		Number of severe/critical COVID-19 cases: 157	
		[b]**Age:** 57.0 (40.0–69.0) years	
	Location(s): Wuhan, China	**Males:** 150/298 (50.3%), **Hypertension:** 86/298 (28.9%), **Diabetes:** 45/298 (15.1%)	
	Study period: 30 Jan 2020–20 Feb 2020		
	Sample size: 298	**Cancer:** NR	
Petrilli *et al.* [61]	**Hospital(s):** NYU Langone Health	**Number of non-severe COVID-19 cases:** 932	**Low**
	Location(s): New York, USA	**Number of severe/critical COVID-19 cases:** 650	
	Study period: 1 March 2020–2 April 2020	[b]**Age:** [non-severe: 58.0(46–71.0) years, severe: 67.0 (56–77.0) years]	
	Sample size: 1582	**Males:** [non-severe: 560/932 (60.1%), severe: 442/650 (68%)]	
		Hypertension: [non-severe: 320/932 (34.3%), severe: 257/650 (39.5%)]	
		Diabetes: [non-severe: 213/932 (22.9%), severe: 176/650 (27.1%)]	
		Cancer: [non-severe: 54/932 (5.8%), severe: 56/650 (8.6%)]	

(*Continued*)

Table 1. (Continued)

Study	Study characteristics	Patient characteristics	[a]Risk of Bias
Qian *et al.* [62]	**Hospital(s):** Five hospitals in Zhejiang province	**Number of non-severe COVID-19 cases:** 82	**Medium**
		Number of severe/critical COVID-19 cases: 9	
	Location(s): Zhejiang province, China	[b]**Age:** 50.0 (36.50–57.0) years	
	Study period: 20 Jan 2020–11 Feb 2020	**Males:** 37/91 (40.66%)	
	Sample size: 91	**Hypertension:** 15/91 (16.48%)	
		Diabetes: 8/91 (8.79%), **Cancer:** NR	
[f]Qin *et al.* [63]	**Hospital(s):** Tongji Hospital	**Number of non-severe COVID-19 cases:** 166	**Low**
	Location(s): Wuhan, China	**Number of severe/critical COVID-19 cases:** 286	
		[b]**Age:** 58.0 (47.0–67.0) years	
	Study period: 10 Jan 2020–12 Feb 2020	**Males:** 235/452 (52%), **Hypertension:** 135/452 (29.50%), **Diabetes:** 75/452 (16.4%), **Cancer:** 14/452 (3.1%)	
	Sample size: 452		
Qu *et al.* [64]	**Hospital(s):** Huizhou Municipal Central Hospital	**Number of non-severe COVID-19 cases:** 27	**Low**
		Number of severe/critical COVID-19 cases: 3	
		[b]**Age:** 50.5 (36.0–65.0) years, **Males:** 16/30 (53.3%)	
	Location(s): Huizhou, China	**Hypertension:** NR, **Diabetes:** NR, **Cancer:** NR	
	Study period: Jan 2020—Feb 2020		
	Sample size: 30		
Tabata *et al.* [16]	**Hospital(s):** Self-Defense Forces Central Hospital	**Number of non-severe COVID-19 cases:** 78	**Low**
		Number of severe/critical COVID-19 cases: 28	
	Location(s): Tokyo, Japan	[b]**Age:** 68.0 (46.75–75.0) years	
	Study period: 11 Feb 2020–25 Feb 2020	**Males:** 47/104 (45.2%), **Hypertension:** NR, **Diabetes:** 7/104 (7.7%)	
	Sample size: 104	**Cancer:** 4/104 (3.8%)	
Wan *et al.* [65]	**Hospital(s):** Chongqing University Three Gorges Hospital	**Number of non-severe COVID-19 cases:** 95	**Low**
		Number of severe/critical COVID-19 cases: 40	
	Location(s): Chongqing, China	[b]**Age:** 47.0 (36.0–55.0) years, **Males:** 72/135 (53.3%), **Hypertension:** 13/135 (9.6%), **Diabetes:** 12/135 (8.9%)	
	Study period: 23 Jan 2020–8 Feb 2020	**Cancer:** 4/135 (3.0%)	
	Sample size: 135		
[i]Wang *et al.* [66]	**Hospital(s):** Union Hospital	**Number of non-severe COVID-19 cases:** 55	**Low**
	Location(s): Wuhan, China	**Number of severe/critical COVID-19 cases:** 14	
	Study period: 16 Jan 2020–29 Jan 2020	[b]**Age:** 42.0 (35.0–62.0) years	
	Sample size: 69	**Males:** 32/69 (46%), **Hypertension:** 9/69 (13%), **Diabetes:** 7/69 (10%)	
		Cancer: 4/69 (6%)	
Wu Chaomin *et al.* [67]	**Hospital(s):** Jinyintan Hospital	**Number of non-severe COVID-19 cases:** 117	**Low**
	Location(s): Wuhan, China	**Number of severe/critical COVID-19 cases:** 84	
	Study period: 25 Dec 2019–26 Jan 2020	[b]**Age:** 51.0 (43.0–60.0) years	
	Sample size: 201	**Males:** 128/201 (63.7%), **Hypertension:** 39/201 (19.4%), **Diabetes:** 22/201 (10.9%), **Cancer:** 1/201 (0.5%)	

(*Continued*)

Table 1. (Continued)

