Meta-Analysis Article

Prognostic Accuracy of Cardiovascular Disease Biomarkers in Patients with COVID-19: A Diagnostic Test Accuracy Meta-Analysis

Atefeh Nasir Kansestani, MSc[1,2], Mohammad Erfan Zare, MSc[1,2], Jun Zhang, PhD[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.*

Received 11 September 2020; Accepted 18 November 2020

Abstract

Background: *Several reports have determined that cardiovascular diseases (CVDs) are common complications in patients with coronavirus disease 2019 (COVID-19) and lead them to poor outcomes. CVD biomarkers have, thus, great potential to be used as prognostic biomarkers. We aimed to determine the accuracy of CVD biomarkers for the prognosis of the COVID-19 patient's outcome via a diagnostic test accuracy (DTA) meta-analysis.*

Methods: *Until September 30, 2020, we searched Web of Sciences, Scopus, and MEDLINE/PubMed databases to obtain related papers. The summary points and lines were calculated using bivariate/HSROC model. As outcomes, we considered critical conditions and mortality.*

Results: *A total of 17 659 patients from 33 studies were included. Five biomarkers, namely increased levels of lactate dehydrogenase (LDH), cardiac troponin I (cTnI), creatine kinase (CK), D-dimer, and thrombocytopenia, met the inclusion criteria. Our results indicated that LDH and cTnI had good accuracy for the prognosis of critical condition (AUCHSROC=0.83 and 0.80, respectively), while LDH, cTnI, and D-dimer had acceptable accuracy (AUCHSROC=0.74, 0.71, and 0.72, respectively) for the prognosis of mortality. LDH and D-dimer had high sensitivity, whereas cTnI had high specificity. The other biomarkers did not have acceptable accuracy. Significant publication bias was found for D-dimer (P=0.053).*

Conclusion: *Among CVD biomarkers, LDH and cTnI had good accuracy for the prognosis of critical outcomes and acceptable accuracy for the prognosis of mortality, without publication bias. Given their different sensitivities and specificities, we recommend the use of these 2 biomarkers concomitantly.*

J Teh Univ Heart Ctr 2021;16(1):1-14

This paper should be cited as: Nasir Kansestani A, Zare ME, Zhang J. Prognostic Accuracy of Cardiovascular Disease Biomarkers in Patients with COVID-19: A Diagnostic Test Accuracy Meta-Analysis. J Teh Univ Heart Ctr 2021;16(1):1-14.

Keywords: *COVID-19; Biomarkers; Lactate dehydrogenase; Troponin I; Prognosis*

Introduction

Since December 2019, a viral strain of pneumonia has attacked all human beings. This virus was named "severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)" by the International Committee on Taxonomy of Viruses,

[*]**Corresponding Author:** ***Jun Zhang,*** *Department of Clinical Laboratory, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, 3 Qingchun East Road, Hangzhou 310016, China. Tel: +86 571 86006611. Fax: +86 571 86006611. E-mail: jameszhang2000@zju.edu.cn.*

and this pneumonia was called "Coronavirus Disease 2019 (COVID-19)" by the World Health Organization (WHO).[1]

COVID-19 contains diverse clinical outcomes ranging from the absence of symptoms to a fatal disease.[1] This pandemic condition has posed many countries formidable challenges regarding the management of medical resources, especially for critical patients. Therefore, the identification of biomarkers with early prognostic utilities for patient outcomes is vitally important. In a pandemic condition, it is recommended that routine biomarkers be introduced as prognostic markers because they can be used in all medical facilities, from simple to advanced.[2, 3]

Evidence indicates that cardiovascular diseases (CVDs) are a common complication among patients with COVID-19 and are responsible for critical conditions and mortality.[4, 5] Thus, the biomarkers of this complication could be used as prognostic biomarkers for poor patient outcomes providing that they have high accuracy. To determine the accuracy of a biomarker and introduce it as a diagnostic/prognostic biomarker, investigators have recommended diagnostic test accuracy (DTA) systematic reviews and meta-analyses.[6, 7] Nonetheless, until now, there has been no DTA study to introduce valid CVD biomarkers for the prognosis of critical conditions and mortality in patients with COVID-19.

Accordingly, for the first time, via a DTA study, we aimed to determine the prognostic accuracy of CVD laboratory biomarkers, including increased levels of lactate dehydrogenase (LDH), cardiac troponin I (cTnI), creatine kinase (CK), creatine kinase-MB (CK-MB), N-terminal proBNP (NT-proBNP), D-dimer, fibrinogen degradation product (FDP), prothrombin time (PT), partial thromboplastin time (PTT), and thrombocytopenia, for the prognosis of the outcome of patients with COVID-19.

Methods

The search strategy of the present systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A systematic search was conducted on the electronic databases Web of Sciences (WOS), Scopus, and MEDLINE/PubMed from December 12, 2019, to September 30, 2020, 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 "cardiac injury" OR "lactate dehydrogenase" OR "troponin" OR "creatine kinase" OR "creatine kinase-MB" OR "N-terminal proBNP" OR "platelet" OR "D-dimer" OR "fibrinogen degradation product"). The reference lists of each selected paper and relevant systematic and narrative reviews on the topic were checked to identify missing studies. Duplicate papers were excluded through the import of records into EndNote, version X9 (Thomson Reuters Corp).

One of the authors screened the title and abstract of all the records obtained.

The inclusion criteria for the present study were as follows: 1) SARS-CoV-2 infection diagnosed with the real-time polymerase chain reaction (PCR) technique, 2) clinical characteristics and the results of laboratory biomarkers determined by the presence of surviving and non-surviving patients or critical conditions (ie, intensive care unit [ICU] admission, need for mechanical ventilation, and/or organ failure due to COVID-19)[8] as opposed to noncritical forms of the disease (ie, mild, moderate, and severe), 3) clear presentation of the type and number of abnormal laboratory biomarker results (changes out of local reference ranges), and 4) presence of at least 4 studies for each laboratory parameter.

Studies were excluded if they met the following criteria: 1) SARS-CoV-2 infection diagnosed with the non–real-time PCR technique, 2) duplicate publications, 3) reviews, meta-analyses, and case reports, 4) investigations failing to discriminate between their different study groups, 5) studies assessing single groups (eg, evaluating non-surviving patients or all patients with COVID-19 as 1 group), and 6) studies performed on special groups of patients such as pregnant women and children.

No recommended tool currently exists for the assessment of the quality of studies included in a prognostic DTA study.[9] Hence, the present study employed a renowned tool for analytical studies: the Newcastle-Ottawa Scale (NOS). The included studies were evaluated for their methodological quality by NOS with a maximum of 9 points in the 3 major categories of selection, comparability, and outcome. Based on previous studies, an overall point of 6 or greater was considered a low bias risk for each study, with such studies being categorized as good quality. Further, studies with overall points of 3 to 5 and less than 3 were categorized as moderate quality and poor quality, respectively.[10] Analyses were restricted to moderate or poor-quality studies.

With the extracted and calculated data obtained from the included studies, 2×2 contingency tables were constructed. For the investigation of the true-positive, false-positive, true-negative, and false-negative values of each biomarker, the number/percentage of the laboratory biomarker results that were out of local reference ranges was extracted from the included studies.

For each biomarker, a 2×2 contingency table was constructed and sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR) were calculated. Summary points, containing pooled sensitivity, pooled specificity, pooled positive likelihood ratio, pooled negative likelihood ratio, and pooled DOR, were considered for the meta-analysis report.

