Review

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Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis

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Abstract

Background: As coronavirus disease 2019 (COVID-19) pandemic rages on, there is urgent need for identification of clinical and laboratory predictors for progression towards severe and fatal forms of this illness. In this study we aimed to evaluate the discriminative ability of hematologic, biochemical and immunologic biomarkers in patients with and without the severe or fatal forms of COVID-19.

Methods: An electronic search in Medline (PubMed interface), Scopus, Web of Science and China National Knowledge Infrastructure (CNKI) was performed, to identify studies reporting on laboratory abnormalities in patients with COVID-19. Studies were divided into two separate cohorts for analysis: severity (severe vs. non-severe and mortality, i.e. non-survivors vs. survivors). Data was pooled into a meta-analysis to estimate weighted mean difference (WMD) with 95% confidence interval (95% CI) for each laboratory parameter.

Results: A total number of 21 studies was included, totaling 3377 patients and 33 laboratory parameters. While 18 studies (n = 2984) compared laboratory findings between patients with severe and non-severe COVID-19, the other three (n = 393) compared survivors and non-survivors of the disease and were thus analyzed separately. Patients with severe and fatal disease had significantly increased white blood cell (WBC) count, and decreased lymphocyte and platelet counts compared to non-severe disease and survivors. Biomarkers of inflammation, cardiac and muscle injury, liver and kidney function and coagulation measures were also significantly elevated in patients with both severe and fatal COVID-19. Interleukins 6 (IL-6) and 10 (IL-10) and serum ferritin were strong discriminators for severe disease.

Conclusions: Several biomarkers which may potentially aid in risk stratification models for predicting severe and fatal COVID-19 were identified. In hospitalized patients with respiratory distress, we recommend clinicians closely monitor WBC count, lymphocyte count, platelet count, IL-6 and serum ferritin as markers for potential progression to critical illness.

Keywords: clinical chemistry; coronavirus; COVID-19.

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Introduction

In the fight against coronavirus disease 2019 (COVID-19), now a worldwide pandemic, urgent identification of clinical and laboratory predictors of progression towards severe and fatal forms is urgently needed. These predictors will enable risk stratification, guide interventional studies to target patients at enhanced risk of developing severe disease and optimize allocation of limited human and technical resources in the ongoing pandemic. Moreover, identification of laboratory parameters capable of discriminating between severe and non-severe cases, or those at high or low risk of mortality, will allow for improved clinical situational awareness.

Though similarities are noted between COVID-19 and the severe acute respiratory syndrome (SARS), the World Health Organization (WHO) has observed differences in the clinical picture of the diseases caused by the two viruses [1]. We have previously described the typical laboratory changes in both children and adults with COVID-19, observing some notable differences in laboratory parameters between COVID-19 and SARS viruses [2, 3].

In earlier reports, we have identified procalcitonin and platelet count as potential predictors of disease severity [2, 3]. However, with an increased volume of COVID-19 reports now published, it has enabled a more comprehensive analysis of laboratory data that is urgently needed by the medical and scientific communities. The aim of this study was to analyze laboratory abnormalities in patients with COVID-19, in order to define which parameters can discriminate between those who are at higher risk of developing severe vs. non-severe forms of disease, as well as those who are less likely to survive.

Materials and methods

Search strategy

We carried out an electronic search in Medline (PubMed interface), Scopus, Web of Science and China National Knowledge Infrastructure (CNKI), using the keywords "laboratory" OR "chemistry" OR "clinical" AND "coronavirus 2019" OR "COVID-19" OR "2019-nCoV" OR "SARS-CoV-2", between 2019 and present time (i.e. March 17, 2020), without date or language restrictions. The reference list of all identified documents was scrutinized with the aim of identifying additional potentially eligible studies. This systematic review and meta-analysis were conducted in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplement 1).

Selection criteria

All studies were assessed for eligibility by two independent reviewers. Each reviewer assessed by title, abstract and full text each article identified in the search. Studies were deemed eligible for inclusion in this meta-analysis if they were (1) case series (at least 10 patients) or observational studies reporting clear extractable data on laboratory abnormalities in laboratory-confirmed COVID-19 patients and (2) compared the laboratory parameters between patients with severe or non-severe disease or between survivors and non-survivors. Editorials, reviews and case reports were excluded. All articles published in Chinese were assessed by a medical professional fluent in both Chinese and English. When data on laboratory parameters were identified, the article was translated into English to enable data collection. Any disagreements arising during the selection assessment were resolved by discussion and consensus.

