REVIEW ARTICLE
Iran J Allergy Asthma Immunol
December 2020; 19(6):557-569.
Doi: 10.18502/ijaai.v19i6.4926

Procalcitonin Has Good Accuracy for Prognosis of Critical Condition and Mortality in COVID-19: A Diagnostic Test Accuracy Systematic Review and Meta-analysis

Mohammad Erfan Zare[1,2], Yanzhong Wang[1], Atefeh Nasir Kansestani[1,2], Afshin Almasi[3], and Jun Zhang[1]

[1] Department of Clinical Laboratory, Sir Run Run Shaw Hospital, Zhejiang University, School of Medicine, Hangzhou, China
[2] Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
[3] Department of Biostatistics, School of Health, Kermanshah University of Medical Sciences, Kermanshah, Iran

Received: 24 August 2020; Received in revised form: 20 September 2020; Accepted: 27 September 2020

ABSTRACT

Several reports have determined that changes in white blood cell counts and inflammatory biomarkers are related to disease outcome of coronavirus disease 2019 (COVID-19) and they can be utilized as prognostic biomarkers. For introducing a factor as a diagnostic/prognostic biomarker, diagnostic test accuracy (DTA) systematic review and meta-analysis are recommended. For the first time, we aimed to determine the accuracies of white blood cell counts and inflammatory biomarkers for prognosis of COVID-19 patient's outcome by a DTA meta-analysis.

Until August 24, 2020, we searched Web of Sciences, Scopus, and MEDLINE/PubMed databases to achieve related papers. Summary points and lines of included studies were calculated from 2×2 tables by bivariate/hierarchical models. Critical condition and mortality were considered as outcomes.

A total of 13387 patients from 28 studies were included in this study. Six biomarkers containing leukocytosis, neutrophilia, lymphopenia, increased level of C-reactive protein, procalcitonin (PCT), and ferritin met the inclusion criteria. Analysis of the area under the curve (AUC_{HSROC}) indicated that the PCT was the only applicable prognostic biomarker for critical condition and mortality (AUC_{HSROC}=0.80 for both conditions). Pooled-diagnostic odds ratios were 6.78 (95% CI, 3.65-12.61) for prognosis of critical condition and 13.21 (95% CI, 3.95-44.19) for mortality. Other biomarkers had insufficient accuracies for both conditions (AUC_{HSROC}< 0.80).

Among evaluated biomarkers, only PCT has good accuracy for the prognosis of both critical condition and mortality in COVID-19 and it can be considered as a single prognostic biomarker for poor outcomes. Also, PCT has more accuracy for the prognosis of mortality in comparison to critical conditions.

Keywords: COVID-19; Procalcitonin; Prognosis; Sensitivity and specificity

Corresponding Author: Jun Zhang, MD, PhD;
Department of Clinical Laboratory, Sir Run Run Shaw Hospital, Zhejiang University, School of Medicine, Hangzhou, China.
Tel: (+86 571) 8600 2260, E-mail:jameszhang2000@zju.edu.cn

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

INTRODUCTION

In December 2019, several cases of pneumonia with unknown causes were reported in Wuhan city, the capital of the Hubei province of China. In January 2020, Chinese scientists succeeded to isolate a novel Coronaviruses from these patients which was first named 2019 novel Coronaviruses (2019-nCoV) and then, was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Finally, in February 2020, this infection disease was called coronavirus disease 2019 (COVID-19) by World Health Organization (WHO). This virus causes a pandemic in the early months of 2020 and infected cases were reported in almost all countries in the world.[1-3]

The clinical outcome of COVID-19 patients is variable, from non-symptom to a critical phase lead them to hospitalization in the intensive care unit (ICU), shock, organ failure, and/or need to mechanical ventilation and eventually may cause death.[1,4] Therefore, prognostic markers are very important for the management of these patients due to the lack of medical resources in pandemic conditions.[5] Because of the pandemic, many countries faced this situation, including undeveloped countries which suffer from limitation of accessibility to complicated medical equipment and tests. On the other hand, due to a large number of infected patients, performing non-routine laboratory tests that often need time and expert operators is not possible, even if exists. Thus, the identification of routine laboratory tests as prognostic biomarkers which are done rapidly and available in all medical facilities seems necessary.[5-7]

Viral infections have a close correlation with the human immune system. Dysregulation of immune system responses is assumed to play important roles in the severity of the virus-induced disease. In this regard, from the beginning of this infection, several reports have determined changes in white blood cell counts and inflammatory biomarkers like acute phase reactants are related to the progression of disease severity.[5,8] Several studies have shown significant correlations between hematological change including leukocytosis, neutrophilia and lymphopenia, and disease severity. The most routine and important inflammatory biomarkers for diagnosis of pneumonia are C-reactive protein (CRP) and procalcitonin (PCT) which have a positive correlation with the level of inflammation and are not affected by different factors such as age, sex, and physical condition as well as patients' co-morbidities that contribute to clinical ambiguity, such as chronic obstructive pulmonary disease and acute heart failure.[5,8]

The above-mentioned pieces of evidence indicate these tests have great potential as prognostic biomarkers for critical condition and mortality in COVID-19 patients. However, only those tests are applicable which have high accuracy to discriminate a favorable characteristic from an unfavorable.[9,10] To ascertain the accuracy of a diagnostic or prognostic laboratory test, diagnostic test accuracy (DTA) systematic review and meta-analysis is recommended.[11,12] These types of studies are used for biomarkers introducing with the diagnostic and prognostic applications.[13] Nonetheless, to date, there isn't any DTA study to introduce applicable laboratory tests for the prognosis of critical condition and mortality in COVID-19 patients. Therefore, for the the first time, a DTA systematic review and meta-analysis was conducted to determine the accuracies of white blood cell counts and inflammatory biomarkers including leukocytosis, neutrophilia, eosinopenia, lymphopenia, increased level of CRP, PCT, ferritin, and Serum Amyloid-A (SAA) in a different outcome of COVID-19 patients.