The separate pooling of these summary points is associated with limitations; consequently, a bivariate model was utilized in the present study. This model accounts for the correlation between sensitivity and specificity and between-study heterogeneity via a random-effects approach.[7] A summary of the line parameters was calculated through a composition of a hierarchical summary receiver operating characteristic (HSROC) curve, and the area under the curve (AUC_{HSROC}) was obtained by trapezoidal integration.[7] AUC_{HSROC} values indicate the diagnostic (prognostic) accuracy of each laboratory biomarker and range between a minimum of 0.5 to a maximum of 1. An AUC_{HSROC} of 1 signifies the most accurate biomarker for discriminating a favorable characteristic from an unfavorable one, while an AUC_{HSROC} of 0.5 indicates a non-discriminating biomarker. In general, AUC_{HSROC} values of 0.5 to 0.69 are regarded as not acceptable, 0.70 to 0.79 acceptable, 0.80 to 0.89 good, and 0.90 to 1 excellent.[11, 12] The diagnostic accuracy was compared between the different biomarkers in the same AUC_{HSROC} category with the aid of the relative diagnostic odds ratio (RDOR) and its P value. All biomarkers were analyzed and summarized for reporting with 95% confidence intervals (95% CI). All the statistical analyses were carried out with STATA 12 (Stata Corp, College Station, TX) and the R software, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria), with Mada package and its online based application, MetaDTA.[13]

Heterogeneity was assessed using the I^2 inconsistency test. An I^2 value of greater than 50% indicates substantial heterogeneity; consequently, the potential sources of heterogeneity regarding covariates, including age, gender, hypertension, CVDs, diabetes mellitus, and chronic respiratory disease, were identified via a univariate meta-regression method utilizing Meta-Disc 1.4 (XI, Cochrane Colloquium, Barcelona, Spain). Further, the Spearman correlation coefficient was calculated to determine the threshold effect as a source of heterogeneity. Additionally, publication bias was investigated by drawing the Deeks funnel plot for each biomarker, with a P value of less than 0.10 for the slope coefficient indicating significant publication bias. The analyses of publication bias were carried out by using STATA 12 (Stata Corp, College Station, TX) with the MIDAS command.

In these meta-analyses, except for publication bias, all the reports were considered to be of statistical significance if they had a P value of 0.05 or less.

Results

Of 3141 studies initially selected, 1394 were excluded due to duplication and 963 were excluded after the screening of titles and abstracts. Finally, 784 studies were subjected to full-text assessment. The most frequent reasons for the exclusion of studies were as follows: 1) non-discrimination between patients with severe and critical diseases, 2) lack of clearance concerning the number/percentage of the laboratory biomarker results that were out of local reference ranges, and 3) inclusion of only 1 group (eg, reporting data regarding only mortality). Ultimately, 33 studies were eligible for assessment (Table 1, Table 2, and Figure 1). Of this total, 14 studies assessed the associations between clinical characteristics and laboratory results and critical/noncritical outcomes,[14, 15-27] 14 studies evaluated the associations between clinical characteristics and laboratory results and mortality,[28-41] and 5 studies assessed the associations between characteristics and laboratory results and both critical/noncritical outcomes and mortality concurrently.[42–46] Totally, 3940 patients were evaluated for critical/noncritical outcomes and 13719 patients for mortality. The NOS score for all the studies was a minimum of 8 (ie, good quality), signifying no risk of bias (Table 1 and Table 2). The differences between the studies in terms of point achievement were associated with the comparability category, and all the studies achieved maximum points in the selection and outcome categories.

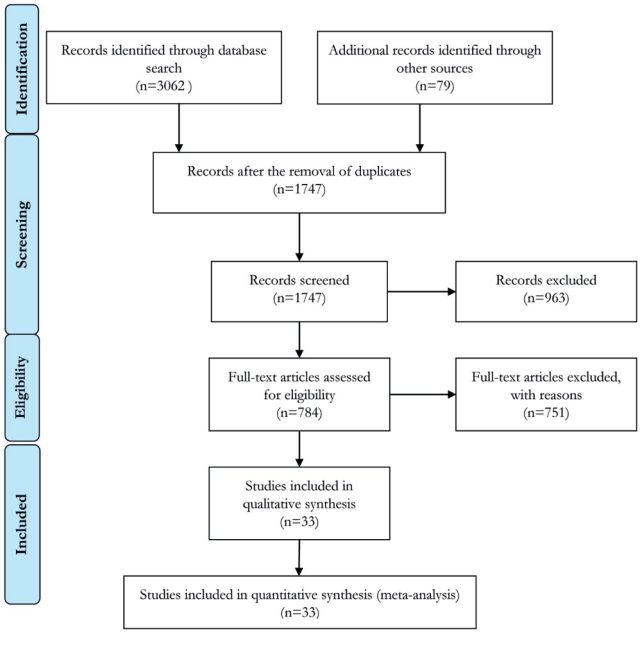


Figure 1. PRISMA flow diagram of the study selection

Increased levels of CK-MB, NT-proBNP, FDP, PT, and PTT failed to meet the inclusion criteria. Except for CK, all the other evaluated biomarkers fulfilled the inclusion criteria in both groups. Increased levels of CK did not meet the inclusion criteria for the assessment of critical outcomes, but it was eligible for the mortality outcome. For the prognosis of critical conditions, LDH and cTnI had good accuracy (AUC_{HSROC}=0.83 and 0.80, respectively), while

Table 1. Characteristics of the included studies in the critical outcome group

First Author	Country	Study design	Sample size	Age	%Male	%HTN	%CVD	%DM	%CRD	Extracted Biomarker(s) (Threshold; Significance)	NOS score
Wang F.[14]	China	C	65	57.1	57	NA	NA	NA	NA	LDH (NA; *); D-D (NA; *)	8
Li H.[15]	China	RC	132	62	56.8	NA	NA	NA	NA	Plt (>350×109/L; NS)	8
Han H.[24]	China	RC	273	58.4	35.5	NA	NA	NA	NA	TnI (>0.04 ng/mL; N/A)	8
Li Y.[25]	China	RC	53	61.8	62.9	27.7	12.9	12.9	7.4	D-D (>0.5 g/mL FEU; ***)	8
Hu R.[26]	China	RC	95	57.6	41	28.4	8.4	13.7	1.1	D-D (>0.5 mg/L;NA)	8
Li X.[27]	China	RC	269	65	71.7	NA	NA	NA	NA	LDH (> 250; *); D-Dimer (>1 mg/L; ***)	8
Chan SSW.16	Singapore	RC	75	50	66.7	NA	NA	NA	NA	Plt (<100×109/L; *)	8
Fan BE.[17]	Singapore	RC	67	42	55.2	NA	NA	NA	NA	LDH (> 550 U/L; ***); Plt (<100×109/L; ***)	8
Huang C.[18]	China	RC	41	49	73	15	15	20	2	LDH (>245 U/L;NA); TnI (≥28 pg/mL; *); Plt (< 100×109/L; NA); CK (>185 U/L; NA)	8
Liu Y.[19]	China	RC	12	53.6	66.6	25	33.3	16.6	8.3	LDH (>240 U/L;NA); TnI (≥0.1 µg/mL; *); Plt (< 100×109/L; NA); CK (>310 U/L; NA)	9
Chen C.[20]	China	RC	150	61	52.3	32.6	6	13.3	NA	TnI (>ng/L;***)	8
Goyal P.[21]	United States	RC	393	62.2	60.6	50.1	13.7	25.2	5.1	TnI (>0.5 ng/mL; NA); D-D (>0.5 mg/L; NA); Plt (<150 ×103 mm3; NA)	8
Feng Y.[22]	China	RC	476	53	56.9	23.7	8	10.3	4.6	TnI (NA; *)	8
Zhou B.[23]	China	RC	34	65	50	NA	NA	NA	NA	LDH (NA;**); TnI (NA;***); CK(NA;*)	8
Zhang J.[42]	China	RC	663	55.6	48.4	NA	24.7	NA	7.7	LDH (NA; *)	9
Chen R.[43]	China	RC	548	56	57.1	27	6.4	11.1	1.3	D-D (>0.5 ug/mL; ***); Plt (< 125 × 109 /L; ***)	9
Liao D.[44]	China	RC	231	64	54	30	6	16	NA	Plt (< 100 × 109 /L; ***)	9
Long H.[45]	China	RC	115	63.5	57.4	NA	NA	NA	NA	D-D (>0.5 mg/L; NA)	9
Yao Y.[46]	China	RC	248	61	54.4	31.4	4.8	17.7	1.6	D-D (>0.5 ug/mL;NA)	9