Study	Study characteristics	Patient characteristics	[a]Risk of Bias
Wu Jian *et al.* [68]	**Hospital(s):** First People's Hospital of Yancheng City, the Second People's Hospital of Fuyang City, the Second People's Hospital of Yancheng City, and the Fifth People's Hospital of Wuxi.	**Number of non-severe COVID-19 cases:** 197	**Medium**
		Number of severe/critical COVID-19 cases: 83	
		[c]**Age:** 43.12 (19.02) years	
		Males: 151/280 (53.93%)	
		CVD and CeVD: 57/280 (20.36%)	
		ESD: 34/280 (12.14%)	
	Location(s): Yancheng, Fuyang, Wuxi, Jiangsu and Anhui provinces, China	**Cancer:** 5/280 (1.79%)	
	Study period: 20 Jan 2020–19 Feb 2020		
	Sample size: 280		
Xiang Jialin *et al.* [69]	**Hospital(s):** The First Affiliated Hospital of Zunyi Medical University and The Fourth People's Hospital of Zunyi city	**Number of non-severe COVID-19 cases:** 20	**Medium**
		Number of severe/critical COVID-19 cases: 8	
		[c]**Age:** [non-severe: 41.0 (19) years, severe: 66.0 (22) years]	
		Males: 15/28 (53.57%)	
	Location(s): Zunyi, Guizhou Province, China	**Hypertension:** 5/28 (17.86%)	
		Diabetes: 4/28 (14.29%)	
	Study period: 29 Jan 2020–21 Feb 2020	**Cancer:** NR	
	Sample size: 28		
Xiang Tianxin *et al.* [70]	**Hospital(s):** The First Affiliated Hospital of Nanchang University	**Number of non-severe COVID-19 cases:** 40	**Low**
		Number of severe/critical COVID-19 cases: 9	
	Location(s): Jiangxi Province, China	[b]**Age:** 42.9 (18–78) years, **Males:** 33/49 (67.3%), **Hypertension:** 6/49 (12.24%), **Diabetes:** 2/49 (4.1%), **Cancer:** NR	
	Study period: 21 Jan 2020–27 Jan 2020		
	Sample size: 49		
[k]Xu *et al.* [71]	**Hospital(s):** Zhongnan Hospital of Wuhan University, Chinese PLA General Hospital, Peking Union Medical College Hospital, and affiliated hospitals of Shanghai University of Medicine & Health Sciences	**Number of non-severe COVID-19 cases:** 44	**Low**
		Number of severe/critical COVID-19 cases: 25	
		[b]**Age:** 57 (43–69) years	
		Males: 35/69 (50.7%)	
	Location(s): Wuhan, Shanghai, Beijing, China	**Hypertension, Diabetes, Cancer:** Patients with comorbidities are excluded	
	Study period: 7 Feb 2020–28 Feb 2020		
	Sample size: 69		
Yan *et al.* [72]	**Hospital(s):** Hospitals in Hainan	**Number of non-severe COVID-19 cases:** 132	**Medium**
	Location(s): Hainan, China	**Number of severe/critical COVID-19 cases:** 36	
	Study period: 22 Jan 2020–13 Mar 2020	[b]**Age:** 51 (36–62) years, **Males:** 81/168 (48.2%), **Hypertension:** 24/168 (14.3%)	
	Sample size: 168	**Diabetes:** 12/168 (17.1%), **Cancer:** 2/168 (1.2%)	
[l]Yuan *et al.* [73]	**Hospital(s):** Chongqing Public Health Center for Medical Treatment	**Number of non-severe COVID-19 cases:** 192	**Low**
		Number of severe/critical COVID-19 cases: 31	
	Location(s): Chongqing, China	[c]**Age:** 46.5 (16.1) years	
	Study period: 24 Jan 2020–23 Feb 2020	**Males:** 105/223 (47.09%), **Hypertension:** 25/223 (11.21%)	
	Sample size: 223	**Diabetes:** 18/223 (8.07%)	
		Cancer: NR	

(*Continued*)

Table 1. (Continued)

Study	Study characteristics	Patient characteristics	[a]Risk of Bias
Young *et al.* [74]	**Hospital(s):** National Centre for Infectious Diseases, Singapore General Hospital, Changi General Hospital, Sengkang General Hospital	**Number of non-severe COVID-19 cases:** 12	**Medium**
		Number of severe/critical COVID-19 cases: 6	
		[d]**Age:** 47 (31–73) years, **Males:** 9/18 (50%), **Hypertension:** 4/18 (22.22%)	
	Location(s): Singapore	**Diabetes:** 1/18 (5.56%), **Cancer:** NR	
	Study period: 23 Jan—3 Feb		
	Sample size: 18		
[e]Zeng *et al.* [75]	**Hospital(s):** Shenzhen Third People's hospital	**Number of non-severe COVID-19 cases:** 262	**Low**
		Number of severe/critical COVID-19 cases: 76	
	Location(s): Shenzhen, China	[c]**Age:** 49.0 (14.5) years	
	Study period: 11 Jan 2020–28 Feb 2020	**Males:** 162/338 (47.9%), **Hypertension:** 51/338 (15.1%), **Diabetes:** 25/338 (7.4%), **Cancer:** 2/338 (0.6%)	
	Sample size: 338		
Zhang Gemin *et al.* [76]	**Hospital(s):** Xinzhou District People's Hospital	**Number of non-severe COVID-19 cases:** 63	**Medium**
		Number of severe/critical COVID-19 cases: 32	
		[d]**Age:** 49.0 (39.0–58.0) years	
	Location(s): Xinzhou District, Wuhan, China	**Males:** 53/95 (55.8%), **Hypertension:** NR, **Diabetes:** NR	
	Study period: 16 Jan 2020–25 Feb 2020	**Cancer:** NR	
	Sample size: 95		
[k]Zhang Guqin *et al.* [77]	**Hospital(s):** Zhongnan Hospital of Wuhan University	**Number of non-severe COVID-19 cases:** 166	**Low**
		Number of severe/critical COVID-19 cases: 55	
		[b]**Age:** 55.0 (39.0–66.5) years	
	Location(s): Wuhan, China	**Males:** 108/221 (48.9%), **Hypertension:** 54/221 (24.4%), **Diabetes:** 22/221 (10%), **Cancer:** 9/221 (4.1%)	
	Study period: 2 Jan 2020–10 Feb 2020		
	Sample size: 221		
[l]Zhang Huizheng *et al.* [78]	**Hospital(s):** Chongqing Public Health Medical Center	**Number of non-severe COVID-19 cases:** 29	**Medium**
		Number of severe/critical COVID-19 cases: 14	
	Location(s): Chongqing, China	[c]**Age:** [non-severe: 44.34 (15.84) years, severe: 61.70 (9.22) years]	
	Study period: 11 Feb 2020–28 Feb 2020	**Males:** 22/43 (51.2%), **Hypertension:** 4/43 (9.3%), **Diabetes:** 6/43 (14%)	
	Sample size: 43		
		Cancer: NR	
Zhang Jin-jin *et al.* [79]	**Hospital(s):** No. 7 Hospital of Wuhan	**Number of non-severe COVID-19 cases:** 82	**Medium**
	Location(s): Wuhan, China	**Number of severe/critical COVID-19 cases:** 58	
	Study period: 15 Jan 2020–3 Feb 2020	[b]**Age:** 57.00 (25.00–87) years	
	Sample size: 140	**Males:** 71/140 (50.7%), **Hypertension:** 42/140 (30%), **Diabetes:** 17/140 (12.1%), **Cancer:** NR	
Zhao *et al.* [80]	**Hospital(s):** Beijing YouAn Hospital	**Number of non-severe COVID-19 cases:** 57	**Low**
	Location(s): Beijing, China	**Number of severe/critical COVID-19 cases:** 20	
	Study period: 21 Jan 2020–8 Feb 2020	[c]**Age:** 52.0 (20.0) years	
	Sample size: 77	**Males:** 34/77 (44.2%), **Hypertension:** 16/77 (20.8%), **Diabetes:** 6/77 (7.8%), **Cancer:** 4/77 (5.2%)	