Data collection

Data were independently extracted from the included COVID-19 studies by two independent reviewers. The data extracted included: authors, year of publication, country, sex, age, outcome, time of blood collection (hospital admission or unclear) and laboratory values. When unavailable, mean and standard deviation of laboratory values were extrapolated from sample size, median and interquartile range (IQR), according to Hozo et al.[4]. Severe disease was defined in this analysis as a composite of acute respiratory distress syndrome (ARDS), need for ventilation support, need for vital life support, or need for intensive care unit (ICU) support.

Statistical analysis

Studies were divided into two separate cohorts for analysis: severity cohort and mortality cohort. A meta-analysis was performed, with calculation of weighted mean difference (WMD) and 95% confidence interval (95% CI) for each laboratory parameter in COVID-19 patients with or without severe disease and non-survival or survival. Laboratory data was pooled whenever two or more studies reported a given parameter. Heterogeneity among the included studies was assessed using the chi square (χ^2) test and the I^2 statistic. For the χ^2 test, significant heterogeneity among the studies was indicated with a Cochran's Q p-value of <0.10. The I^2 statistic results were interpreted as 25%, 50% and 75% representing low, moderate and high heterogeneity, respectively [5]. To probe the sources of heterogeneity, when $I^2 > 50\%$, sensitivity analysis was performed employing a leave-one-out analysis and subgroup analysis was performed excluding studies with unclear timepoints of laboratory measures. The statistical analysis was performed with MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia).

Results

Study identification and characteristics of included studies

A flow chart of studies through the analysis is presented in Figure 1. After duplicate screening, a total number of 90 articles were initially identified, 74 of were excluded because they were review articles (n = 17), did not report data on COVID-19 disease (n = 38), did not provide laboratory data on COVID-19 patients with or without severe disease or mortality (n = 10), or were editorial material (n = 9). Five additional studies could be identified from the reference list of selected articles. Thus, the pooled analysis finally included 21 studies [6–26], with a total sample of 3377 confirmed COVID-19 patients, reporting data on 33 laboratory parameters. Most studies were from China, with the exception of two studies from Singapore [8, 23]. All studies reported laboratory values measured at admission or earliest time point in hospitalization, except for six studies [7, 14, 16–18, 23], where the timepoint was unclear. The essential characteristics of the included studies are presented in Table 1.

Meta-analysis of laboratory abnormalities by disease severity

A total of 18 studies [6–9, 11–13, 15–21, 23–25], totaling 2984 COVID-19 patients, reported laboratory data with comparison between those with severe and non-severe disease. Full results are shown in Table 2 and forest plots in Supplement 2. With respect to sensitivity analysis, a leave-one-out analysis for white blood cell (WBC) count excluding the largest study by Guan et al., a significant increase in the difference between severe and non-severe COVID patients was observed (WMD: 1.25×10^9/L [95% CI: 0.91–1.59×10^9/L]). No significant differences were noted in any other sensitivity analysis or sub-group analysis excluding studies which had unclear timepoints of collection.