HTN, Hypertension; CVD, Cardiovascular diseases; DM, Diabetes mellitus; CRD, Chorionic respiratory disease; NOS, Newcastle-Ottawa Scale; C, Cohort; NA, Not available; RC, Retrospective cohort; WBC, White blood cells leukocytosis); LDH, Lactate dehydrogenase; TnI, Troponin I; CK, Creatine kinase; D-D, D-dimer; Plt, Platelet; NS, No significant difference; *: P<0.05; **: P<0.01; ***: P<0.001

Table 2. Characteristics of the included studies in the mortality outcome group

First Author	Country	Study design	Sample size	Age	%Male	%HTN	%CVD	%DM	%CRD	Extracted Biomarker(s) (Threshold; Significance)	NOS score
Yang X.[28]	China	RC	1476	61.5	52.5	NA	NA	NA	NA	Plt (<125 ×109/L; ***)	8
Chen T.[29]	China	RC	274	62	62	34	8	17	7	LDH (>350 U/L); TnI (>15.6 pg/m)	9
Si D.[38]	China	RC	1159	62.5	NA	NA	NA	NA	NA	TnI (> 26.2 pg/mL; ***)	8
Liu Y.[41]	China	RC	383	46	42.3	21.1	3.7	9.4	4.4	Plt (<105 ×109/L; ***)	8
Shang Y.[39]	China	RC	113	66	64.6	44.2	24.8	17.7	4.4	D-D (>0.5 ug/mL; ***); Plt (<150 ×109/L; NS)	8
Xu J.[40]	China	RC	239	62.5	59.8	43.9	14.6	18.4	5	Plt (< 125 × 109 /L; ***)	8
Cao J.[30]	China	C	102	54	52	27.5	4.9	10.8	9.8	TnI (≥26 pg/m; NA); D-D (≥500 mg/L; NA)	8
Mikami T.[31]	United States	RC	2820	59	54.5	25.2	NA	17.7	2.7	LDH (> 440 U/L; NA); TnI (> 0.03 ng/dL; NA); D-D (> 2 µg/mL; NA)	8
Perez-Guzman PN.[32]	UK	RC	614	69	62.2	46	7.8	35.1	4.8	LDH (>243 IU/L; NS); TnI (>34 ng/L; **); CK (>320 U/L; **); D-D (>3000 ng/mL; NS); Plt (<130×109/L; **)	9
Pan F.[33]	China	RC	124	68	68.5	50	15.3	20.2	8.9	LDH (>481IU/L; NA); TnI (>19.3µg/L; NA); D-D (>3.06 mg/mL; NA); Plt (≤187×109/L; NS)	8
Zhou F.[34]	China	RC	191	56	62	30	8	19	3	LDH (>245 U/L;***); TnI (>28 pg/m; ***); CK (>185 U/L; *); D-D (>0.5 ug/mL; NS); Plt (< 100 × 109 /L; ***)	8
Yang K.[35]	China	RC	205	63	47	33	8	11	2	LDH (>245 U/L;*); CK (>185 U/L; *); D-D (>0.5 mg/L; ***); Plt (< 100 × 109 /L; *)	8
Berenguer J.[36]	Spain	RC	4035	70	61	51.2	23.3	21.8	17.9	LDH (>250IU/L; ***); CK (>190 U/L; ***); D-D (>500 ng/mL; ***); Plt (<150 ×103 mm3; ***)	8
Du R-H.[37]	China	C	179	57.6	54.2	32.4	16.2	18.4	NA	TnI (>0.1 ng/mL; ***); D-D (>0.5 mg/L; *)	8
Zhang J.[42]	China	RC	663	55.6	48.4	NA	24.7	NA	7.7	LDH (NA; *)	9
Chen R.[43]	China	RC	548	56	57.1	27	6.4	11.1	1.3	D-D (>0.5 ug/mL; ***); Plt (< 125 × 109 /L; ***)	9
Liao D.[44]	China	RC	231	64	54	30	6	16	NA	LDH (>250IU/L; ***); D-D (>0.5 mg/L; ** *); Plt (< 100 × 109 /L; ***)	9
Long H.[45]	China	RC	115	63.5	57.4	NA	NA	NA	NA	D-D (>0.5 mg/L; NA)	9
Yao Y.[46]	China	RC	248	61	54.4	31.4	4.8	17.7	1.6	D-D (>0.5 ug/mL;NA	9

HTN, Hypertension; CVD, Cardiovascular diseases; DM, Diabetes mellitus; CRD, Chorionic respiratory disease; NOS, Newcastle-Ottawa Scale; C, Cohort; NA, Not available; RC, Retrospective cohort; WBC, White blood cells leukocytosis); LDH, Lactate dehydrogenase; TnI, Troponin I; CK, Creatine kinase; D-D, D-dimer; Plt, Platelet; NS, No significant difference; *: P<0.05; **: P<0.01; ***: P<0.001

none of the other CVD biomarkers had acceptable accuracy (AUC_{HSROC}<0.70). According to another accuracy summary point (ie, pooled DOR), cTnI had higher accuracy than LDH for the prognosis of critical conditions (cTnI=9.53; 95% CI: 9.39–9.68 vs LDH=5.80; 95% CI: 2.51–13.41) (Table 3). However, based on RDOR, there was no significant difference between the accuracy of cTnI and LDH (RDOR cTnI/LDH=1.37; 95% CI: 0.05–38.64; P=0.831). Moreover, LDH had higher sensitivity than cTnI, whereas cTnI had higher specificity than LDH (Table 3 and Figure 2). These findings revealed that the parallel use of these 2 biomarkers could augment accuracy for the early prognosis of critical conditions.

For the prognosis of mortality, LDH, cTnI, and D-dimer had acceptable accuracy (AUC_{HSROC}=0.74, 0.71, and 0.72, correspondingly). Among these 3 biomarkers, based on pooled-DOR, for the prognosis of mortality, cTnI was the most accurate biomarker, followed by D-dimer and LDH (Table 3). Nonetheless, based on RDOR, there were no significant differences between the accuracy of cTnI, LDH, and D-dimer (RDOR cTnI/LDH=1.07; 95% CI: 0.26–4.39; P=0.916 and RDOR cTnI/D-dimer=1.06; 95% CI: 0.31–3.57; P=0.924). Additionally, LDH and D-dimer had more sensitivity than cTnI, whereas cTnI had the highest specificity (Table 3 and Figure 3).