(*Continued*)

Table 1. (Continued)

Study	Study characteristics	Patient characteristics	[a]Risk of Bias
Zheng *et al.* [37]	**Hospital(s):** The First Affiliated Hospital of Anhui Medical University and Fuyang second people's Hospital	**Number of non-severe COVID-19 cases:** 55	**Medium**
		Number of severe/critical COVID-19 cases: 13	
		[d]**Age:** 47.13 (11–84) years	
		Males: 36/68 (52.9%)	
	Location(s): Hefei, Fuyang, China	**Hypertension:** NR	
		Diabetes: NR	
	Study period: NR	**Cancer:** NR	
	Sample size: 68		
[j]Zhou *et al.* [81]	**Hospital(s):** Central Hospital Wuhan	**Number of non-severe COVID-19 cases:** 260	**Low**
		Number of severe/critical COVID-19 cases: 117	
	Location(s): Wuhan, China	[c]**Age:** [non-severe: 48.35 (16.17) years, severe: 65.63 (14.03) years]	
	Study period: 1 Jan 2020–28 Feb 2020	**Males:** [non-severe: 102/260(39.23%), severe: 68/117 (58.12%)]	
	Sample size: 377	**Hypertension:** [non-severe: 63/260(24.23%), severe: 70/117 (59.83%)]	
		Diabetes: [non-severe: 42/260(16.15%), severe: 42/117 (35.9%)]	
		Cancer: NR	

NR: Not Reported.

Age is reported as

[c]mean (SD) /median(IQR)[b] /median (range)[d].

[a]Overall Risk of Bias by professional judgement and consensus by authors. See S5 Table in S1 File for detailed judgement.

[e]Matched to Shenzhen Third People's hospital; Parameters extracted from Cai et al. were only those not reported by Zeng et al.

[f]Matched to Tongji hospital; Parameters extracted from Chen G et al. were only those not reported by Qin et al.

[g]Multicenter study; possibly overlapping with Wu Chaomin et al. (Jinyintan Hospital).

[h]Matched to Renmin Hospital of Wuhan University; Parameters extracted from Han et al. were only those not reported by Luo et al.

[i]Matched to Union Hospital; Parameters extracted from Wang et al. were only those not reported by Liu Tao et al.

[j]Matched to Central Hospital Wuhan; Parameters extracted from Zhou et al. were only those not reported by Liu Yanli et al.

[k]Matched to Zhongnan Hospital of Wuhan, however data collected over different periods.

[l]Matched to Chongqing Public Health Medical Center; Parameters extracted from Zhang et al. were only those not reported by Yuan et al.

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reported in a single study was 30 [31] and the lowest number of laboratory parameters reported in a single study was 2 [32].

The median (or mean) age of patients in the included studies ranged from 35 years to 67 years, and the proportion of male patients ranged from 30% to 81%. Patients in the included studies had varying proportions of comorbidities such as hypertension, diabetes and cancer as detailed in Table 1 (and S3 Table in S1 File).

Synthesis of results

Results of meta-analyses are reported in Table 2, and Forest plots and Leave-One-Out analysis are displayed in S4 Fig in S1 File.

As pertains to haematological parameters, the majority of studies reported higher white cell count and higher neutrophil count in severe or critical COVID-19 patients relative to non-severe COVID-19 patients. Median difference in individual studies ranged from -1.6 to 7.3 ($\times 10^9$ cells/L) for white cell count and from -1.0 to 5.2 ($\times 10^9$ cells/L) for neutrophil count. The MMD estimates (10^9 cells/L) were 0.87 (95% CI: 0.35 to 1.40; I^2: 80.5%) for white cell count and 1.23 (95% CI 0.58 to 1.88; I^2: 90%) for neutrophil count. When the results were expressed in terms of ratio measures, patients with severe or critical COVID-19 had significantly higher

Table 2. Meta-estimates for severe or critical COVID-19 compared to non-severe COVID-19.