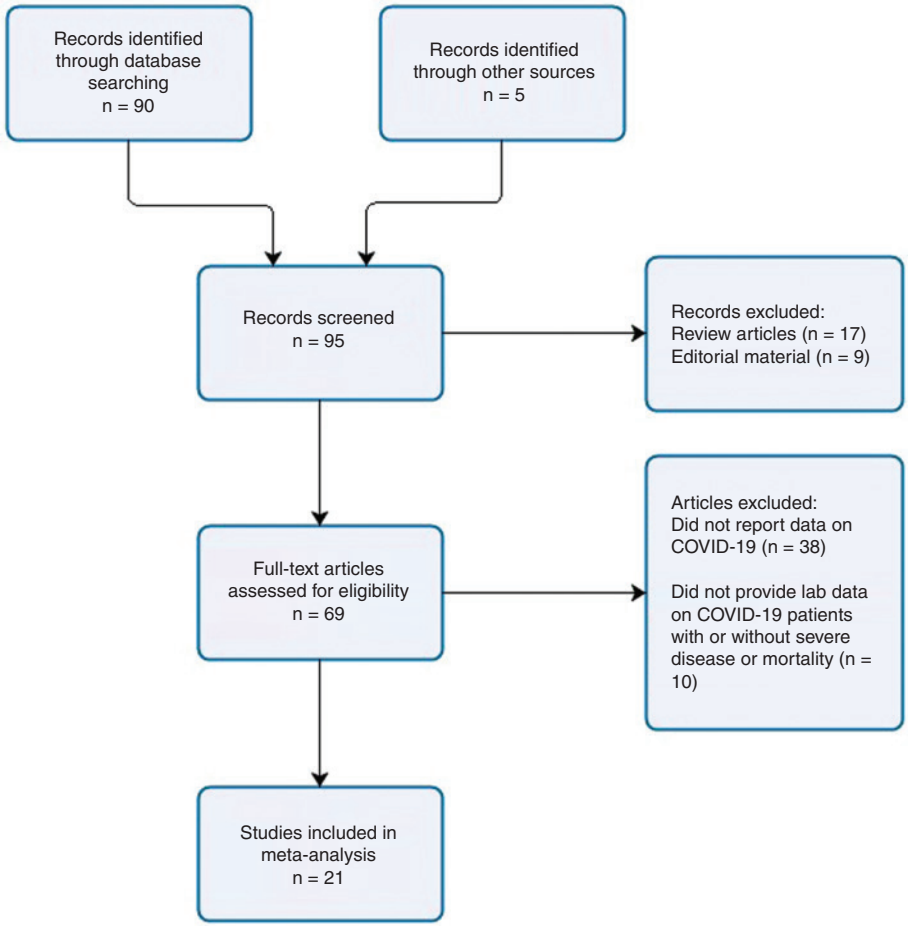

Figure 1: Study flow chart.

Table 1: Characteristics of included studies.

Study	Setting	Sample size	Outcomes	Severe patients			Non-severe patients		
				n (%)	Age, years[a]	Women, %	n (%)	Age, years[a]	Women, %
Chen et al. [7]	China	150	Respiratory distress/insufficiency	24 (16%)	68.5 (13.6)	25%	126 (84%)	51.1 (15.6)	47.6%
Chen et al. [6]	China	29	Respiratory distress/insufficiency	14 (48.3%)	NR	NR	15 (51.7%)	NR	NR
Fan et al. [8]	China	65	ICU admission	9 (13.8%)	54 (47–62)	33.3%	56 (86.2%)	41 (32–53)	48.6%
Guan et al. [9]	China	1099	Admission to ICU, MV, Death	173 (15.7%)	52 (40–65)	42%	926 (84.3%)	45 (34–57)	42%
Huang et al. [10]	China	41	ICU care	13 (31.7%)	49 (41–61)	15%	28 (68.3%)	49 (41–58)	32%
Liu et al. [16]	China	30	Respiratory distress/insufficiency	4 (13.3%)	NR	NR	26 (86.7%)	NR	NR
Liu et al. [12]	China	78	Admission to ICU, MV, death	11 (14.1%)	66 (51–70)	36%	67 (85.9%)	37 (32–41)	52%
Liu et al. [11]	China	12	Respiratory failure, MV	6 (50%)	64 (63–65)	50%	6 (50.0%)	44 (35–55)	17%
Qian et al. [17]	China	91	Respiratory distress/insufficiency	9	66 (54–80)	NR	82	49 (35.5–56)	NR
Qin et al. [13]	China	452	Respiratory distress/insufficiency	286 (63.3%)	61 (51–69)	45.8%	166 (36.7%)	53 (41.25–62)	51.8%
Qu et al. [15]	China	30	Respiratory distress/insufficiency	3	60 (5.29)	NR	27	49.4 (14.86)	NR
Ruan et al. [14]	China	150	Death	68 (45.3%)	67 (15–81)	28%	82 (54.6%)	50 (44–81)	35%
Tianxin et al. [18]	China	49	Respiratory distress/insufficiency	9 (18.4%)	53 (14)	11.1%	40 (81.6%)	40.6 (14.3)	37.5%
Wang et al. [19]	China	138	Clinical variables, MV, death	36 (26.1%)	66 (57–78)	39%	102 (73.9%)	51 (37–62)	48%
Wang et al. [20]	China	69	SpO2 < 90%	14 (20.3%)	70.5 (62–77)	50%	55 (79.7%)	37 (32–51)	55%
Wu et al. [21]	China	201	ARDS	84 (41.8%)	58.5 (50–69)	28.6%	117 (58.2%)	48 (40–54)	41.9%
Yang et al. [22]	China	52	Death	32 (61.5%)	64.6 (11.2)	34%	20 (38.5%)	51.9 (12.9)	30%
Young et al. [23]	Singapore	18	Treatment, ICU care, death	6 (33.3%)	56 (47–73)	67%	12 (66.6%)	37 (31–56)	42%
Yun et al. [24]	China	292	Respiratory distress/insufficiency	21 (7.2%)	65 (15.7)	9.5%	271 (92.8%)	48.7 (15.7)	50.2%
Zhang et al. [25]	China	140	Respiratory distress/insufficiency	58 (41.4%)	64 (25–87)	43%	82 (58.6%)	52 (26–78)	54%
Zhou et al. [26]	China	140	Death	54 (28.3%)	69 (63–76)	30%	137 (71.7%)	52 (45–58)	41%

[a]Age data presented as median (IQR) or mean (SD). MV, mechanical ventilation; ICU, intensive care unit; NR, not reported.