MATERIALS AND METHODS

Search Strategy

The search strategy and article review were conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Until August 24, 2020, we did a systematic search on comprehensive databases consist of Web of Sciences (WOS), Scopus, and MEDLINE/PubMed for finding relative studies without any language restriction. The following search keywords were used: ("Novel coronavirus" OR "Novel coronavirus 2019" OR "2019 nCoV" OR "COVID-19" OR "SARS-CoV-2") AND ("Severity" OR "Critical" OR "ICU" OR "Death" OR "Survivors" OR "Laboratory tests" OR "inflammation" OR "White Blood Cell" OR "Neutrophil" OR "Lymphocyte" OR "Procalcitonin" OR "C-reactive protein" OR "Ferritin" OR "Eosinophil" OR "Serum Amyloid-A"). The reference lists were checked manually for each selected paper and relevant systematic and narrative reviews on the topic to identify missing studies. To exclude

the duplicated papers, we imported records into the EndNote software (Version X9, Thomson Reuters).

Study Selection

The title and abstract of all obtained records were screened by one of the authors. Different severity of COVID-19 patients was assessed into 4 groups based on "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)" as follows: 1) Mild: the clinical symptoms were mild and there was no sign of pneumonia on imaging; 2) Moderate: patients who are show fever and respiratory symptoms with radiological findings of pneumonia; 3) Sever: in patients who met one of the following criteria: respiratory distress (respiration rate ≥ 30 times/min), oxygen saturation (SpO2) ≤ 93% in the resting state, and arterial partial pressure of O2 and the fraction of inspired oxygen (PaO2/FiO2) ratio ≤ 300 mmHg; 4) Critical: respiratory failure requiring mechanical ventilation, shock, organ failure, and ICU admission.[14]

In this study, only "on admission" laboratory tests' results were collected and used for meta-analysis. The including criteria for this study were: 1) all patients were diagnosed with SARS-CoV-2 by Real-time PCR technique, 2) Clinical characteristics and the results of laboratory tests were separated by the presence of survivor vs. non-survivor patients or critical vs. non-critical (including mild, moderate, and severe form of the disease), 3) For each group of studies, the type and number of abnormal laboratory test results were clear (change out of local reference range), 4) For each laboratory parameter, at least 4 studies should be found, 5) the methods of biomarkers' assay are quantitative. Studies were excluded if they met the following criteria: 1) Patients were diagnosed with SARS-CoV-2 infection by non-real-time PCR technique, 2) duplicate publications, 3) reviews, meta-analysis and case reports, 4) studies which failed to clearly distinguish different mentioned groups, 5) studies which assessed single group, like non-survivor patients or all of the COVID-19 patients were assessed as a group, 6) studies which done on a special group of patients like pregnant women, children and, 7) qualitative method for evaluating of serum biomarkers.

Quality Assessment and Sensitivity Analysis

There isn't any recommended tool for assessing the quality of included studies in a prognostic test accuracy systematic review.[13] Hence, we used the Newcastle-Ottawa Scale (NOS) tool which applicable to analytical studies, including cohort studies. Included studies were assessed for their methodological quality using NOS with a maximum of 9 points.[15] This scale consists of three major categories including "Selection", "Comparability" and "Outcome". There isn't any validation study that suggests a cut-off point for rating "low" bias risk studies, however, some studies use the overall point ≥6 for low bias risk and these studies will be categorized as "good quality". Further, studies with overall point 3-5 have a "moderate quality" and<3 will be categorized as "poor" quality.[16] Therefore, we used the same categorization. Analyses were restricted by "moderate" or "poor" quality studies.

Data Extraction

The data from the included studies were extracted and calculated to achieve 2×2 contingency tables. First, all included studies were assessed for the laboratory tests, and the number or percentage of results that were out of local reference ranges were extracted. Then true positive (TP), false positive (FP), true negative (TN), and false negative (FN) of each test were calculated for all obtained tests.

Data Synthesis and Statistical Analysis

Based on extracted data, we constructed 2×2 contingency tables for each test, separately. Sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic odds ratio (DOR) were calculated for each test. For a meta-analysis report of summary points, we considered Pooled-Sensitivity, Pooled-Specificity, Pooled-LR+, Pooled-LR- and Pooled-DOR. Separately pooling of these summary points could be affected by a threshold effect. Thus, to eliminate this limitation, we used a bivariate model, which accounts for the correlation between sensitivity and specificity and between-study heterogeneity as well as the threshold effect by a random effect approach.[11] For achieving a summary of line parameters, we were drawn hierarchical summary receiver operating characteristic (HSROC) and the area under the curve (AUC_{HSROC}) was calculated by trapezoidal integration to obtain a global measure of test performance.[11] AUC_{HSROC} value reflected the diagnostic (prognostic) accuracy of each laboratory test and it has a value range between minimum 0.5 to maximum 1. If the value of AUC_{HSROC} is 1, it's the perfect biomarker to discriminate

favorable characteristics from unfavorable ones whereas 0.5 reflects a non-discriminating biomarker. The relationship between AUC_{HSROC} value and diagnostic (prognostic) accuracy is defined as follow: 0.90-1=excellent; 0.80-0.89=good; 0.70-0.79=fair; 0.60-0.69=poor and 0.50-0.59=fail.[17] In the present study, we consider only "good" or "excellent" values ($AUC_{HSROC} \geq 0.80$) as clinically applicable biomarkers for prognosis of critical condition and mortality in COVID-19 patients.[18] All biomarkers were done and summarized for reporting with considering 95% confidence interval (95% CI). All statistical analysis were performed by Stata (Stata Corporation, College Station, TX, USA, version 12.0) and R software online based application, MetaDTA.[19]

To find potentially confounding covariates, including age, gender, hypertension, cardiovascular disease, diabetes mellitus, and chorionic respiratory disease we performed the Moses-Shapiro-Littenberg meta-regression method by Meta-Disk 1.4 software.

In this meta-analysis, all reports were considered as statistical significance when $p \leqslant 0.05$.

RESULTS

Study Selection and Quality Assessment

From 3079 initial records, 1052 studies were excluded due to duplication, and 1367 studies were excluded after the screening of title and abstract. Finally, 660 studies were undergone a full-text assessment. Most of the studies were excluded due to three major reasons: 1) Critical patients didn't separate from severe type patients; 2) the number or percentage of laboratory test results that were out of the references ranges were not mentioned, and 3) some studies reported just a group (for example some studies reported the data of death patients). Eventually, 28 studies were achieved to eligibility criteria (Table 1 and Figure 1). From these 28 studies, 14 studies assessed laboratory results of critical/non-critical outcome[20-33] and 12 studies appraised laboratory results of mortality outcome.[34-45] Two studies reported laboratory results of both outcomes at the same time.[46,47] Totally, 2999 patients were classified in critical/non-critical groups and 10388 patients in the survivor/non-survivor group. All included studies achieved aNOS score ≥8 and ranked as "high" quality (Table 1). Thus, no study restriction was performed base on the risk of bias. All studies achieved maximum points in the "Selection" and "Outcome" categories and differences of studies in point achievement were related to the "Comparability" category.