Parameter	Number of studies	Number of persons	Meta estimate (95% CI)	*p* value	Prediction interval	I^2	Q test p-value
Hematological parameters							
White cell count							
Continuous, MMD ($\times 10^9$/L)	28	4749	0.87 (0.35, 1.40)	0.001	-1.54, 3.30	80.5%	<0.001
Without outlier studies	*23*		*0.72 (0.36, 1.07)*	*<0.001*	*-0.46, 1.89*	*45.8%*	*0.009*
Leukocytosis, MPR	11	3455	3.95 (2.35, 6.65)	<0.001	0.86, 18.22	64.3%	0.002
Without outlier studies	*10*		*3.21 (2.13, 4.82)*	*<0.001*	*1.18, 8.65*	*41.5%*	*0.081*
Neutrophils							
Continuous, MMD ($\times 10^9$/L)	21	3091	1.23 (0.58, 1.88)	0.001	-1.59, 4.05	89.9%	<0.001
Without outlier studies	*19*		*1.07 (0.71, 1.44)*	*<0.001*	*-0.04, 2.18*	*46.0%*	*0.015*
Neutrophilia, MPR	6	1237	4.29 (1.74, 10.64)	0.002	0.22, 84.80	85.6%	<0.001
Lymphocytes							
Continuous, MMD ($\times 10^9$/L)	27	6465	-0.38 (-0.46, -0.30)	<0.001	-0.77, 0.01	84.0%	<0.001
Without outlier studies	*24*		*-0.38 (-0.45, -0.31)*	*<0.001*	*-0.64, -0.12*	*57.3%*	*0.001*
Lymphocytopenia, MPR	14	3875	1.74 (1.43, 2.12)	<0.001	0.88, 3.42	92.5%	<0.001
Without outlier studies	*9*		*1.85 (1.47, 2.33)*	*<0.001*	*0.97, 3.56*	*64.0%*	*0.005*
Monocytes							
Continuous, MMD ($\times 10^9$/L)	14	2002	-0.03 (-0.06, 0.01)	0.102	-0.14, 0.08	57.2%	0.004
Without outlier studies	*13*		*-0.02 (-0.05, 0.01)*	*0.188*	*-0.11, 0.06*	*44.6%*	*0.041*
Platelets							
Continuous, MMD ($\times 10^9$/L)	24	3877	-21.47 (-41.12, -1.83)	0.032	-114.89, 71.94	92.0%	<0.001
Without outlier studies	*23*		*-18.95 (-28.52, -9.39)*	*<0.001*	*-50.30, 12.38*	*47.9%*	*0.006*
Thrombocytopenia, MPR	10	2421	1.79 (1.30, 2.48)	<0.001	0.81, 3.98	48.4%	0.042
Hemoglobin							
Continuous, MMD (g/dl)	17	2931	-0.33 (-0.57, -0.08)	0.010	-0.95, 0.30	32.5%	0.096
Without outlier studies	*16*		*-0.31 (-0.53, -0.09)*	*0.005*	*-0.79, 0.17*	*21.2%*	*0.212*
CD3 count							
Continuous, MMD (cells/μl)	6	601	-380.82 (-515.30, -246.36)	<0.001	-835.46, 73.80	80.1%	<0.001
CD4 count							
Continuous, MMD (cells/μl)	7	669	-204.86(-302.63, -107.10)	<0.001	-539.07, 129.35	86.8%	<0.001
CD8 count							
Continuous, MMD (cells/μl)	6	600	-123.63 (-170.64,– 76.61)	<0.001	-270.44, 23.19	66.2%	0.011
NLR							
Continuous, MMD	5	1377	2.71 (1.82, 3.61)	<0.001	-0.44, 5.87)	79.7%	<0.001
SII							
Continuous, MMD	2	487	394.00 (38.11, 749.87)	0.030	-	84.6%	0.010
Infection/inflammation-related indices							
C-reactive protein (CRP)							
Continuous, MMD (mg/L)	26	4959	38.62 (29.16, 48.07)	<0.001	-6.01, 83.23	88.4%	<0.001
Without outlier studies	*21*		*36.95 (29.30, 44.60)*	*<0.001*	*9.36, 64.53*	*59.8%*	*<0.001*
Elevated CRP, MPR	13	2740	1.60 (1.32, 1.93)	<0.001	0.78, 3.27	93.4%	<0.001
Without outlier studies	*11*		*1.59 (1.42, 1.77)*	*<0.001*	*1.18, 2.13*	*53.9%*	*0.021*
Erythrocyte sedimentation rate (ESR)							
Continuous, MMD (mm/hr)	8	1705	20.01 (10.14, 29.87)	<0.001	-13.27, 53.28	86.4%	<0.001
Without outlier studies	*7*		*15.4 (7.14, 23.73)*	*<0.001*	*-11.09, 41.96*	*79.4%*	*<0.001*
Elevated ESR, MPR	3	545	1.67 (0.67, 4.17)	0.271	0.00, >100	97.9%	<0.001
Interleukin-6 (IL6)							

(*Continued*)

Table 2. (Continued)