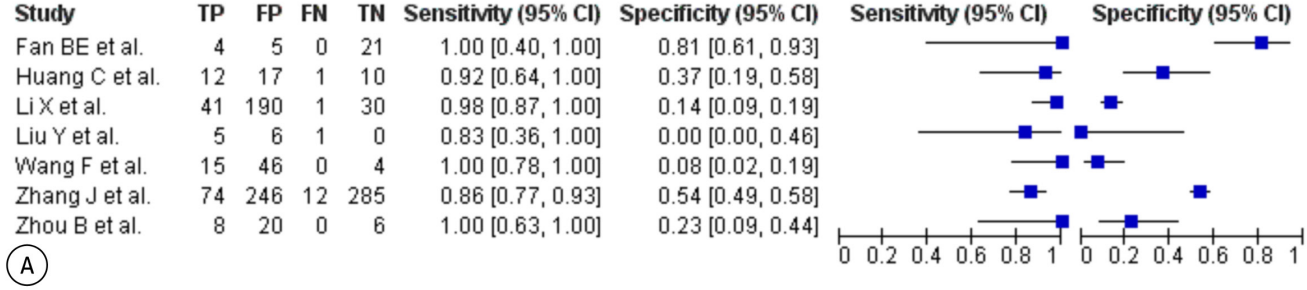
Regarding LDH, cTnI, and D-dimer, substantial heterogeneity was found between the selected studies when pooled sensitivity and specificity were calculated in the critical outcome and mortality groups (Table 3). Since the first primary cause of heterogeneity is the threshold effect in diagnostic accuracy studies, the present study evaluated it as an important source of heterogeneity. The Spearman correlation test showed that the threshold effect made no significant contribution to the heterogeneity of LDH and cTnI in the critical outcome group (P=0.381 and 0.457, respectively) and the heterogeneity of LDH and D-dimer in the mortality outcome group (P=0.653 and 0.871, respectively). Still, the threshold effect made a significant contribution as a source of heterogeneity for cTnI in the mortality outcome group (P=0.022). For this biomarker, the proportion of heterogeneity likely due to the threshold effect was 22%.

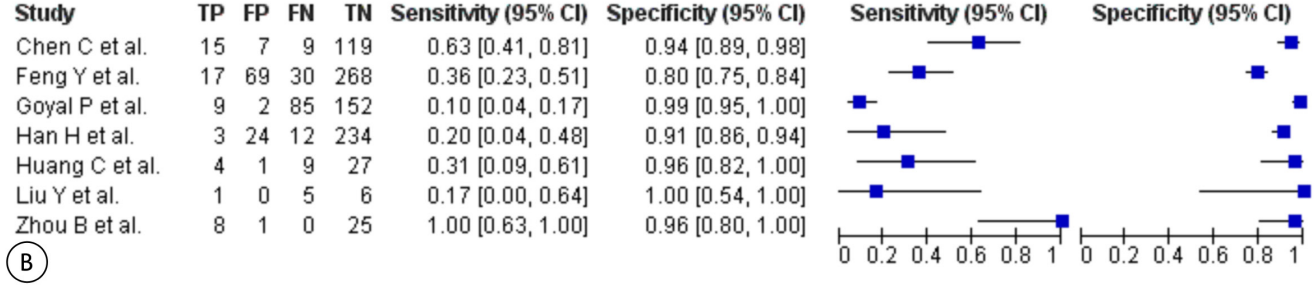
Other potential sources of heterogeneity were determined via a meta-regression analysis for extractable covariates, comprised of age, gender, hypertension, CVDs, diabetes mellitus, and chorionic respiratory disease (Table 4). In the critical/noncritical group, for LDH and cTnI, this analysis indicated no source of heterogeneity among the covariates (P>0.05), whereas, in the surviving/non-surviving group, the meta-regression analysis indicated that hypertension and diabetes mellitus for cTnI (P=0.004 for both covariates) and diabetes mellitus and chorionic respiratory disease for D-dimer (P=0.040 and 0.024, respectively) contributed as a source of heterogeneity.

The Deeks funnel plot showed that publication bias was not statistically significant for LDH and cTnI in both critical and mortality outcome groups (P>0.1). However, significant publication bias was found for D-dimer in the mortality outcome group, leading to the overestimation of its accuracy (P=0.053) (Figure 4).

Discussion

Only after a few months following its emergence, COVID-19 became a pandemic, with many people all





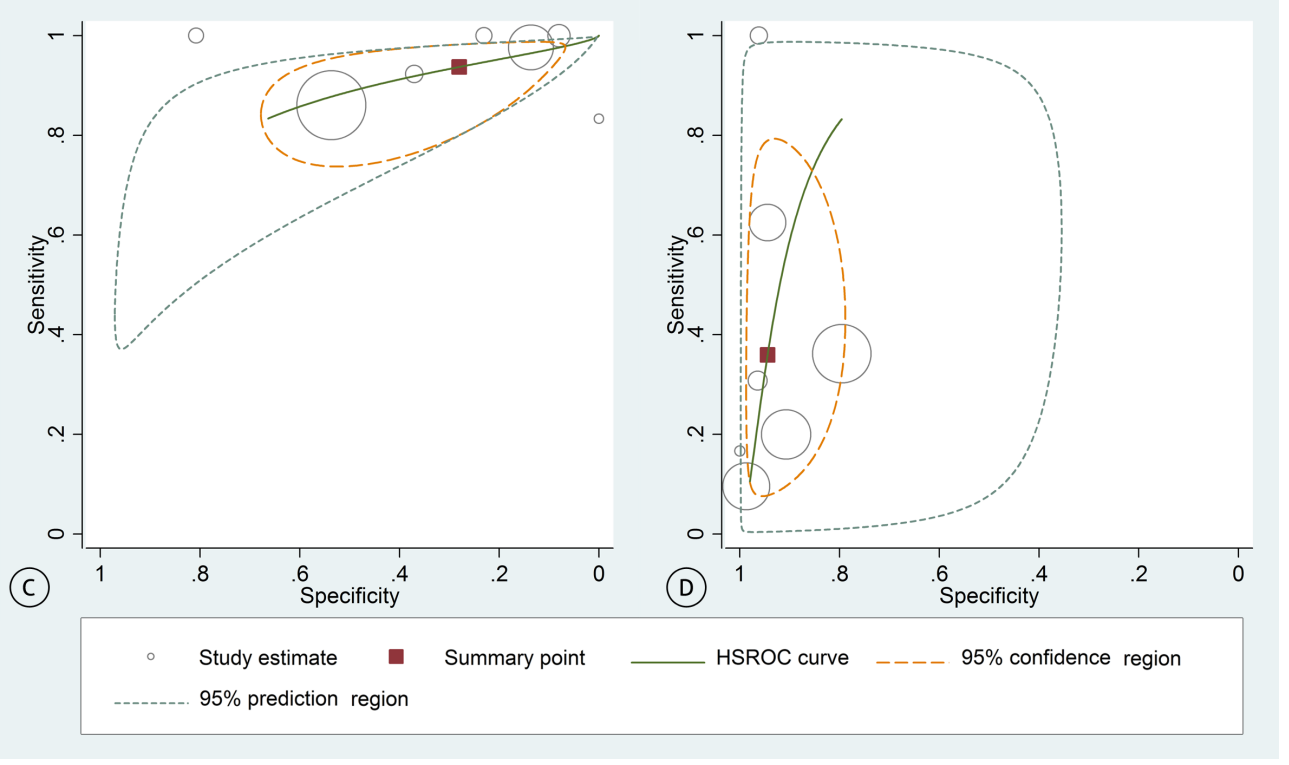


Figure 2. Evaluation of LDH and TnI for the prognosis of critical conditions: A) Forest plot for the sensitivity and specificity of LDH; B) Forest plot for the sensitivity and specificity of TnI; C) HSROC of LDH; and D) HSROC of TnI
TP, True positive; FP, False positive; FN, False negative; TN, True negative; LDH, Lactate dehydrogenase; TnI, Troponin I; HSROC, Hierarchical summary receiver operating characteristic