Prognostic Accuracy of Laboratory Tests

Eosinopenia and SAA didn't meet inclusion criteria. All other considered biomarkers met inclusion criteria in both groups, except ferritin. Ferritin didn't meet inclusion criteria in critical/non-critical, but it was eligible for assessment in the survivor/non-survivor group. Among the 6 assessed biomarkers, only PCT had "good" accuracy for the prognosis of both critical condition and mortality (AUC_{HSROC}=0.80 for both conditions) (Table 2 and Figure 2). Based on these results, the accuracies of PCT for the prognosis of both conditions are the same. However, based on another accuracy summary point, pooled-DOR, PCT has more accuracy for the prognosis of mortality in comparison to critical condition (pooled-DOR for the critical condition is 6.78 (95% CI, 3.65-12.61) and for mortality is 13.21 (95% CI, 3.95-44.19)) (Table 2). Pooled-sensitivity of PCT was 0.54 (95% CI, 0.29-0.77) and pooled-specificity was 0.84 (95% CI, 0.76-0.90) for prognosis of critical condition. Following, pooled-sensitivity and pooled-specificity for prognosis of mortality were 0.89 (95% CI, 0.24-0.99) and 0.60 (95% CI, 0.11-0.94), respectively (Figure 2). Neutrophilia and lymphopenia had "fair" accuracies for the prognosis of both critical condition and mortality, whereas leukocytosis and increased level of CRP had different accuracies for each group. leukocytosis had "fail" and "fair" accuracies for the prognosis of critical condition and mortality, respectively. Also, the increased level of CRP had "fair" and "fail" accuracies for those conditions.

Meta-regression Analysis

Regarding PCT, since the forest plot of sensitivity and specificity suggested heterogeneity, meta-regression analysis was conducted to find potentially confounding covariates, including age, gender, hypertension, cardiovascular disease, diabetes mellitus, and chorionic respiratory disease (Table 3). In the critical/non-critical group, this analysis did not indicate any source of heterogeneity among covariates (p>0.05). Nonetheless, in the survivor/non-survivor group, meta-regression analysis indicated that chorionic respiratory disease (p=0.034) contributed to a source of heterogeneity.

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

Table 1. Characteristics of included studies in this meta-analysis

Author	Country	Study design	Sample size	Age	%Male	%HTN	%CVD	%DM	%CRD[†]	Extracted Biomarker (s) (Threshold; Significance)[§]	NOS score
Critical vs. non-Critical											
Wang et al[20]	China	Cohort	65	57.1	57	NA[£]	NA	NA	NA	WBC (NA; *); N (NA; *); L (NA; *); CRP (NA; *); PCT (NA; *); Ferritin (NA; *)[‡]	8
Wang et al[21]	China	Retrospective Cohort	138	56	54.3	31.2	14.5	10.1	2.9	PCT (≥0.05 ng/mL; ***)	9
Fan et al[22]	Singapore	Retrospective Cohort	67	42	55.2	NA	NA	NA	NA	L (<1×10^9/L; ***)	8
Huang et al[23]	China	Retrospective Cohort	41	49	73	15	15	20	2	WBC (>10×10^9/L; NS); L (<1×10^9/L; *); PCT (≥0.1 ng/mL;*)	8
Liu et al[24]	China	Retrospective Cohort	12	53.6	66.6	25	33.3	16.6	8.3	WBC (>9.5×10^9/L; NA); N (>6.3×10^9/L; NA); L(<1.1×10^9/L; NA); CRP(≥10 mg/mL; NA); PCT (≥0.5 ng/mL; NA)	9
Lei et al[25]	China	Retrospective Cohort	34	55	41.2	38.2	20.6	23.5	2.9	L(<1.1×10^9/L; NS); PCT (≥0.1 ng/mL; *)	8
Li et al[26]	China	Retrospective Cohort	132	62.05	56.8	NA	NA	NA	NA	WBC (>9.5×10^9/L; *); L (<1.1×10^9/L; ***); CRP (≥3 mg/ml; ***); PCT (≥0.5 µg/L; *)	8
Chen et al[27]	China	Retrospective Cohort	54	58.9	66.6	29.6	11.1	46.3	0	WBC (NA; *)	8
Goyal et al[28]	United States	Retrospective Cohort	393	62.2	60.6	50.1	13.7	25.2	5.1	WBC (>10×10^3/mm^3; NA); L (<1500/mm^3; NA); CRP (>10 mg/dl; NA); PCT (≥0.5 ng/mL; NA); Ferritin (>300 µg/L; NA)	8
Chan et al[29]	Singapore	Retrospective Cohort	75	50	66.7	NA	NA	NA	NA	N (>6.6×10^9/L; ***); L (<1×10^9/L; ***)	8
Feng et al[30]	China	Retrospective Cohort	476	53	56.9	23.7	8	10.3	4.6	WBC (>10×10^9/L; ***); L (<1×10^9/L; ***); CRP (>10 mg/L; ***)	8
Zheng et al[31]	China	Retrospective Cohort	34	66	67.6	64.7	11.8	23.5	5.9	WBC (>10×10^9/L; NS); L (<0.8×10^9/L; NS)	8
Urra et al[32]	Spain	Retrospective Cohort	172	61.7	60.4	50.5	16.2	22.6	9.8	L (<1000/µL; **)	8
Hu et al[33]	China	Retrospective Cohort	95	57.6	41	28.4	8.4	13.7	1.1	WBC (>10×10^9/L; NA); N (>6.3×10^9/L; NA); PCT (≥0.1 ng/mL; NA)	8
Survivors vs. non-Survivors											
Chen et al[34]	China	Retrospective Cohort	274	62	62	34	8	17	7	WBC (>10×10^9/L; NA); N (>6.3×10^9/L; NA); L (<1×10^9/L; NA); PCT (≥0.05 ng/mL; NA)	8