Parameter	Number of studies	Number of persons	Meta estimate (95% CI)	*p* value	Prediction interval	I^2	Q test p-value
Continuous, MMD (pg/ml)	7	1183	17.37 (4.74, 30.00)	0.007	-24.70, 59.56	94.7%	<0.001
Without outlier studies	*6*		*20.61 (9.88, 31.33)*	*<0.001*	*-13.45, 54.67*	*81.4%*	*<0.001*
Elevated IL6, MPR	3	357	2.15 (0.94, 5.00)	0.067	0.00, >100	87.4%	<0.001
Without outlier studies	*2*		*1.33 (1.07, 1.66)*	*0.001*	-	*0.0%*	*0.770*
Procalcitonin (PCT)							
Continuous, MMD (ng/ml)	18	4225	0.06 (0.04, 0.08)	<0.001	-0.03, 0.15	89.5%	<0.001
Without outlier studies	*13*		*0.05 (0.04, 0.06)*	*<0.001*	*0.03, 0.07*	*9.8%*	*0.348*
Elevated PCT, MPR	12	2311	2.48 (1.78, 3.43)	<0.001	0.99, 6.19	53.6%	0.014
Liver function parameters							
Alanine aminotransferase (ALT)							
Continuous, MMD (U/L)	25	4450	6.53 (4.43, 8.93)	<0.001	1.09, 11.97	25.4%	0.122
Without outlier studies	*21*		*5.21 (3.68, 6.73)*	*<0.001*	*3.59, 6.82*	*0.0%*	*0.754*
Elevated ALT, MPR	12	2540	1.59 (1.36, 1.87)	<0.001	1.21, 2.09	10.3%	0.344
Aspartate aminotransferase (AST)							
Continuous, MMD (U/L)	25	4320	11.95 (8.80, 15.11)	<0.001	-0.04, 23.95	68.8%	<0.001
Without outlier studies	*22*		*10.63 (7.06, 14.19)*	*<0.001*	*7.06, 14.19*	*11.8%*	*0.302*
Elevated AST, MPR	14	2705	2.14 (1.80, 2.54)	<0.001	1.43, 3.21	29.5%	0.141
Total bilirubin							
Continuous, MMD (μmol/l)	18	2104	1.62 (0.87, 2.37)	<0.001	0.81, 2.43	0.0%	0.490
Hyperbilirubinemia, MPR	5	1704	1.70 (1.23, 2.35)	0.001	1.01, 2.87	0.0%	0.699
Total protein							
Continuous, MMD (g/L)	5	482	-1.49 (-3.19, 0.20)	0.085	-4.24, 1.26	0.0%	0.763
Hypoproteinemia, MPR	2	208	1.65 (1.33, 2.04)	<0.001	-	0.0%	0.658
Albumin							
Continuous, MMD (g/L)	21	2891	-4.58 (-6.21, -2.94)	<0.001	-11.95, 2.79	95.4%	<0.001
Without outlier studies	*19*		*-4.27 (-5.21, -3.33)*	*<0.001*	*-7.69, -0.85*	*67.9%*	*<0.001*
Hypoalbuminemia, MPR	4	554	2.23 (1.93, 2.93)	<0.001	1.50, 3.77	0.0%	0.726
Prealbumin							
Continuous, MMD (mg/dl)	3	367	-40.14 (-52.95, -27.33)	<0.001	-133.59, 53.31	6.9%	0.342
Globulin							
Continuous, MMD (g/L)	4	476	2.31 (0.58, 4.04)	0.009	-4.61, 9.22	63.2%	0.043
Without outlier studies	*3*		*1.31 (0.30, 2.32)*	*0.011*	*-5.26, 7.88*	*0.0%*	*0.452*
Kidney function parameters							
Blood urea							
Continuous, MMD (mmol/l)	19	2623	1.02 (0.66, 1.38)	<0.001	-0.13, 2.17)	46.1%	0.015
Without outlier studies	*18*		*1.09 (0.76, 1.42)*	*<0.001*	*0.16, 2.02*	*36.1%*	*0.064*
Elevated blood urea, MPR	3	624	3.63 (1.73, 7.65)	<0.001	0.01, >100	39.9%	0.189
Creatinine							
Continuous, MMD (μmol/l)	26	4467	5.57 (3.12, 8.03)	<0.001	-0.43, 11.57	18.7%	0.197
Elevated creatinine, MPR	8	2019	1.90 (1.07, 3.36)	0.027	0.48, 7.43	40.5%	0.108
Cystatin C							
Continuous, MMD (mg/l)	4	426	0.20 (0.10, 0.29)	<0.001	-0.16, 0.55	52.8%	0.095
Myocardial biomarkers							
Creatine kinase muscle-brain							
Continuous, MMD (U/L)	10	1324	1.48 (0.36, 2.59)	0.009	-0.75, 3.71	19.6%	0.263
Continuous, MMD (ng/ml)	3	293	0.67 (0.19, 1.15)	0.007	-2.47, 3.18	0.0%	0.964
Troponin I							

(*Continued*)

Table 2. (Continued)

Parameter	Number of studies	Number of persons	Meta estimate (95% CI)	*p* value	Prediction interval	I^2	Q test p-value
Continuous, MMD (ng/ml)	8	2379	0.02 (0.00, 0.04)	0.038	-0.03, 0.08	79.7%	<0.001
Elevated Troponin I	3	831	4.00 (1.22, 13.2)	0.022	0.00, >100	85.8%	0.001
α-hydroxybutyric dehydrogenase							
Continuous, MMD (U/L)	6	465	89.17 (45.26, 133.08)	<0.001	-46.20, 224.55	67.6%	0.009
Other biochemical parameters							
Glucose							
Continuous, MMD (mmol/L)	7	1343	1.02 (0.64, 1.39)	<0.001	0.20, 1.83	26.8%	0.224
Elevated glucose, MPR	2	491	1.40 (1.15, 1.72)	0.001	-	0.0%	0.411
Cholinesterase							
Continuous, MMD (U/ml)	2	229	-1.11 (-1.79, -0.45)	0.001	-	0.0%	0.941
Lactate dehydrogenase (LDH)							
Continuous, MMD (U/L)	22	2297	122.76 (94.14, 151.39)	<0.001	8.83, 236.70	72.6%	<0.001
Without outlier studies	*20*		*114 (91.60, 138.21)*	*<0.001*	*39.84, 189.97*	*49.6%*	*0.006*
Elevated LDH, MPR	10	1893	2.41 (1.65, 3.51)	<0.001	0.70, 8.34	87.7%	<0.001
Without outlier studies	*8*		*2.35 (1.65, 3.35)*	*<0.001*	*0.77, 7.17*	*85.7%*	*<0.001*
Serum ferritin							
Continuous, MMD (μg/L)	5	2342	430.28 (289.12, 571.45)	<0.001	-5.40, 865.97	61.6%	<0.001
Elevated ferritin, MPR	2	412	2.3 (1.67, 3.17)	<0.001	-	0.0%	0.511
Serum electrolytes							
Sodium							
Continuous, MMD (mmol/L)	10	1503	-1.67 (-2.60, -0.74)	0.001	-3.98, 0.64	43.0%	0.072
Potassium							
Continuous, MMD(mmol/L)	12	1790	-0.19 (-0.30, -0.10)	<0.001	-0.46, 0.07	50.8%	0.022
Reduced potassium, MPR	3	667	1.70 (1.14, 2.54)	0.010	0.02, >100	58.5%	0.090
Chloride							
Continuous, MMD(mmol/L)	6	1074	-1.49 (-3.08, 0.09)	0.065	-6.01, 3.03	57.5%	0.038
Calcium							
Continuous, MMD(mmol/L)	5	486	-0.13 (-0.18, -0.09)	<0.001	-0.26, -0.01	40.8%	0.149
Coagulation parameters							
Prothrombin time							
Continuous, MMD (s)	16	1650	0.39 (0.14, 0.64)	0.002	-0.44, 1.22	68.2%	<0.001
Without outlier studies	*15*		*0.29 (0.09, 0.48)*	*0.004*	*-0.22, 0.79*	*39.4%*	*0.058*
Activated partial thromboplastin							
Continuous, MMD (s)	14	1918	-0.49 (-1.95, 0.97)	0.509	-5.70, 4.72	77.6%	<0.001
Without outlier studies	*12*		*-0.33 (-1.50, 0.83)*	*0.575*	*-3.78, 3.11*	*55.2%*	*0.011*
D-dimer							
Continuous, MMD (mg/L)	23	4740	0.52 (0.37, 0.66)	<0.001	-0.02, 1.05	82.4%	<0.001
Without outlier studies	16		0.36 (0.27, 0.44)	<0.001	0.27, 0.45	0.0%	0.561
Elevated D-Dimer, MPR	9	2030	2.27 (1.67, 3.09)	<0.001	0.87, 5.92	76.9%	<0.001
Without outlier studies	7		2.14 (1.81, 2.52)	<0.001	1.72, 2.65	0.0%	0.435