Table 3. Meta-analysis of the accuracy of cardiovascular disease tests for the prognosis of critical conditions and mortality in patients with COVID-19

Test	P-Se (95% CI)/%I^2	P-Sp (95% CI)/%I^2	P-LR+ (95% CI)	P-LR- (95% CI)	P-DOR (95% CI)	AUC
Critical vs. Noncritical						
LDH†	0.93 (0.85-0.97) /44.3	0.28 (0.12-0.50) /96.4	1.30 (1.02-1.65)	0.22 (0.11-0.45)	5.80 (2.51-13.41)	0.83
TnI	0.35 (0.35-0.36)/89.0	0.94 (0.94-0.94)/89.8	6.47 (6.39-6.55)	0.67 (0.67-0.68)	9.53 (9.39-9.68)	0.80
CK	-	-	-	-	-	-
D-D	0.86 (0.70-0.94)/89.3	0.40 (0.29-0.53)/91.4	1.45 (1.29-1.64)	0.33 (0.19-0.59)	4.30 (2.45-7.55)	0.62
Plt	0.16 (0.07-0.31)/79.8	0.93 (0.83-0.97)/89.1	2.61 (0.95-7.15)	0.89 (0.78-1.01)	2.93 (0.97-8.87)	0.62
Survivors vs. Non-Survivors						
LDH	0.82 (0.70-0.89)/91.5	0.48 (0.31-0.66)/98.1	1.59 (1.16-2.17)	0.37 (0.23-0.58)	4.31 (2.21-8.37)	0.74
TnI	0.59 (0.51-0.66)/80.8	0.88 (0.74-0.95)/98.3	5.06 (2. 31-11.06)	0.45 (0.38-0.54)	11.02 (4.64-26.16)	0.71
CK	0.27 (0. 20-0.36)/64.9	0.84 (0.76-0.90)/86.9	1.77 (1.30-2.40)	0.85 (0.79-0.92)	2.07 (1.44-2.96)	0.55
D-D	0.82 (0.71-0.89)/92.7	0.63 (0.42-0.80)/98.3	2.24 (1.30-3.86)	0.27 (0.15-0.49)	8.10 (2.94-22.30)	0.72
Plt	0.41 (0.31-0.52)/94.1	0.85 (0.76-0.91)/97.2	2.80 (1.83-4.27)	0.68 (0.58-0.81)	4.06 (2.39-6.91)	0.68

LDH, Lactate dehydrogenase; TnI, Troponin I; CK, Creatine kinase; D-D, D-Dimer; Plt, Platelet; P-Se, Pooled sensitivity; P-Sp, Pooled specificity; P-LR, Pooled likelihood ratio; P-DOR, Pooled diagnostic odds ratio; AUC, Area under the curve

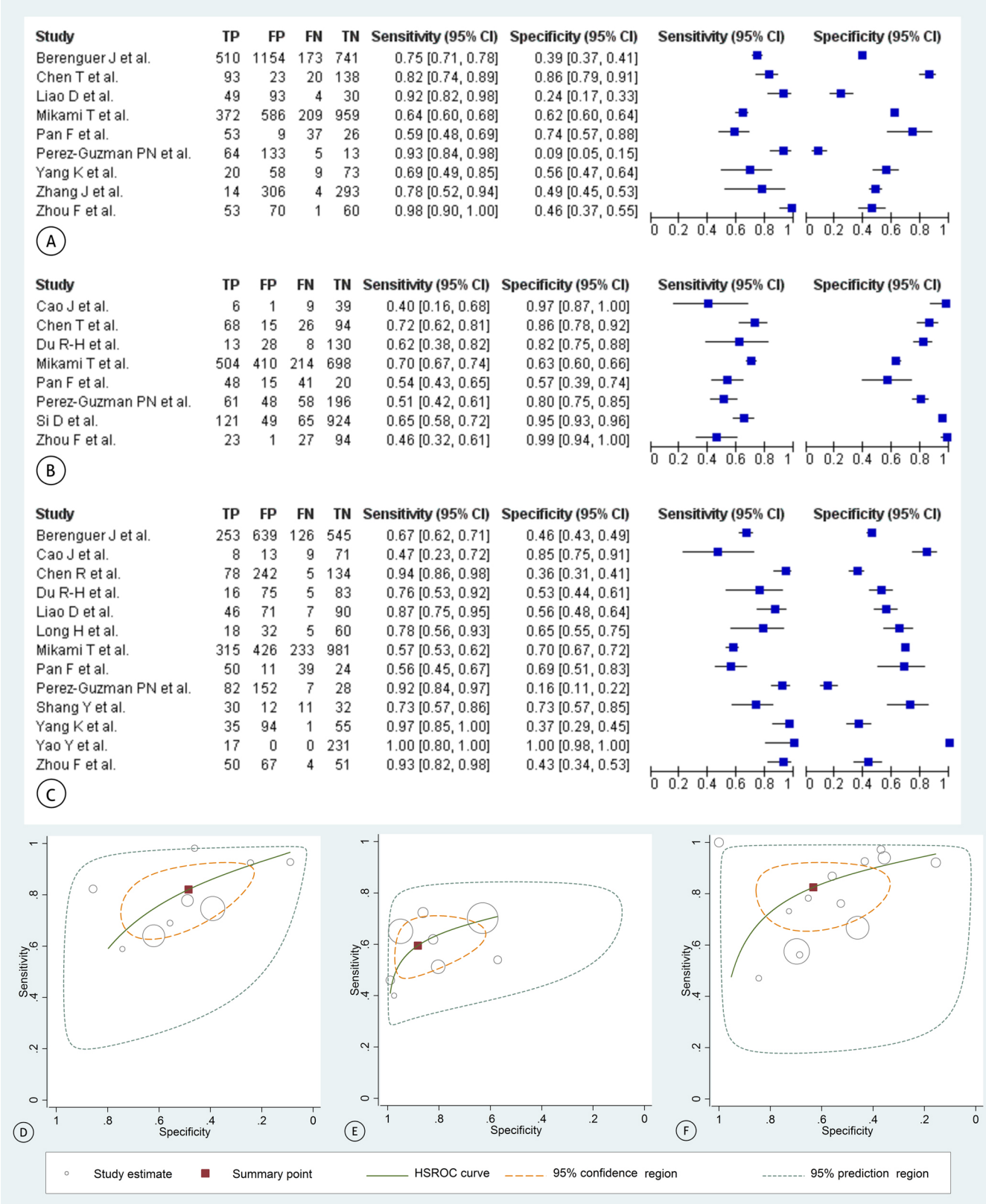


Figure 3. Evaluation of LDH, TnI, and D-dimer for the prognosis of mortality: A) Forest plot for the sensitivity and specificity of LDH; B) Forest plot for the sensitivity and specificity of TnI; C) Forest plot for the sensitivity and specificity of D-dimer; D) HSROC of LDH; E) HSROC of TnI; and F) HSROC of D-dimer

TP, True positive; FP, False positive; FN, False negative; TN, True negative; LDH, Lactate dehydrogenase; TnI, Troponin I; HSROC, Hierarchical summary receiver operating characteristic