Table 2: Results of meta-analysis comparing Lab Abnormalities in COVID-19 patients with and without severe illness or mortality.

Lab	Severe vs. non-severe				Non-survival vs. survival			
	# of studies (# of pts)	WMD[a] (95% CI)	I^2	Cochran's Q p-value	# of studies (# of pts)	WMD[a] (95% CI)	I^2	Cochran's Q p-value
Hematologic								
White blood cell count, $\times 10^9$/L	14 (2635)	0.41 (0.16, 0.66)	90.3%	0.00	2 (341)	4.15 (3.15, 5.15)	0%	0.53
Neutrophil count, $\times 10^9$/L	12 (1506)	1.7 (1.57, 1.85)	93.5%	0.00	NA			
Lymphocyte count, $\times 10^9$/L	15 (2556)	−0.28 (−0.32, −0.25)	61.3%	0.00	3 (393)	−0.44 (−0.54, −0.35)	83.4%	0.00
CD4, %	3 (99)	−3.94 (−8.02, 0.13)	53.4%	0.12	NA			
CD8, %	3 (99)	−2.22 (−5.01, 0.57)	0%	0.41	NA			
Monocyte count, $\times 10^9$/L)	4 (410)	−0,03 (−0,07, 0,01)	0%	0.82	NA			
Eosinophil count, $\times 10^9$/L	4 (347)	−0.01 (−0.02, −0.01)	74.4%	0.01	NA			
Platelet count, $\times 10^9$/L	12 (1894)	−23.36 (−30.82, −15.89)	51.6%	0.02	3 (393)	−48.3 (−57.67, −38.93)	86.9%	0.00
Hemoglobin, g/L	8 (1582)	−6.52 (−9.2, −3.85)	0%	0.80	3 (393)	−1.34 (−4.85, 2.18)	0%	0.64
Biochemical								
Albumin, g/L	8 (794)	−4.60 (−5.31, −3.88)	69.8%	0.00	2 (341)	−4.2 (−5.06, −3.34)	0%	0.5
Alanine aminotransferase, U/L	11 (1031)	8.07 (4.87, 11.27)	44.6%	0.05	2 (341)	11.08 (4.76, 17.4)	0%	0.35
Aspartate aminotransferase, U/L	11 (1031)	7.27 (5.23, 9.31)	66.2%	0.00	NA			
Total bilirubin, μmol/L	5 (441)	2.25 (1.26, 3.23)	48%	0.10	2 (202)	5.64 (3.19, 8.1)	0%	0.69
Blood urea nitrogen, mmol/L	5 (491)	1.63 (1.19, 2.07)	0%	0.46	NA			
Creatinine, mmol/L	11 (1121)	6.72 (2.83, 10.62)	49.5%	0.04	2 (202)	12.81 (2.07, 23.55)	43.3%	0.18
Creatine kinase, U/L	6 (592)	32.25 (5.88, 58.62)	60.3%	0.03	2 (341)	42.75 (15.7, 70)	0%	0.75
Lactate dehydrogenase, U/L	10 (664)	173.6 (145.84, 201.35)	54.9%	0.02	2 (341)	198.21 (95.68, 300.73)	41.4%	0.19
Cardiac troponin I, ng/L	NA				2 (341)	32.7 (18.25, 47.09)	0%	0.73
Myoglobin, ng/mL	2 (304)	71.23 (16.88, 125.59)	0%	0.79	NA			
Creatine kinase-MB, IU/L	2 (339)	2.02 (0.53, 3.51)	84.9%	0.01	NA			
Coagulation								
Prothrombin time, s	4 (429)	0.94 (0.68, 1.19)	29.1%	0.24	2 (243)	0.94 (0.41, 1.48)	50.2%	0.16
APTT, s	4 (429)	−1.11 (−2.33, 0.10)	0%	0.72	NA			
D-dimer, μg/L	9 (1001)	0.71 (0.48, 0.94)	48.8%	0.05	NA			
Inflammatory biomarkers								
Erythrocyte sedimentation rate, mm/h	6 (1141)	8.49 (4.93, 12.05)	73.4%	0.01	NA			
CRP, mg/L	10 (1423)	37.78 (31.24, 44.32)	59.6%	0.01	NA			
Serum ferritin, ng/mL	2 (653)	408.28 (311.12, 505.44)	87.5%	0.01	2 (341)	760.18 (560.84, 959.53)	0%	0.49
PCT, ng/mL	7 (1062)	0.02 (0.01, 0.02)	81.8%	0.00	NA			
IL-1beta, pg/mL	2 (481)	0.00 (0.00, 0.00)	0%	0.881	NA			
IL-2R, pg/mL	2 (481)	235.84 (183.12, 288.56)	94.4%	0.000	NA			
IL-6, pg/mL	4 (725)	1.70 (0.8, 2.6)	74.3%	0.01	2 (341)	4.6 (3.4, 5.8)	0%	1
IL-8, pg/mL	2 (481)	5 (3.03, 6.98)	0%	0.61				NA
IL-10, pg/mL	3 (524)	1.94 (1.36, 2.52)	0%	0.74	NA			
TNF α, pg/mL	3 (524)	0.16 (−0.11, 0.43)	60.5%	0.08	NA			