A study was considered an outlier if the study's confidence interval did not overlap with the confidence interval of the pooled effect.

MMD: meta-median difference; MPR: meta-prevalence ratio; NLR: neutrophil-to-lymphocyte ratio; SII: systemic inflammation Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL-6: interleukin-6,; PCT: procalcitonin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase.

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likelihood of having leucocytosis (MPR: 3.95 [95% CI: 2.35, 6.65], I^2: 64%) and neutrophilia (MPR: 4.29 [95% CI: 1.74, 10.64], I^2: 86%). All but one of 27 studies reported lower lymphocyte

count in severe or critical COVID-19 patients relative to patients with non-severe disease. Median difference in individual studies ranged from -0.8 to 0.2 ($\times 10^9$ cells/L). The MMD for lymphocyte count ($\times 10^9$ cells/L) was -0.39 (95% -0.47, -0.31; I^2: 78%), and the MPR for lymphopenia was 2.02 (95% CI: 1.52, 2.69; I^2: 92%). Also, severe or critical COVID-19 patients had relatively lower CD3 count (MMD: -380.8 [-515.3, -246.4], I^2: 80%), CD4 count (MMD: -204.9 [-302.6, -107.1], I^2: 87%) and CD8 count (MMD: -123.6 [-170.6, -76.6] I^2: 66%); all differences measured in terms of cells/μl.

All studies that examined data on inflammation indices reported higher CRP, ESR and IL-6 level in severely or critically ill patients. Median difference in individual studies ranged from 8.1 to 83.3 mg/L for CRP, from 4.7 to 52.4 mm/hr for ESR, and from 1.1 to 101.4 pg/ml for IL-6. The corresponding MMD (95% CI; I^2) estimates were 36.97 (27.58, 46.35; 85%), 21.93 (10.59, 33.28; 88% for ESR, and 17.37 (4.74, 30.00; 95%) for IL-6. The MPR values for elevated CRP, ESR and IL-6 were 1.50 [95% CI: 1.26, 1.77; I2: 91%), 1.67 (95% CI: 0.67, 4.18; I^2: 98%) and 2.15 (95% CI: 0.95, 4.90; I^2: 87%), respectively, although the data for the last two parameters were limited to just three studies. Higher levels of ferritin, a positive acute-phase reactant, were positively associated with severe or critical COVID-19 (MMD: 451.86 μg/L [95% CI: 212.91, 690.82] I^2: 71%), whereas the same association with albumin, a negative acute-phase reactant, was in the opposite direction (MMD: -4.99 g/L [95% CI: -6.47, -3.51], I^2: 87%).

Additional significant differences between patients with severe or critical COVID-19 and their non-severely ill counterparts were observed for liver enzymes, ALT (MMD: 6.89 U/L [95% CI; 4.69, 9.10], I^2: 17%) and AST (MMD: 11.96 U/L [95% CI: 8.56, 15.37] I^2: 68%); kidney function parameters, urea (MMD: 1.04 mmol/l [95% CI: 0.64, 1.45], I^2: 48%) and creatinine (MMD: 4.87 μmol/l [95% CI: 2.40, 7.35], I^2: 7%); biomarkers of myocardial function, troponin I (MMD: 0.01 ng/ml [95% CI: 0.00, 0.02], I^2: 0%) and CK-MB (MMD: 1.46 U/L [95% CI:0.22, 2.70], I^2: 28%); measures of coagulation, D-dimer (MMD: 0.65 mg/ml [95% CI: 0.45, 0.85], I^2: 84%) and platelet count (MMD: -21.48 $\times 10^9$ cells/L [95% CI: -41.12, -1.83], I^2: 92%); and lactate dehydrogenase, a marker of tissue damage (MMD: 124.26 U/L [95% CI: 92.89, 155.64], I^2: 74%).

Assessment of threats to validity

The threats to validity in this meta-analysis fall into two broad categories: risk of bias in individual studies, and publication bias across the body of literature. Assessments of these two categories of threat to validity are presented below.

Using the NIH study quality assessment tools, 28 studies (62.2%) were rated as having a low risk of bias, 14 studies (31.1%) were rated as having a medium risk of bias, and 3 studies (6.7%) were rated as having a high risk of bias. The majority of studies had a clearly defined study objective (97.8%), a well-defined study population (100%), and had comparable subjects (100%). In contrast, no study provided a sample size calculation or power description. All the studies were rated as having a high risk of bias for the element assessing a temporal sequence between the laboratory measure and disease severity, and none of the reported results was adjusted for potential confounding (Fig 2 and S5 Table in S1 File). Our results did not markedly differ in sensitivity analyses after excluding studies with a high risk of bias.