Table 4. Meta-regression analyses of the covariates for TnI, LDH, and D-dimer

Covariate	Coefficient	Standard Error	RDOR (95% CI)	P
Critical vs. Noncritical for LDH				
Age	-0.005	0.0797	1.00 (0.80-1.24)	0.953
Male	0.010	0.0489	1.01 (0.88-1.16)	0.845
Hypertension	-0.063	0.0546	0.94 (0.81-1.09)	0.315
Cardiovascular Disease	-0.071	0.0426	0.93 (0.83-1.05)	0.171
Diabetes Mellitus	-0.034	0.0528	0.97 (0.83-1.12)	0.553
Chorionic Respiratory Disease	-0.205	0.1386	0.81 (0.55-1.20)	0.213
Survivors vs. Non-Survivors for LDH				
Age	-0.103	0.0727	0.90 (0.76-1.08)	0.207
Male	-0.019	0.0851	0.98 (0.80-1.21)	0.830
Hypertension	-0.036	0.0290	0.96 (0.90-1.04)	0.261
Cardiovascular Disease	-0.003	0.0568	1.00 (0.87-1.15)	0.960
Diabetes Mellitus	-0.080	0.0518	0.92 (0.81-1.05)	0.173
Chorionic Respiratory Disease	-0.043	0.0835	0.96 (0.78-1.18)	0.626
Critical vs. Noncritical for TnI				
Age	0.163	0.1072	1.18 (0.87-1.58)	0.203
Male	0.025	0.0616	1.03 (0.86-1.22)	0.700
Hypertension	0.020	0.0474	1.02 (0.89-1.16)	0.697
Cardiovascular Disease	-0.013	0.0833	0.99 (0.78-1.24)	0.888
Diabetes Mellitus	0.066	0.1010	1.07 (0.81- 1.41)	0.548
Chorionic Respiratory Disease	-0.196	0.2488	0.82 (0.41-1.64)	0.474
Survivors vs. Non-Survivors for TnI				
Age	-0.074	0.0604	0.93 (0.80-1.08)	0.275
Male	-0.018	0.0123	0.98 (0.95-1.01)	0.210
Hypertension	-0.033	0.0066	0.97 (0.95-0.98)	0.004
Cardiovascular Disease	-0.059	0.0443	0.94 (0.84-1.06)	0.239
Diabetes Mellitus	-0.046	0.0097	0.95 (0.93-0.98)	0.004
Chorionic Respiratory Disease	-0.099	0.0861	0.91 (0.73-1.13)	0.301
Survivors vs. Non-Survivors for D-dimer				
Age	-0.066	0.0371	0.94 (0.86-1.02)	0.103
Male	-0.062	0.0465	0.94 (0.85-1.04)	0.214
Hypertension	-0.027	0.0147	0.97 (0.94-1.01)	0.097
Cardiovascular Disease	-0.033	0.0298	0.97 (0.91-1.03)	0.291
Diabetes Mellitus	-0.059	0.0250	0.94 (0.89-1.00)	0.040
Chorionic Respiratory Disease	-0.082	0.0310	0.92 (0.86-0.99)	0.024

LDH, Lactate dehydrogenase; TnI, Troponin I; RDOR, Relative diagnostic odds ratio

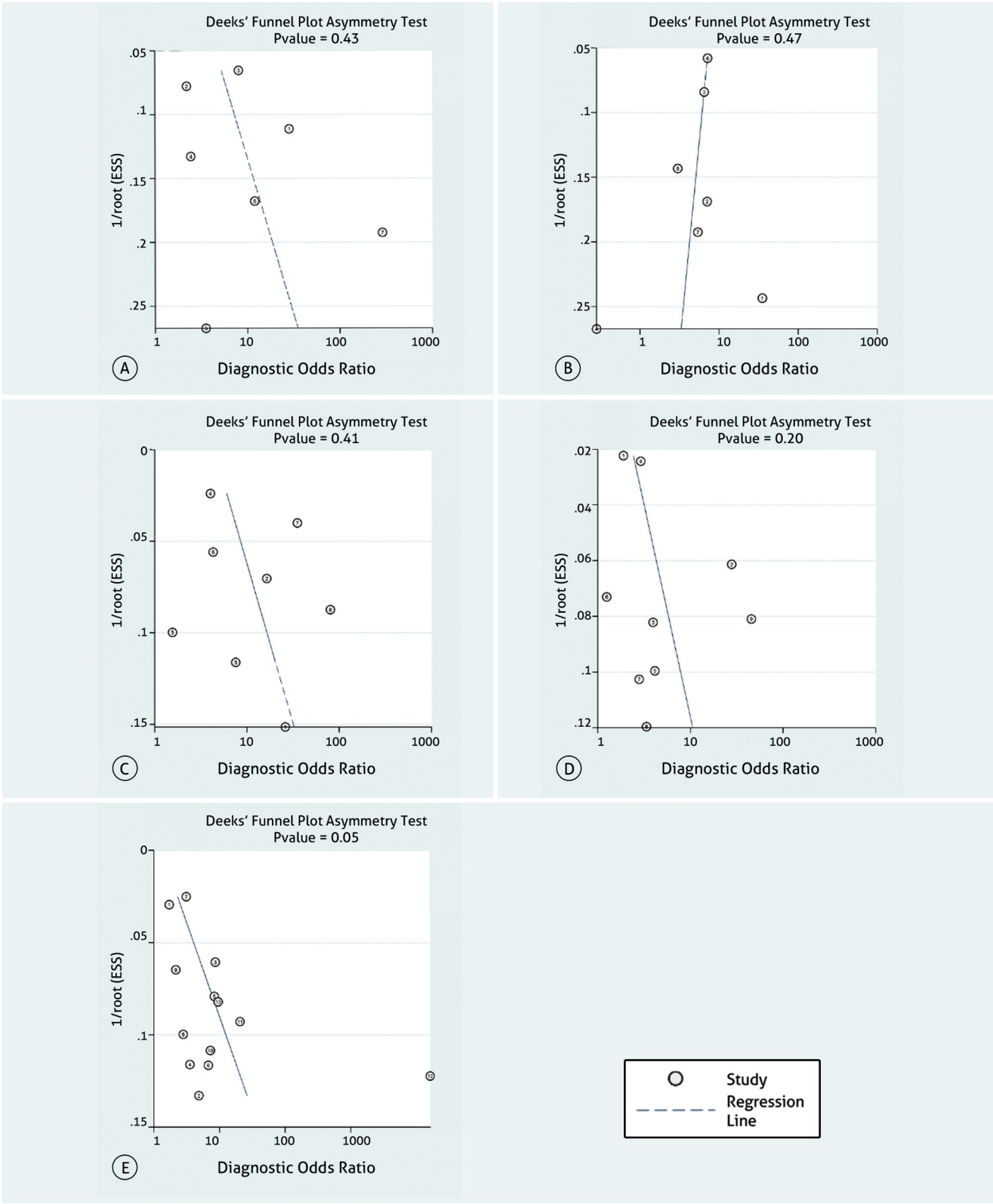


Figure 4. Deeks funnel plot of publication bias: A: Troponin I in the critical outcome group (P=0.435); B: Lactate dehydrogenase in the critical outcome group (P=0.472); C: Troponin I in the mortality outcome group (P=0.413); D: Lactate dehydrogenase in the mortality outcome group (P=0.205); and E: D-dimer in the mortality outcome group (P=0.053)

Asymmetrically distributed studies with the regression line's coefficient having a P value of less than 0.1 indicate a high likelihood of publication bias.

ESS, Effective sample size

over the world infected by SARS-CoV-2. The outcomes of these patients are very different, ranging from the absence of symptoms to fatal pneumonia.[1] Thus, finding prognostic biomarkers for the outcomes of the disease is strongly recommended, especially for critical conditions and mortality. On the other hand, preference should be given to routine biomarkers given the pandemic condition and the paucity of advanced medical facilities.[3] Evidence indicates that CVDs are common complications in patients with more severe COVID-19 and their biomarkers could be efficient for prognostic utilization.[5] However, no research has hitherto investigated the prognostic accuracy of these biomarkers. Hence, for the first time, we aimed to determine the prognostic accuracy of CVD biomarkers for critical conditions and mortality via a DTA systemic review and meta-analysis.