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

Cao et al[35]	China	Cohort	102	54	52	27.5	4.9	10.8	9.8	L (<1.1×10^9/L; NA); CRP (>10 mg/L; NA); PCT (≥0.1 ng/mL; NA)	8
Zhou et al[36]	China	Retrospective Cohort	191	56	62	30	8	19	3	WBC (>10×10^9/L; NS); L (<0.8×10^9/L; ***); PCT (≥0.1 ng/mL; ***); Ferritin (>300 µg/L; ***)	8
Du et al[37]	China	Cohort	179	57.6	54.2	32.4	16.2	18.4	NA	WBC (>10×10^9/L; *); N (>6.3×10^9/L; ***); L (<1.1×10^9/L; NS); CRP (>10 mg/L; NS)	8
Liao et al[38]	China	Retrospective Cohort	231	64	54	30	6	16	NA	WBC (>9.5×10^9/L; ***); N (>6.3×10^9/L; ***); L (<1.1×10^9/L; *); CRP (>4 mg/L; NS); Ferritin (>500 µg/L; NS)	8
Mikami et al[39]	United States	Retrospective Cohort	2820	59	54.5	25.2	NA	17.7	2.7	WBC (>12×10^3/µl; NA); CRP (>150 mg/L; NA); PCT (≥0.5 ng/mL; NA); Ferritin (>400 ng/mL; NA)	8
Berengur et al[40]	Spain	Retrospective Cohort	4035	70	61	51.2	23.3	21.8	17.9	WBC (>12×10^9/L;***); L (<1000/µl;***); CRP (>5 mg/L;***); PCT (≥0.5 µg/L;***); Ferritin (>300 µg/L;*)	8
Perez-Guzman et al[41]	UK	Retrospective Cohort	614	69	62.2	46	7.8	35.1	4.8	WBC (>10.5×10^9/L; *); L (<1×10^9/L; NS); CRP (>10 mg/L; **); Ferritin (>300 ng/mL; NS)	8
Yang et al[42]	China	Retrospective Cohort	205	63	47	33	8	11	2	WBC (>10×10^9/L; NS); L (<1×10^9/L; ***); CRP (>10 mg/L; ***)	8
Pan et al[43]	China	Retrospective Cohort	124	68	68.5	50	15.3	20.2	8.9	WBC (>7.52×10^9/L; NS); N (>6.46×10^9/L; *); L (<0.64×10^9/L; ***); CRP (77 mg/L; ***); PCT (≥0.2 µg/L; ***)	8
Shang et al[44]	China	Retrospective Cohort	113	66	64.6	44.2	24.8	17.7	4.4	WBC (>9.5×10^9/L; NS); N (>6.3×10^9/L; **); L (<0.5×10^9/L; ***); CRP (>55 mg/L; ***); PCT (≥0.15 ng/mL; ***)	8
Xu et al[45]	China	Retrospective Cohort	239	62.5	59.8	43.9	14.6	18.4	5	L (<1.1×10^9/L; *)	8
Critical/non-Critical & Survivors/non-Survivors											
Chen et al[46]	China	Retrospective Cohort	548	56	57.1	27	6.4	11.1	1.3	L (<1.1×10^9/L; ***); CRP (>5 mg/L; ***); PCT (≥0.5 ng/mL; ***); Ferritin (>275 ng/mL; ***)	9
Zhang et al[47]	China	Retrospective Cohort	663	55.6	48.4	NA	24.7	NA	7.7	WBC (NA; ***); N (NA; ***); L (NA; **); CRP (NA; *)	9

† HTN: Hypertension; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; CRD: Chorionic Respiratory Disease

‡ WBC: Leukocytosis; N: Neutrophilia; L: Lymphopenia; CRP: increased level of C-reactive protein; PCT: increased level of procalcitonin; Ferritin: increased level of ferritin. £ N/A: not available.§ NS: no-significant difference; *: p<0.05; **: p<0.01; ***: p<0.001.

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

PRISMA 2009 Flow Diagram

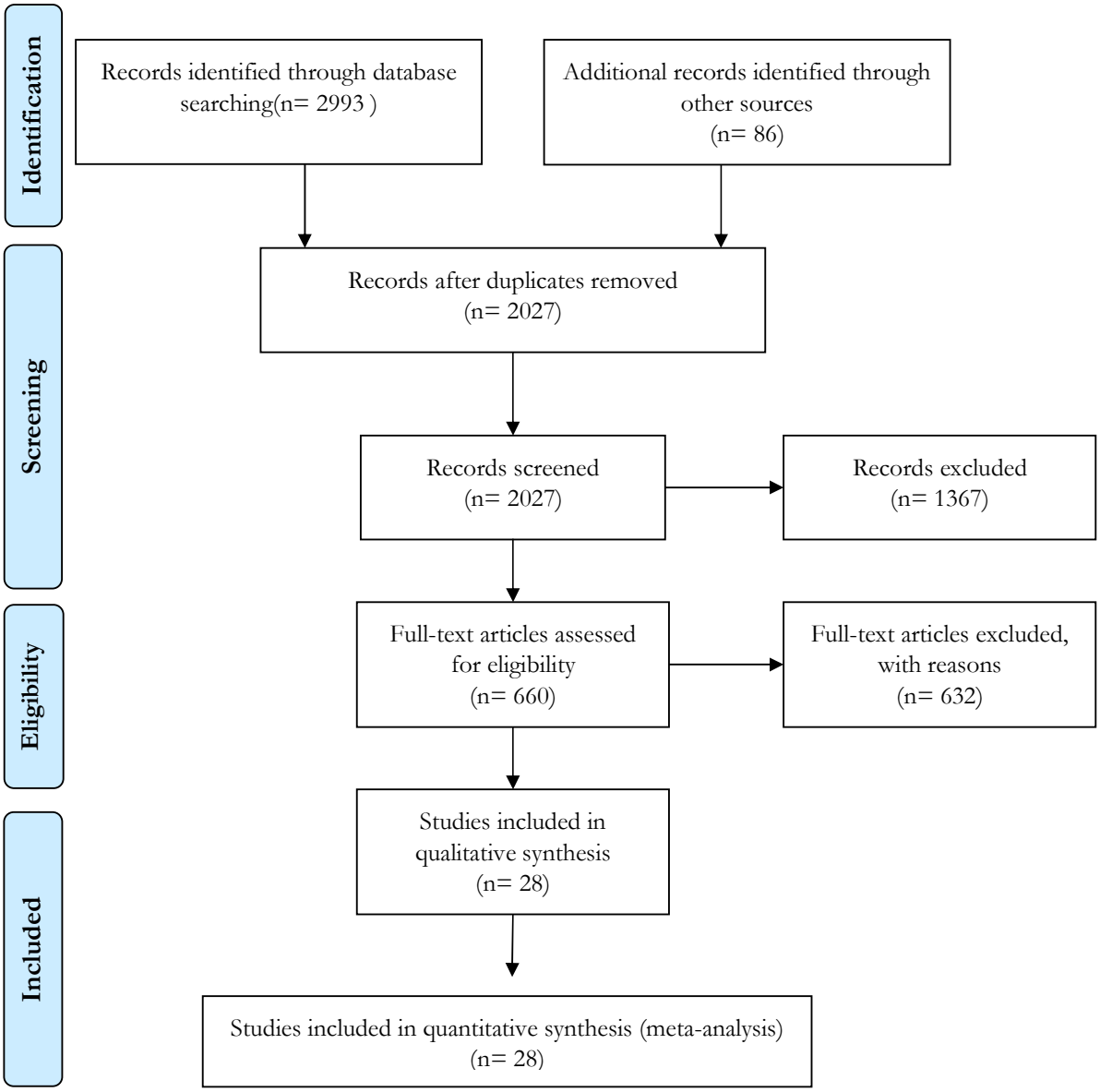
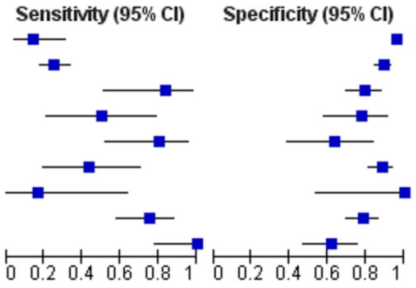