The symmetry of funnel plots obtained from the 4 laboratory parameters with the highest number of individual studies was assessed using Egger's test. The symmetrical funnel plots for C-reactive protein (p: 0.155) and creatinine (p: 0.415) suggested no evidence of publication bias whereas asymmetrical funnel plot for white cell count (p: 0.004) and lymphocyte count (p: 0.005) indicated significant influence of smaller studies, which may be indicative of publication bias (Fig 3). Important to note that Egger's test may not be robust for C-reactive protein, white cell count and lymphocyte parameters due to substantial heterogeneity (I^2>75%).



Fig 2. Summary plot for risk of bias assessment. A: Risk of bias assessment for 38 retrospective cohort/cross sectional studies; B: Risk of bias assessment for 7 case series studies.

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Additional analysis

In sensitivity analyses excluding outlier studies, statistical heterogeneity was reduced, and the meta-estimate of most laboratory parameters were not markedly altered. In sensitivity analysis using mean differences (S6 Table in S1 File), there was substantial heterogeneity for most laboratory parameters, and the associations observed from using median differences persisted.

Discussion

COVID-19 is a rapidly evolving pandemic with significant global morbidity and mortality. The aim of this meta-analysis was to investigate which clinical laboratory parameters may be associated with severe or critical COVID-19 disease. Out of the 39 clinical laboratory parameters evaluated, we found that derangements in 36 clinical laboratory parameters were

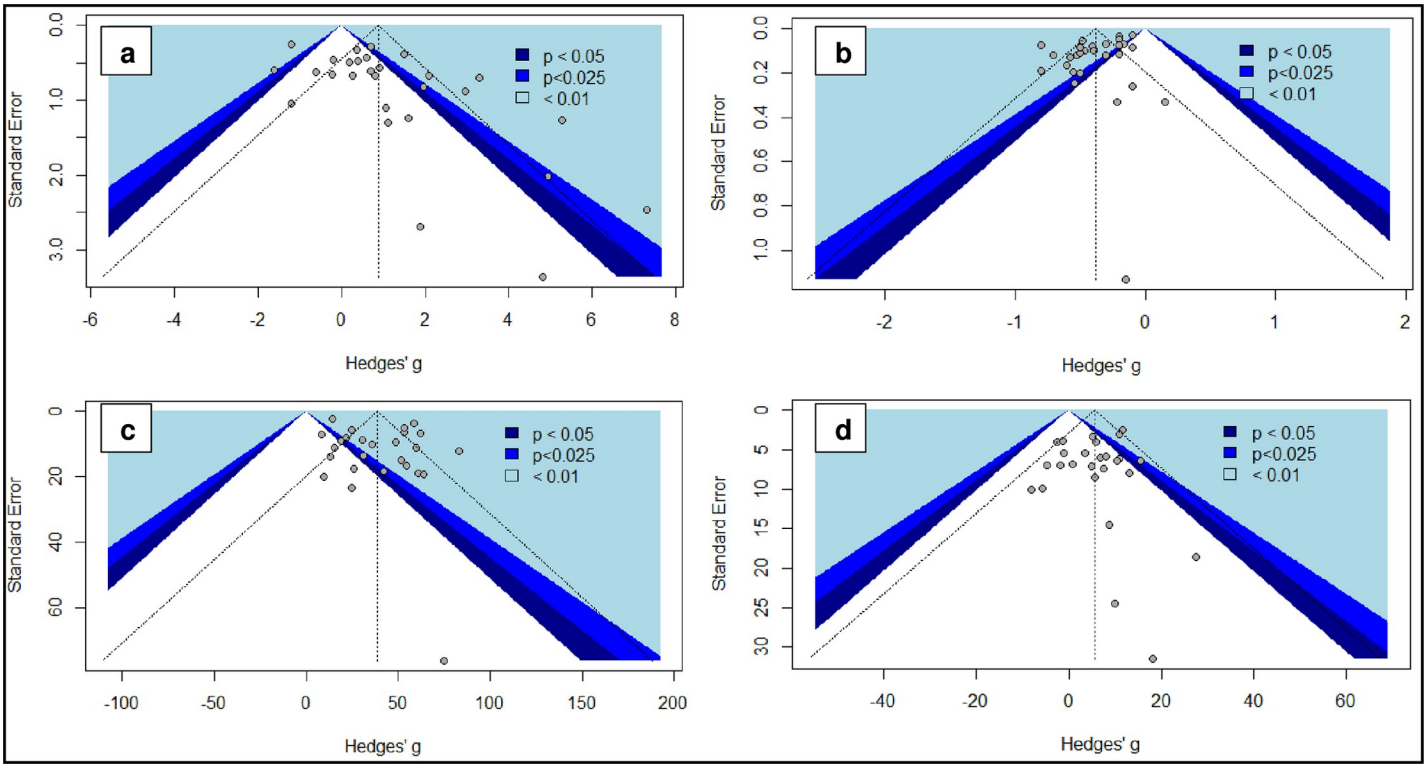


Fig 3. Funnel plots. a: White cell count, Egger's test, p = 0.004; b: Lymphocytes, Egger's test, p = 0.005; c: C-Reactive protein, Egger's test, p = 0.155; d: Creatinine, Egger's test, p = 0.415.

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significantly associated with severe or critical COVID-19. Whilst some of the observed associations may not be clinically relevant, certain, more pronounced laboratory abnormalities may have important clinical implications. Markers of an overactive innate immune system such as markedly elevated neutrophil-to-lymphocyte ratio (NLR), IL-6, serum ferritin and C-reactive protein, and markers of a deficient adaptive immune system such as lymphocytes and CD4 count could help recognise potential severe infections during triage, while markers of organ failure could be helpful in monitoring evolution of hospitalised COVID-19 patients.