We selected 33 studies that fulfilled our search strategy and inclusion criteria. Based on the NOS tool for study quality assessment, we ranked all the included studies as high quality and, therefore, did not perform any study restriction for our analyses. The studies included in the present investigation assessed a total of 3940 patients for critical/noncritical outcomes and 13 719 patients for the mortality outcome. Ours is the first study of its kind to contain such a considerable number of patients with different outcomes.

While respiratory diseases are the primary symptoms of patients with COVID-19, cardiac injury is deemed one of the most frequent comorbidities in these patients.[21, 34] SARS-CoV-2 enters cells via its surface spike protein and binds with the angiotensin-converting enzyme 2 (ACE2) receptor.[47] Lung alveolar cells highly express ACE2. Furthermore, myocardial cells widely express ACE2, and they can be infected directly by this virus.[48] According to a meta-analysis on 16 studies, about 25% of the patients hospitalized due to COVID-19 had cardiac injury complications, and the mortality rate of patients who had cardiac injury was 72.6% compared with 14.5% for patients who had no cardiac injury.[4] We indicated the accuracy of cTnI as the gold-standard biomarker for myocardial necrosis besides another myocardial injury biomarker (ie, LDH). We found that increased levels of LDH and cTnI had good accuracy for the prognosis of critical conditions (AUC_{HSROC}=0.83 and 0.80, respectively) and acceptable accuracy for the prognosis of mortality (AUC_{HSROC}=0.74, 0.71, and 0.72, correspondingly). Consequently, in general, they can be considered prognostic biomarkers for poor outcomes. Further, concerning critical conditions and mortality, LDH had higher sensitivity than cTnI, whereas cTnI had higher specificity. Thus, we strongly recommend that these 2 biomarkers be performed in tandem.

Coagulopathy is another important complication in patients with COVID-19. After SARS-CoV-2 enters the body, the immune response is activated to clear the virus. In some cases, the overactivation of the immune system leads to a cytokine storm, which could cause vascular endothelial damage.[49] As a result, the coagulation system is activated and the fibrinolytic system is inhibited. Ultimately, disseminated intravascular coagulation is engendered by excessive thrombosis in the microvascular system, resulting in microcirculatory disorders and serious multiple organ dysfunction syndrome.[50] This complication is one of the most important progressive factors concerning critical conditions and mortality in patients with COVID-19. Therefore, coagulopathy biomarkers could have great potential as prognostic factors. Routinely, D-dimer, FDP, PT, PTT, and platelet count are used as laboratory biomarkers for the detection of coagulopathy. The results of a meta-analysis showed that D-dimer had a significant correlation with disease severity. Based on our results, D-dimer lacked acceptable accuracy for the prognosis of critical conditions (AUC_{HSROC}=0.62), but it had acceptable accuracy for the mortality outcome (AUC_{HSROC}=0.72). Thrombocytopenia had no acceptable accuracy for both outcomes (AUC_{HSROC}<0.70) (Table 3). A poor outcome is the indicator of either critical conditions or mortality, and publication bias concerning D-dimer causes an overestimation of its accuracy; hence, D-dimer cannot be considered a single prognostic biomarker. Nevertheless, it can be used in parallel with other biomarkers such as LDH and cTnI.

Our previous research on white blood cells and inflammatory biomarkers for the prognosis of the outcome of patients suffering from COVID-19 revealed that among leukocytosis, neutrophilia, lymphopenia, and elevated serum levels of procalcitonin, C-reactive protein, and ferritin, procalcitonin was the only biomarker possessing good accuracy for the prognosis of both critical and mortality outcomes (AUC_{HSROC}≥0.80 for both conditions) with high sensitivity and relatively low specificity.[51] Accordingly, in light of the results of our previous and current investigations, we can conclude that increased serum levels of procalcitonin, LDH, and cTnI could be regarded as reliable prognostic biomarkers for poor outcomes.

In the current study, our forest plots of sensitivity and specificity suggested heterogeneity, prompting us to perform a meta-regression analysis to find potential confounding covariates, including age, gender, hypertension, CVDs, diabetes mellitus, and chorionic respiratory disease (Table 4). The meta-regression analysis revealed no factor that accounted for this heterogeneity in the critical/noncritical group, while hypertension and diabetes mellitus for cTnI and diabetes mellitus and chorionic respiratory disease for D-dimer in the surviving/non-surviving group contributed to heterogeneity.

The salient strength of the present study is its inclusion of a sizable number of patients with COVID-19: 3940 in the critical outcome group and 13719 patients in the mortality outcome group. Be that as it may, given that the

most notable limitation of the previous meta-analyses was the inability to include diverse nationalities and races, the following weaknesses should be taken into account in the interpretation of our results. First, retrospective cohorts comprised the majority of the studies subjected to the current meta-analysis. Such studies are associated not only with inadequate demonstration ability but also with restricted ability to infer definitive causalities. Second, all the prospective cohort studies were from China, undermining the generalizability of the results to patients from other countries. Third, the presence of publication bias concerning D-dimer in the mortality outcome group signified the overestimation of the diagnostic performance of D-dimer insofar as studies with higher DOR results have a higher chance to be published.

Conclusion

Our results indicated that LDH and cTnI possessed good accuracy for the prognosis of critical conditions and there was no statistically significant difference between their accuracy for the prognosis of critical outcomes. Further, LDH and cTnI exhibited acceptable accuracy for the prognosis of mortality; and similar to the critical outcome group, they were not statistically significantly different in terms of accuracy for the prognosis of mortality. LDH had high sensitivity, whereas cTnI had high specificity. We would, therefore, recommend the concomitant use of these 2 biomarkers. Despite the acceptable accuracy of D-dimer, we would not recommend it as a prognostic factor given publication bias and the resultant significant overestimation of its accuracy associated with it. Other CVD biomarkers such as CK and thrombocytopenia lacked sufficient accuracy as prognostic markers. Taking into account our results from a previous investigation and the present study, we can conclude that elevated serum levels of procalcitonin, LDH, and cTnI are strong prognosticators of poor outcomes in patients with COVID-19.