[a]WMD: Weighted mean difference as follows: Overall (patients with bad vs. good prognosis), Survival (non-survivors vs. survivors), Critical illness (critically ill patients vs non-critically ill patients). CRP, C-reactive protein; IL, interleukin; NA, not available; PCT, procalcitonin.

Meta-analysis of laboratory abnormalities by survival

A total of three studies [14, 22, 26], n = 393 reported laboratory data with comparison between patients who survived and patients who did not survive. The analyses are presented in Table 2 and forest plots in Supplement 3. No differences were observed for any sensitivity or subgroup analysis. With respect to the severity cohort, non-survivors compared to survivors had more significant increases in WBC count, total bilirubin, creatine kinase, serum ferritin, and interleukin 6 (IL-6), and more significant decreases in lymphocyte count and platelet count. While patients with severe disease had significantly reduced hemoglobin values compared to non-severe, the same trend was not observed in non-survivors compared to survivors, with no significant difference in mean difference between groups.

Discussion

In this comprehensive meta-analysis, a clear pattern of inflammatory, hematologic, biochemical and immune biomarker abnormalities could be found between patients with or without severe disease, which may enable significant discrimination to warrant inclusion in risk stratification models. To the best of our knowledge, this is the first meta-analysis systematically comparing laboratory abnormalities in either a severity or mortality cohort. The overall results of this investigation are further summarized in Table 3.

Several differences were observed between the severity and mortality cohorts. Patients with severe disease had only a mild increased in WBC count (WMD: 0.41×10^9/L), while patients who died had a more clinically significant increase in this parameter (WMD: 4.15×10^9/L). As such, in patients with severe disease, a significant increase in WBCs may signify clinical worsening and increased risk of a poor outcome. Our data indicates that the increase in WBCs is driven by elevated neutrophils, as decreasing trends were observed for lymphocytes, monocytes and eosinophils. In patients with severe disease, a decrease in both CD4 and CD8 was observed. With the SARS virus, it was suspected that lymphocytes are essential to eliminating virally infected cells [27], while with COVID-19 it has been further hypothesized that survival may be dependent on ability to replenish lymphocytes which are killed by the virus [28]. As such, lymphocyte count, especially CD4, may serve as a clinical predictor of severity and prognosis.

Table 3: Summary of laboratory changes in patients with severe or fatal COVID-19.

Hematologic
↑ WBC count
↑ Neutrophil count
↓ Lymphocyte count
↓ Platelet count
↓ Eosinophil count
↓ Hemoglobin
Biochemical
↓ Albumin
↑ Alanine aminotransferase
↑ Aspartate aminotransferase
↑ Total bilirubin
↑ Blood urea nitrogen
↑ Creatinine
↑ Creatine kinase
↑ Lactate dehydrogenase
↑ Myoglobin
↑ Creatine kinase-MB
↑ Cardiac troponin I
Coagulation
↑ Prothrombin time
↑ D-dimer
Inflammatory biomarkers
↑ Erythrocyte sedimentation rate
↑ CRP
↑ Serum ferritin
↑ PCT
↑ IL-2R
↑ IL-6
↑ IL-8
↑ IL-10

CRP, C-reactive protein; IL, interleukin; PCT, procalcitonin; WBC, white blood cell.