Figure 1. PRISMA flow diagram of Study selection

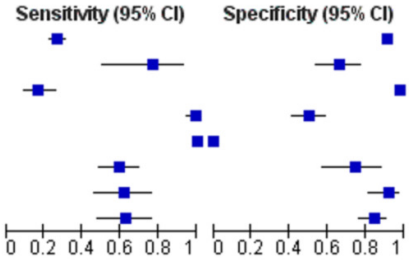
A

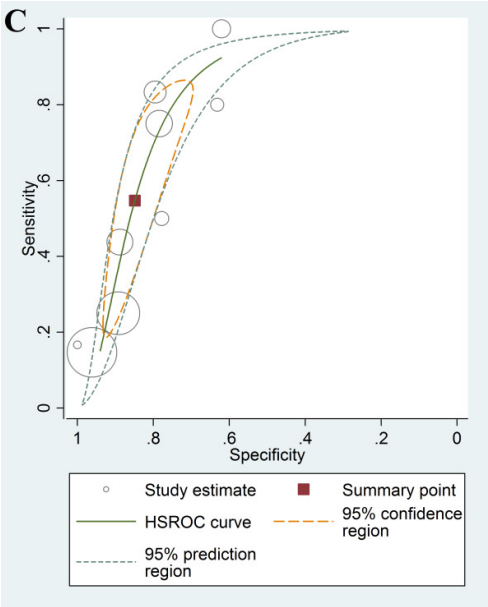
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chen R et al.	5	17	29	426	0.15 [0.05, 0.31]	0.96 [0.94, 0.98]
Goyal et al.	31	25	93	207	0.25 [0.18, 0.34]	0.89 [0.85, 0.93]
Hu et al.	10	17	2	66	0.83 [0.52, 0.98]	0.80 [0.69, 0.88]
Huang et al.	6	6	6	21	0.50 [0.21, 0.79]	0.78 [0.58, 0.91]
Lei et al.	12	7	3	12	0.80 [0.52, 0.96]	0.63 [0.38, 0.84]
Li et al.	7	13	9	103	0.44 [0.20, 0.70]	0.89 [0.82, 0.94]
Liu et al.	1	0	5	6	0.17 [0.00, 0.64]	1.00 [0.54, 1.00]
Wang D et al.	27	22	9	80	0.75 [0.58, 0.88]	0.78 [0.69, 0.86]
Wang F et al.	15	19	0	31	1.00 [0.78, 1.00]	0.62 [0.47, 0.75]



B

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berenguer et al.	119	105	320	1030	0.27 [0.23, 0.32]	0.91 [0.89, 0.92]
Cao et al.	13	22	4	43	0.76 [0.50, 0.93]	0.66 [0.53, 0.77]
Chen R et al.	14	8	70	385	0.17 [0.09, 0.26]	0.98 [0.96, 0.99]
Chen T et al.	95	70	1	70	0.99 [0.94, 1.00]	0.50 [0.41, 0.59]
Mikami et al.	581	1545	0	0	1.00 [0.99, 1.00]	0.00 [0.00, 0.00]
Pan et al.	53	9	36	26	0.60 [0.49, 0.70]	0.74 [0.57, 0.88]
Shang et al.	28	5	17	54	0.62 [0.47, 0.76]	0.92 [0.81, 0.97]
Zhou et al.	32	18	19	95	0.63 [0.48, 0.76]	0.84 [0.76, 0.90]





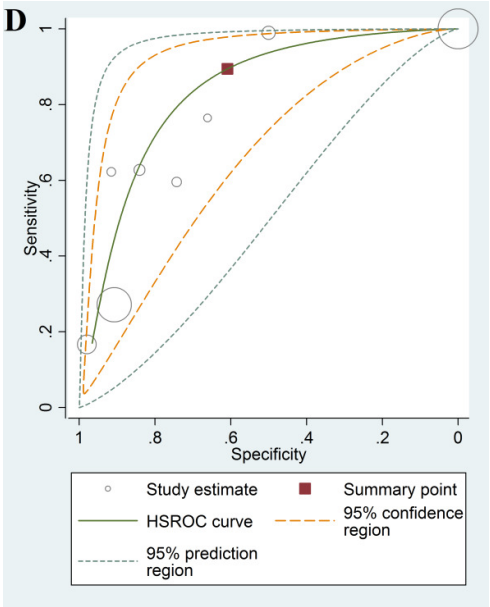


Figure 2. Evaluation of PCT for the prognosis of different outcomes. A. Forest plot of sensitivity and specificity for the prognosis of critical condition; B. Forest plot of sensitivity and specificity for the prognosis of mortality; C. HSROC for the prognosis of critical condition and D. HSROC for the prognosis of mortality (PCT: procalcitonin; HSROC: hierarchical summary receiver operating characteristic)