Acknowledgments

This research received no grant from any financial organization 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, Singh KP, Chaicumpa W, Bonilla-Aldana DK, Rodriguez-Morales AJ. Coronavirus disease 2019-COVID-19. Clin Microbiol Rev 2020;33:e00028- e00020.
2. Soraya GV, Ulhaq ZS. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: an updated meta-analysis. Med Clin (Barc) 2020;155:143-151.
3. 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;58:1063-1069.
4. Zou F, Qian Z, Wang Y, Zhao Y, Bai J. Cardiac injury and COVID-19: a systematic review and meta-analysis. CJC Open 2020;2:386-394.
5. Aboughdir M, Kirwin T, Abdul Khader A, Wang B. Prognostic value of cardiovascular biomarkers in COVID-19: a review. Viruses 2020;12:527.
6. 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;16:1175-1187.
7. 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;16:1188-1196.
8. Zhao JY, Yan JY, Qu JM. Interpretations of "Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial Version 7)". Chin Med J (Engl) 2020;133:1347-1349.
9. 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;8:226.
10. Sabbagh HJ, Hassan MH, Innes NP, 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:e0116963.
11. Safari S, Baratloo A, Elfil M, Negida A. Evidence based emergency medicine; part 5 receiver operating curve and area under the curve. Emerg (Tehran) 2016;4:111-113.
12. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol 2010;5:1315-1316.
13. 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;19:81.
14. Wang F, Hou H, Luo Y, Tang G, Wu S, Huang M, Liu W, Zhu Y, Lin Q, Mao L, Fang M, Zhang H, Sun Z. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI Insight 2020;5:e137799.
15. Li H, Xiang X, Ren H, Xu L, Zhao L, Chen X, Long H, Wang Q, Wu Q. Serum amyloid a is a biomarker of severe coronavirus disease and poor prognosis. J Infect 2020;80:646-655.
16. Chan SSW, Christopher D, Tan GB, Chong VCL, Fan BE, Lin CY, Ong KH. Peripheral lymphocyte subset alterations in COVID-19 patients. Int J Lab Hematol 2020;42:e199-e203.
17. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, Mucheli SS, Kuperan P, Ong KH. Hematologic parameters in patients with COVID-19 infection. Am J Hematol 2020;95:E131-E134.
18. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.
19. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, Zhang Z, Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C, Liu L. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63:364-374.
20. Chen C, Chen C, Yan JT, Zhou N, Zhao JP, Wang DW. [Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19]. Zhonghua Xin Xue Guan Bing Za Zhi 2020;48:567-

571.
21. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion TR, Jr, Nahid M, Ringel JB, Hoffman KL, Alshak MN, Li HA, Wehmeyer GT, Rajan M, Reshetnyak E, Hupert N, Horn EM, Martinez FJ, Gulick RM, Safford MM. Clinical characteristics of Covid-19 in New York city. N Engl J Med 2020;382:2372-2374.
22. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, Xiong W, Yang D, Chen R, Lu F, Lu Y, Liu X, Chen Y, Li X, Li Y, Summah HD, Lin H, Yan J, Zhou M, Lu H, Qu J. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med 2020;201:1380-1388.
23. Zhou B, She J, Wang Y, Ma X. The clinical characteristics of myocardial injury in severe and very severe patients with 2019 novel coronavirus disease. J Infect 2020;81:147-178.
24. Han H, Xie L, Liu R, Yang J, Liu F, Wu K, Chen L, Hou W, Feng Y, Zhu C. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. J Med Virol 2020;92:819-823.
25. Li Y, Hu Y, Yu J, Ma T. Retrospective analysis of laboratory testing in 54 patients with severe- or critical-type 2019 novel coronavirus pneumonia. Lab Invest 2020;100:794-800.
26. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. Int J Antimicrob Agents 2020;56:106051.
27. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, Shi J, Zhou M, Wu B, Yang Z, Zhang C, Yue J, Zhang Z, Renz H, Liu X, Xie J, Xie M, Zhao J. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020;146:110-118.
28. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, Shang Y. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost 2020;18:1469-1472.
29. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.
30. Cao J, Tu WJ, Cheng W, Yu L, Liu YK, Hu X, Liu Q. Clinical features and short-term outcomes of 102 patients with Coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020;71:748-755.
31. Mikami T, Miyashita H, Yamada T, Harrington M, Steinberg D, Dunn A, Siau E. Risk Factors for Mortality in Patients with COVID-19 in New York City. J Gen Intern Med 2021;36:17-26.
32. Perez-Guzman PN, Daunt A, Mukherjee S, Crook P, Forlano R, Kont MD, Løchen A, Vollmer M, Middleton P, Judge R, Harlow C, Soubieres A, Cooke G, White PJ, Hallett TB, Aylin P, Ferguson N, Hauck K, Thursz MR, Nayagam S. 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:ciaa1091.
33. Pan F, Yang L, Li Y, Liang B, Li L, Ye T, Li L, Liu D, Gui S, Hu Y, Zheng C. Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): a case-control study. Int J Med Sci 2020;17:1281-1292.
34. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet.2020;395(10229):1054-1062.
35. Yang K, Sheng Y, Huang C, Jin Y, Xiong N, Jiang K, Lu H, Liu J, Yang J, Dong Y, Pan D, Shu C, Li J, Wei J, Huang Y, Peng L, Wu M, Zhang R, Wu B, Li Y, Cai L, Li G, Zhang T, Wu G. 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;21:904-913.
36. Berenguer J, Ryan P, Rodríguez-Baño J, Jarrín I, Carratalà J, Pachón J, Yllescas M, Arribas JR. haracteristics and predictors of death among 4,035 consecutively hospitalized patients with COVID-19 in Spain. Clin Microbiol Infect 2020;26:1525–1536.
37. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, Guo GY, Du J, Zheng CL, Zhu Q, Hu M, Li XY, Peng P, Shi HZ. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020;55:2000524.
38. Si D, Du B, Ni L, Yang B, Sun H, Jiang N, Liu G, Massé S, Jin L, Nanthakumar J, Bhaskaran A, Yang P, Nanthakumar K. Death, discharge and arrhythmias among patients with COVID-19 and cardiac injury. CMAJ 2020;192:E791-E798.
39. Shang Y, Liu T, Wei Y, Li J, Shao L, Liu M, Zhang Y, Zhao Z, Xu H, Peng Z, Zhou F, Wang X. Scoring systems for predicting mortality for severe patients with COVID-19. EClinicalMedicine 2020;24:100426.
40. Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, Zhou T, Yuan Y, Qi H, Fu S, Liu H, Xia J, Xu Z, Yu Y, Li R, Ouyang Y, Wang R, Ren L, Hu Y, Xu D, Zhao X, Yuan S, Zhang D, Shang Y. 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;24:394.
41. Liu Y, Sun W, Guo Y, Chen L, Zhang L, Zhao S, Long D, Yu L. Association between platelet parameters and mortality in coronavirus disease 2019: retrospective cohort study. Platelets 2020;31:490-496.
42. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, Wei J, Gong Z, Zhou C, Yu H, Yu M, Lei H, Cheng F, Zhang B, Xu Y, Wang G, Dong W. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect 2020;26:767-772.
43. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, Xie J, Guan W, Liang W, Ni Z, Hu Y, Liu L, Shan H, Lei C, Peng Y, Wei L, Liu Y, Hu Y, Peng P, Wang J, Liu J, Chen Z, Li G, Zheng Z, Qiu S, Luo J, Ye C, Zhu S, Zheng J, Zhang N, Li Y, He J, Li J, Li S, Zhong N; Medical Treatment Expert Group for COVID-19. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol 2020;146:89-100.
44. Liao D, Zhou F, Luo L, Xu M, Wang H, Xia J, Gao Y, Cai L, Wang Z, Yin P, Wang Y, Tang L, Deng J, Mei H, Hu Y. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol 2020;7:e671-e678.
45. Long H, Nie L, Xiang X, Li H, Zhang X, Fu X, Ren H, Liu W, Wang Q, Wu Q. D-dimer and prothrombin time are the significant indicators of severe COVID-19 and poor prognosis. Biomed Res Int 2020;2020:6159720.
46. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, Chen X, Chen S, Yu K, Huang Z, Hu B. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care 2020;8:49.
47. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-280.e8.
48. Guo J, Huang Z, Lin L, Lv J. Coronavirus disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. J Am Heart Assoc 2020;9:e016219.
49. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94:e00127- e00120.
50. Cohen J. The immunopathogenesis of sepsis. Nature 2002;420:885-891.
51. Zare ME, Wang Y, Nasir Kansestani A, Almasi A, Zhang J.

Procalcitonin has good accuracy for prognosis of critical condition and mortality in COVID-19: a diagnostic test accuracy systematic review and meta-analysis. Iran J Allergy Asthma Immunol 2020;19:557-569.