Biomarkers of cardiac and muscle injury were elevated in patients with both severe and fatal COVID-19. Patients who died had significantly elevated cardiac troponin levels at presentation (WMD: 32.7 ng/L), thus suggesting potential for viral myocarditis, cardiac injury from progression towards multiple organ failure (MOF), as well as secondary cardiac injury from organ targeted pathologies (e.g. renal or liver failure). Combined with significant elevations in liver enzymes (alanine aminotransferase and aspartate aminotransferase), renal biomarkers (blood urea nitrogen, creatinine), and coagulation measures, a picture of MOF becomes very apparent in patients who develop the severe form of the disease, even with laboratory parameters measured primarily at admission.

With respect to immunologic biomarkers, significantly greater increases were observed for IL-6 and serum ferritin in non-survivors vs. survivors (WMD: 4.6 pg/mL and 760.2 ng/mL, respectively) as compared to severe

vs. non-severe form (WMD: 1.7 pg/mL and 408.3 ng/mL, respectively). We suggest both parameters thus be used for monitoring prognosis in COVID-19 patients over the course of hospitalization. These elevations, along with elevated C-reactive protein (CRP), point to development of a systemic inflammatory response syndrome (SIRS) picture in patients with a severe form of the disease. The exaggerated elevation of inflammatory cytokines such as IL-6, which can lead to a so-called "cytokines storm," may be a driver behind acute lung injury and ARDS and lead to other tissue damage progressing to MOF [29]. Additionally, elevated interleukin-10 (IL-10) was observed in patients with the severe form of the disease. We suspect this may be related to compensatory anti-inflammatory response (CARS), which may be responsible for higher number of secondary infections (50%) and sepsis (100%) reported in non-survivors [26].

Importantly, while this study investigated discriminative ability, measured as the WMD in a given laboratory parameter between patients with severe and non-severe form or non-survivors and survivors, a lack of a statistically significant or even clinically significant difference does not imply a lack of association with the outcome. For example, in this study, only a 0.2 ng/mL difference in procalcitonin (PCT) level was observed between severe and non-severe forms of the disease. However, when we analyzed this in a prior study as a categorical variable, nearly a 5-fold higher risk of severe COVID-19 infection (OR, 4.76; 95% CI, 2.74–8.29) was observed for patients who had elevated PCT [3]. While only minimal discriminative ability is observed for severity, and lack of data prevented this analysis for mortality, we postulate that elevated PCT may be driven by the 50% secondary infection rate seen in non-survivors versus only 1% survivors [26]. Moreover, this highlights that both discriminative ability and odds of severity are factors that must be considered in building predictive risk stratification models in COVID-19. As more categorical data becomes available for analysis in the coming weeks and months, this should be a priority for future analyses.

Several limitations of this study should be noted. As included studies used variable definitions to define severity, we were forced to employ a composite measure which may have accounted for some heterogeneity in the meta-analysis. Six studies had unclear time points of laboratory collection, however, subgroup analysis excluding studies that did not use specifically admission laboratory measurements yielded no significant differences. Due to the nature of reporting in the emerging outbreak, we did not perform a risk of bias assessment, and presume it to be high across studies. This should be taken into consideration when interpreting results.

In addition, a major limitation of the evaluated studies is represented by the poor description of the analytical performance characteristics of the methods used and the adoption of different measurement units for results reporting. While patient overlap is possible between a few of the studies, after careful evaluation we estimated this to be present in <1% of the total sample. All studies were from East Asia, mostly from China. As such, as more data from other regions becomes available, it should be compared to this analysis as it cannot be excluded that the virus may interplay differently with genetic, epigenetic and even environmental factors. Lastly, the sample size for the mortality cohort and for some variables in the severity cohort were limited. These should be further evaluated in future studies.

In conclusion, we identified many candidate variables for risk stratification models that may serve as clinical predictors of severe and fatal COVID-19. In hospitalized patients with respiratory distress, we recommend clinicians closely monitor WBC count, lymphocyte count, platelet count, IL-6 and serum ferritin as markers for potential progression to critical illness. PCT should be regularly measured to serve as a marker of secondary bacterial infection, which is frequently found in non-survivors, thus mirroring earlier evidence garnered with SARS [30]. Lastly these findings should be continually re-evaluated in the coming months as more data becomes available in prospective cohorts, with longer follow-up.

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