Table 2. The meta-analysis of white blood cell counts and inflammatory tests accuracies for the prognosis of critical condition and mortality in coronavirus disease 2019 (COVID-19) patients

Test	P-Se (95% CI)	P-Sp (95% CI)	P-LR+(95% CI)	P-LR-(95% CI)	P-DOR (95% CI)	AUC †
Critical vs. non-Critical						
Leukocytosis	0.32 (0.26-0.40)	0.91 (0.85-0.95)	3.82 (2.53-5.77)	0.73 (0.67-0.79)	5.20 (3.39-7.99)	0.55
Neutrophilia	0.60 (0.52-0.68)	0.88 (0.72-0.95)	5.10 (2.01-13.34)	0.44 (0.35-0.56)	11.58 (3.81-35.20)	0.72
Lymphopenia	0.86 (0.80-0.91)	0.42 (0.32-0.53)	1.51 (1.29-1.77)	0.31 (0.23-0.42)	4.85 (3.31-7.08)	0.75
Inc. PCT‡	0.54 (0.29-0.77)	0.84 (0.76-0.90)	3.62 (2.85-4.59)	0.53 (0.32-0.88)	6.78 (3.65-12.61)	0.80
Inc. CRP	0.97 (0.86-0.99)	0.20 (0.07-0.45)	1.22 (0.99-1.50)	0.11 (0.03-0.36)	11.05 (3.68-33.15)	0.73
Inc. Ferritin	-	-	-	-	-	-
Survivors vs. non-Survivors						
Leukocytosis	0.41 (0.26-0.57)	0.84 (0.76-0.90)	2.71 (2.13-3.46)	0.69 (0.56-0.84)	3.92 (2.83-5.43)	0.72
Neutrophilia	0.61 (0.56-0.66)	0.76 (0.69-0.82)	2.58 (1.92-3.48)	0.50 (0.43-0.59)	5.09 (3.31-7.84)	0.70
Lymphopenia	0.81 (0.72-0.87)	0.48 (0.37-0.60)	1.58 (1.31-1.92)	0.38 (0.27-0.53)	4.15 (2.66-6.46)	0.71
Inc. PCT	0.89 (0.24-0.99)	0.60 (0.11-0.94)	2.28 (0.70-7.41)	0.17 (0.02-1.32)	13.21 (3.95-44.19)	0.80
Inc. CRP	0.93 (0.83-0.97)	0.31 (0.17-0.49)	1.36 (1.12-1.65)	0.20 (0.10-0.39)	6.50 (3.40-12.68)	0.68
Inc. Ferritin	0.88 (0.79-0.94)	0.26 (0.22-0.31)	1.21 (1.11-1.31)	0.42 (0.23-0.77)	2.82 (1.45-5.49)	0.62

† P-Se: Pooled-sensitivity; P-Sp: Pooled-specificity; P-LR: Pooled-likelihood ratio; P-DOR: Pooled-diagnostic odds ratio; AUC: area under the curve.

‡ Inc.: increase in level; PCT: procalcitonin; CRP: C-reactive protein.

Table 3. Meta-regression analyses of covariates for procalcitonin

Covariate	Coefficient	Standard Error	Relative-DOR (95% CI) †	*p*
Critical vs. non-Critical				
Age	-0.017	0.0522	0.98 (0.87-1.12)	0.761
%Male	-0.032	0.0301	0.97 (0.90-1.04)	0.333
Hypertension	-0.014	0.0118	0.99 (0.96-1.02)	0.286
Cardiovascular Disease	-0.046	0.0328	0.96 (0.88-1.04)	0.214
Diabetes Mellitus	-0.039	0.0221	0.96 (0.91-1.02)	0.130
Chorionic Respiratory Disease	-0.150	0.1007	0.86 (0.67;1.10)	0.186
Survivors vs. non-Survivors				
Age	-0.056	0.0222	0.95 (0.89;1.01)	0.065
%Male	-0.011	0.0742	0.99 (0.80;1.22)	0.888
Hypertension	-0.038	0.0137	0.96 (0.93;1.00)	0.051
Cardiovascular Disease	-0.014	0.0455	0.99 (0.87;1.12)	0.774
Diabetes Mellitus	-0.097	0.0364	0.91 (0.82;1.00)	0.056
Chorionic Respiratory Disease	-0.063	0.0200	0.94 (0.89;0.99)	0.034

†Relative-DOR: relative-diagnostic odds ratio.

DISCUSSION

Many studies from the emerging of this infection have reported changes in inflammatory biomarkers and immune cell counts have a tight correlation with disease severity.[5,8] However, before the present study, there wasn't any data about their accuracies for the prognosis of different outcomes. Hence, in this DTA meta-analysis for the first time, we tried to determine the accuracies of white blood cell counts and inflammatory biomarkers which have prognostic utility for critical condition and mortality of COVID-19 patients. Based on our results, among white blood cell counts changes and inflammatory biomarkers, PCT is the only biomarker that has sufficient accuracy for the prognosis of poor outcomes including critical condition and mortality.

Based on our search strategy and inclusion criteria,

we finally found 28 studies in which all of them had "high" quality; using the NOS tool. Due to the low risk of bias for all included studies, we didn't perform the study restriction for our analyses. From these studies, 2999 patients were evaluated for critical/non-critical outcomes and 10388 patients for mortality outcomes. This is the first report that evaluated this number of patients with a different outcome. We could extract usable data for total white blood cell count, neutrophil count, lymphocyte count, serum level of CRP, and PCT in both groups. Nevertheless, the data of ferritin couldn't reach the inclusion criteria in the critical outcome group. Also, eosinopenia and SAA didn't meet the inclusion criteria for both groups.