Following infection with a virus, the innate immune system in activated. This early response is nonspecific and serves to limit virus multiplication during the acute phase [33]. The adaptive immune system is activated a few days later and is responsible for a more specific response, which is immunomodulatory (via engagement of helper T cells and regulatory T cells) and produces 'immunological memory' [33]. Elevated lymphocyte count is commonly found in most viral infections, and the magnitude and quality of T cell responses may determine the fate of these infections [34, 35]. Failure to mount an appropriate adaptive immune response means the innate immune response remains continuously stimulated with deleterious effects on the lungs and other organs. We found that severe or critical COVID-19 patients had increased markers of innate immune system activity compared to patients with non-severe disease. This is evidenced in the significantly higher levels of neutrophils, IL-6, and acute phase reaction markers such as CRP, ESR and serum ferritin, as well as decreased concentrations of albumin and prealbumin. Severe or critical COVID-19 patients also exhibited defective adaptive immune response evidenced by significantly lower levels of lymphocytes and their subsets (CD3, CD4, CD8). CD4 count is currently being used to define severe cases of HIV infection [36]. In the case of HIV, the virus directly infects CD4 cells using the envelope

glycoprotein gp120. Various authors have suggested that SARS-CoV-2 could deplete lymphocytes directly by infecting T lymphocytes, or indirectly through lymphocyte apoptosis induced by persistent elevated inflammatory cytokines [15, 37, 38]. Since severe COVID-19 patients display reduced lymphocyte count, it is likely that the cytokine release syndrome observed in some patients with severe or critical COVID-19 is mediated by interferons, TNFs, and cytokines secreted by non-T cell leucocytes such as macrophages, neutrophils and NK cells which are all key elements of innate immunity to viruses [39].

These findings could be applied clinically to identify severe or critical COVID-19 patients. For example, routine monitoring of NLR may provide insight into the functioning of both the innate and adaptive immune responses and help predict the clinical course of COVID-19. Despite the 45 studies included in this review, only five reported results for NLR; all these five studies found a significant association between increased NLR and severe or critical COVID-19 disease.

We also found that patients with severe or critical COVID-19 had significantly higher biomarkers of tissue and organ damage such as LDH, liver enzymes, kidney function parameters and markers of myocardial function. These observed associations could be explained by 3 mechanisms. First, the virus may cause direct organ damage by attaching to the ACE2 receptors, which are commonly expressed in the lungs, heart, arteries, kidneys and intestines [40]. The second, more indirect mechanism is systemic hyperinflammation caused by the cytokine release syndrome mediated by the innate immune system [40]. Systemic hyperinflammation affects all organs and could also explain the significantly increased expression of markers of disseminated intravascular coagulation (high D-dimer and depleted platelet count) in severely or critically ill patients [41, 42]. The third, also indirect, mechanism by which severe or critical COVID-19 causes multiple organ damage is hypoxia resulting from respiratory failure.

Once the mechanisms of COVID-19 induced organ damage are better understood, markers reflecting the pathophysiological changes caused by these mechanisms may find their way into clinical practice. Based on the results of our meta-analysis especially promising may be markers of immune function such as NLR, IL-6, C-reactive protein, serum ferritin, lymphocytes, CD4 count, and markers of coagulation and organ damage such as D-dimer, LDH, troponin I and liver enzymes.

The strengths and limitations of this review and meta-analysis need to be considered in the context of rapidly evolving literature. On the one hand, our study identified some associations that deserve further consideration and may lead to improvements in the risk stratification, monitoring and management of COVID-19 patients. On the other hand, it is important to emphasize that our analyses need to be viewed as hypothesis-generating rather than hypothesis-testing. Due to the large number of associations examined simultaneously there is a considerable likelihood of false-positive findings. This limitation can be addressed in future, more focused, studies that will take into consideration prior knowledge and reduce the likelihood of false-positive results through application of Bayesian and empirical-Bayes methods [43]. Our review is also affected by the limitations of the underlying literature. Of those, perhaps the most important is the cross-sectional nature of the analyses used in most publications. Although it is plausible that markers of immune function can be used to predict disease severity, the evidence would have been stronger if the studies were able to perform laboratory testing of COVID-19 patients before their disease severity was known. In addition, many studies from China reported on overlapping patient populations. While we tried to exclude studies that relied on the same data, it is possible that some of the associations examined in this meta-analysis were based on non-independent observations.

In conclusion, compared to non-severe COVID-19, severe or critical COVID-19 is associated with increased markers of innate immune response such as neutrophil count, NLR, IL-6,

CRP and serum ferritin; decreased markers of adaptive immune response such as lymphocyte, CD4 and CD8 counts; and increased markers of tissue damage and major organ failure including D-dimer LDH, Troponin I, CK-MB, AST, ALT, urea, and creatinine. Based on the results of our meta-analysis, especially promising markers are NLR, IL-6, serum ferritin, lymphocyte and CD4 counts, D-dimer and troponin I. The clinical value of these markers should be explored further to assess the risk of severe or critical disease and to monitor the clinical course of COVID-19.

Supporting information

S1 Checklist.
(DOC)

S1 File.
(DOCX)

Author Contributions

Conceptualization: Jude Moutchia, Pratik Pokharel, Aldiona Kerri, Miriam Nji.

Data curation: Jude Moutchia, Pratik Pokharel, Kaodi McGaw, Shreeshti Uchai.

Formal analysis: Jude Moutchia.

Funding acquisition: Jude Moutchia.

Project administration: Michael Goodman.

Supervision: Michael Goodman.

Validation: Aldiona Kerri, Miriam Nji, Michael Goodman.

Visualization: Kaodi McGaw, Shreeshti Uchai.

Writing – original draft: Kaodi McGaw, Shreeshti Uchai.

Writing – review & editing: Jude Moutchia, Pratik Pokharel, Aldiona Kerri, Miriam Nji, Michael Goodman.

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