PCT, CRP, and ferritin are important positive acute phase reactants in infectious diseases.[48] Some pieces of evidence increased serum levels of CRP and ferritin are associated with progression of disease severity in COVID-19 patients.[49,50] However, according to our results, these two biomarkers have not sufficient accuracy for the prognosis of critical condition and mortality. The results of assessed studies in our meta-analysis showed the levels of these two biomarkers increased in most SARS-CoV-2 infected patients with different outcomes lead to high TP and FP numbers in each study that is indicated by high sensitivity and low specificity. Thus, the accuracy of increased levels of CRP and ferritin achieved insufficient (AUC_{HSROC}< 0.80). In contrast, our results revealed an increased level of PCT has "good" accuracy for the prognosis of both critical condition and mortality (AUC_{HSROC}=0.80 for both conditions). Meanwhile, according to its pooled-DOR, PCT has more accuracy for the prognosis of mortality in comparison to critical conditions (Table 2). It has been shown PCT level increases in COVID-19 patients and it is more common in patients with higher severity of the disease. The results of two meta-analyses showed PCT level has a significant positive correlation with severity progression in SARS-CoV-2 infected patients and has a great potential as a prognostic biomarker for disease outcome,[8,49] although its accuracy wasn't determined.PCT is known as a peptide precursor of calcitonin hormone which is mainly produced by thyroidal cells. Serum level of PCT rises in bacterial infections in response to increases of pro-inflammatory cytokines like TNF-α and IL-6. However, it was shown serum level of PCT does not rise significantly in viral or non-infectious inflammations. Therefore, increases in PCT level is observed mainly in a more severe form of SARS-CoV-2 infected patients who had bacterial complications or higher levels of pro-inflammatory cytokines.

The results of previous studies have shown a change in the white blood cell population is one of the most prominent factors related to the severity and outcomes of SARS-CoV-2 infected patients.[5,8,49] It has been revealed that increased levels of total white blood cells and neutrophil count have a significant correlation with disease severity.[5,8] One of the suggested mechanisms for this increase is bacterial or fungal co-morbidity in a high number of SARS-CoV-2 infected patients with poor outcome.[23,36] Anyway, based on our results, total white blood cells, and neutrophil count haven't sufficient accuracy for the prognosis of critical condition and mortality (AUC_{HSROC}<0.80).

Another important biomarker in COVID-19 patients is lymphopenia.[5,8] Basically, lymphocytes count an increase in viral infection for the clearing of viral pathogens. However, a decrease in lymphocyte count in SARS-CoV-2 infected patients is important due to an understanding of its mechanism that may lead us to find an effective strategy for the treatment of COVID-19 patients. According to previous studies, there are some hypotheses for explaining this phenomenon. First, due to the expression of SARS-CoV-2 receptors, angiotensin-converting enzyme- 2 (ACE-2), lymphocytes can be directly infected by the virus and lead them to death.[51]The second hypothesis represents lymphocyte apoptosis induced by inflammatory and pro-inflammatory cytokines which increased in COVID-19 patients.[52] Other hypotheses propose a decrease of lymphocyte count may be caused by destroying of lymphatic organs or suppress the proliferation by lactic acidosis following COVID-19.[36,53] The exact mechanism of lymphopenia in COVID-19 patients and its correlation with disease severity is still unclear. Although a significant correlation between the lower count and the more disease severity has been revealed,[5,8] our results indicated lymphopenia has "fair" accuracy for the prognosis of both critical condition and mortality (AUC_{HSROC}=0.75 and 0.71, respectively). Lymphopenia is a common complication in SARS-CoV-2 infected patients with different outcomes leads to high TP and FP numbers in each study that is indicated by high sensitivity, low specificity, and insufficient accuracy.

The forest plots of sensitivity and specificity suggested heterogeneity, so we performed meta-

regression analysis to find potentially confounding covariates, including age, gender, hypertension, cardiovascular disease, diabetes mellitus, and chorionic respiratory disease (Table 3). Meta-regression did not reveal any factor that accounted for this heterogeneity in the critical/non-critical groups while chorionic respiratory disease in the survivor/non-survivor group contributed to heterogeneity.

There were other tests like eosinophil count and Serum Amyloid-A which couldn't meet the inclusion criteria. Further studies for assessing the prognostic accuracy of these tests seem necessary due to their important role in the prognosis of outcomes which were shown in some studies.[26,54]

Although we conducted this meta-analysis on a large number sample size (2999 COVID-19 patients in the critical outcome and 10388 patients in mortality outcome) and different countries with diverse patient races which were the most important limitations of previous meta-analyses, some limitations should be noted meanwhile. First, the most included studies were retrospective cohorts that have insufficient demonstration ability and limiting their ability to infer definitive causality. Second, all prospective cohort studies were from China make limitations for evaluating other patient populations in other countries.

In conclusion, our results indicated PCT has "good" accuracy for the prognosis of critical condition and mortality outcome COVID-19 patients and it can use as a single prognostic laboratory biomarker for poor outcomes. Besides, according to its pooled-DOR, PCT has more accuracy for the prognosis of mortality in comparison to critical conditions. Other immunological biomarkers containing leukocytosis, neutrophilia, lymphopenia, increased level of CRP and ferritin haven't sufficient accuracy as prognostic markers for those conditions.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

This research received no grant from any financial organizations or funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, et al. Coronavirus disease 2019–COVID-19. Clin Microbiol Rev. 2020;33(4):1–48.
2. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): A literature review. J Infect Public Health. 2020;13(5):667–73.
3. Nourizadeh M, Rasaee MJ, Moin M. COVID-19 Pandemic: A Big Challenge in Iran and the World. Iran J Allergy Asthma Immunol. 2020;19(S1):1–2.
4. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.
5. Soraya GV, Ulhaq ZS. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: An updated meta-analysis. Med Clin (Barc). 2020;155(4):143–51.
6. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020;58(7):1131–4.
7. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med. 2020;58(7):1063–9.
8. Feng X, Li S, Sun Q, Zhu J, Chen B, Xiong M, et al. Immune-inflammatory parameters in COVID-19 cases: A systematic review and meta-analysis. Front Med. 2020;7:1–14.
9. Gatsonis C, Paliwal P. Meta-analysis of diagnostic and screening test accuracy evaluations: methodologic primer. Am J Roentgenol. 2006;187(2):271–81.
10. Šimundić A-M. Measures of diagnostic accuracy: basic definitions. Ejifcc. 2009;19(4):203.
11. Lee J, Kim KW, Choi SH, Huh J, Park SH. Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers-part II. Statistical methods of meta-analysis. Korean J Radiol. 2015;16(6):1188–96.
12. Kim KW, Lee J, Choi SH, Huh J, Park SH. Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: A practical review for clinical researchers–part I. general guidance and tips. Korean J Radiol. 2015;16(6):1175–87.
13. Mathes T, Pieper D. An algorithm for the classification of study designs to assess diagnostic, prognostic and predictive test accuracy in systematic reviews. Syst Rev. 2019;8(1):226.

14. Zhao J-Y, Yan J-Y, Qu J-M. Interpretations of "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)". Chin Med J (Engl). 2020;133(11):1347–9.
15. Zeng X, Zhang Y, Kwong JSW, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015;8(1):2–10.
16. Sabbagh HJ, Hassan MHA, Innes NPT, Elkodary HM, Little J, Mossey PA. Passive smoking in the etiology of non-syndromic orofacial clefts: A systematic review and meta-analysis. PLoS One. 2015;10(3):1–21.
17. Safari S, Baratloo A, Elfil M, Negida A. Evidence-based emergency medicine; part 5 receiver operating curve and area under the curve. Emergency. 2016;4(2):111.
18. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol. 2010;5(9):1315–6.
19. Freeman SC, Kerby CR, Patel A, Cooper NJ, Quinn T, Sutton AJ. Development of an interactive web-based tool to conduct and interrogate meta-analysis of diagnostic test accuracy studies: MetaDTA. BMC Med Res Methodol. 2019;19(1):81.
20. Wang F, Hou H, Luo Y, Tang G, Wu S, Huang M, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI Insight. 2020;5(10):e137799.
21. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020;323(11):1061–9.
22. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020;95(6):E131–4.
23. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
24. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63(3):364–74.
25. Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine. 2020;21:100331.
26. Li H, Xiang X, Ren H, Xu L, Zhao L, Chen X, et al. Serum Amyloid A is a biomarker of severe Coronavirus Disease and poor prognosis. J Infect. 2020;80(6):646–55.
27. Chen Q, Xu L, Dai Y, Ling Y, Mao J, Qian J, et al. Cardiovascular manifestations in severe and critical patients with COVID-19. Clin Cardiol. 2020;43(7):796–802.
28. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372–4.
29. Chan SSW, Christopher D, Tan GB, Chong VCL, Fan BE, Lin CY, et al. Peripheral lymphocyte subset alterations in COVID-19 patients. Int J Lab Hematol. 2020;1–5.
30. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with different severities: A multicenter study of clinical features. Am J Respir Crit Care Med. 2020;201(11):1380–8.
31. Zheng Y, Sun L jun, Xu M, Pan J, Zhang Y tao, Fang X ling, et al. Clinical characteristics of 34 COVID-19 patients admitted to intensive care unit in Hangzhou, China. J Zhejiang Univ Sci B. 2020;21(5):378–87.
32. Urra JM, Cabrera CM, Porras L, Ródenas I. Selective CD8 cell reduction by SARS-CoV-2 is associated with a worse prognosis and systemic inflammation in COVID-19 patients. Clin Immunol. 2020;217:108486.
33. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. Int J Antimicrob Agents. 2020;56(2):8–10.
34. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ. 2020;368:m1091.
35. Cao J, Tu WJ, Cheng W, Yu L, Liu YK, Hu X, et al. Clinical Features and Short-term Outcomes of 102 Patients with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71(15):748–55.
36. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
37. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J. 2020;55(5):2000524.
38. Liao D, Zhou F, Luo L, Xu M, Wang H, Xia J, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol. 2020;3026(Dic):1–8.

39. Mikami T, Miyashita H, Yamada T, Harrington M, Steinberg D, Dunn A, et al. Risk Factors for Mortality in Patients with COVID-19 in New York City. J Gen Intern Med. 2020;1–10.
40. Berenguer J, Ryan P, Rodríguez-Baño J, Jarrín I, Carratalà J, Pachón J, et al. Characteristics and predictors of death among 4,035 consecutively hospitalized patients with COVID-19 in Spain. Clin Microbiol Infect. 2020;(ahead of print).
41. Perez-Guzman PN, Daunt A, Mukherjee S, Crook P, Forlano R, Kont MD, et al. Clinical characteristics and predictors of outcomes of hospitalized patients with COVID-19 in a multi-ethnic London NHS Trust: a retrospective cohort study. Clin Infect Dis. 2020;(ahead of print).
42. Yang K, Sheng Y, Huang C, Jin Y, Xiong N, Jiang K, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):904–13.
43. Pan F, Yang L, Li Y, Liang B, Li L, Ye T, et al. Factors associated with death outcome in patients with severe coronavirus disease-19 (Covid-19): A case-control study. Int J Med Sci. 2020;17(9):1281–92.
44. Shang Y, Liu T, Wei Y, Li J, Shao L, Liu M, et al. Scoring systems for predicting mortality for severe patients with COVID-19. EClinicalMedicine. 2020;24:100426.
45. Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: A multicenter retrospective study from Wuhan, China. Crit Care. 2020;24(1):1–11.
46. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol. 2020;146(1):89–100.
47. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect. 2020;26(6):767–72.
48. Markanday A. Acute Phase Reactants in Infections: Evidence-Based Review and a Guide for Clinicians. Open Forum Infect Dis. 2015;2(3):ofv098.
49. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;S0163-4453(20):30234–6.
50. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis. 2020;14:1–14.
51. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12(1):1–5.
52. Liao Y-C, Liang W-G, Chen F-W, Hsu J-H, Yang J-J, Chang M-S. IL-19 induces production of IL-6 and TNF-α and results in cell apoptosis through TNF-α. J Immunol. 2002;169(8):4288–97.
53. Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, et al. Inhibitory effect of tumor cell–derived lactic acid on human T cells. Blood. 2007;109(9):3812–9.
54. Liu F, Xu A, Zhang Y, Xuan W, Yan T, Pan K, et al. Patients of COVID-19 may benefit from sustained Lopinavir-combined regimen and the increase of Eosinophil may predict the outcome of COVID-19 progression. Int J Infect Dis. 2020;95:183–91.