



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

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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.

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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,

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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.

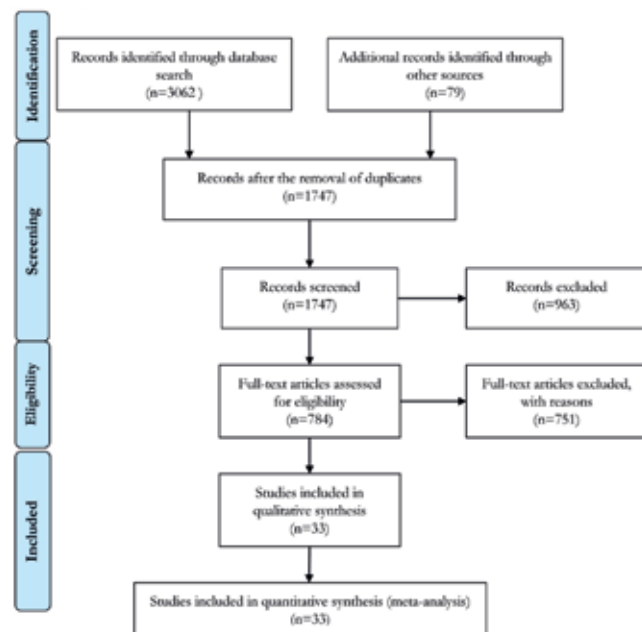


Figure 1. PRISMA flow diagram of the study selection

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 (>48 IU/L; NA); TnI (>19.3 μg/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 ($AUC_{HSROC}=0.74, 0.71, \text{ and } 0.72$, 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

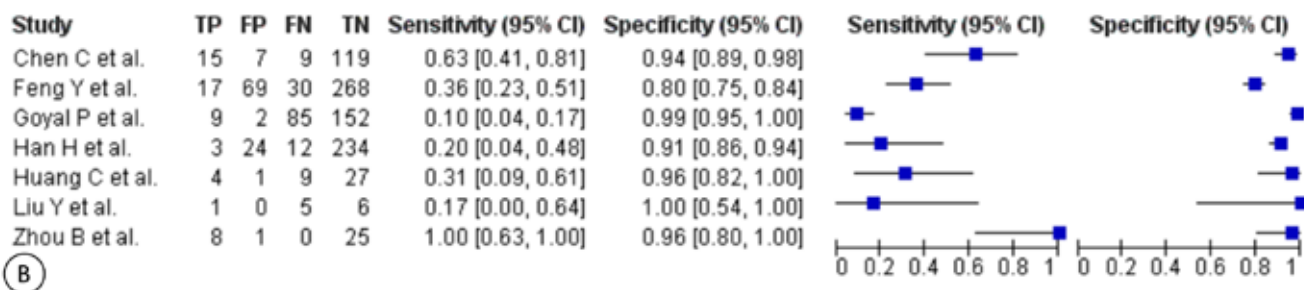
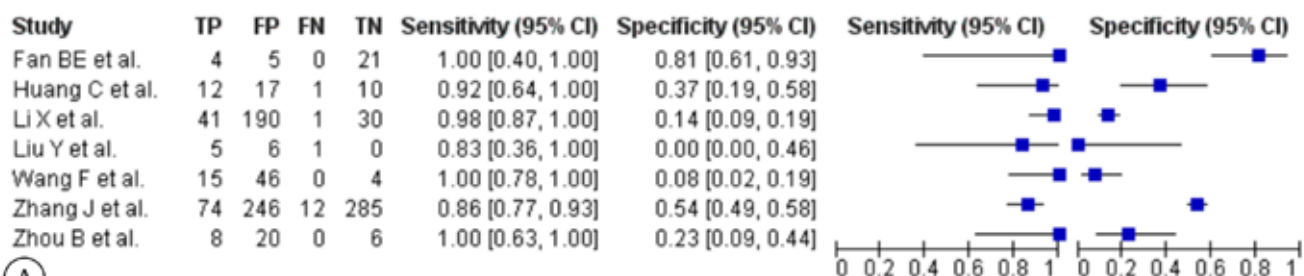
significant contribution to the heterogeneity of LDH and cTnI in the critical outcome group ($P=0.381$ and 0.457 , respectively) and the heterogeneity of LDH and D-dimer in the mortality outcome group ($P=0.653$ and 0.871 , respectively). Still, the threshold effect made a significant contribution as 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



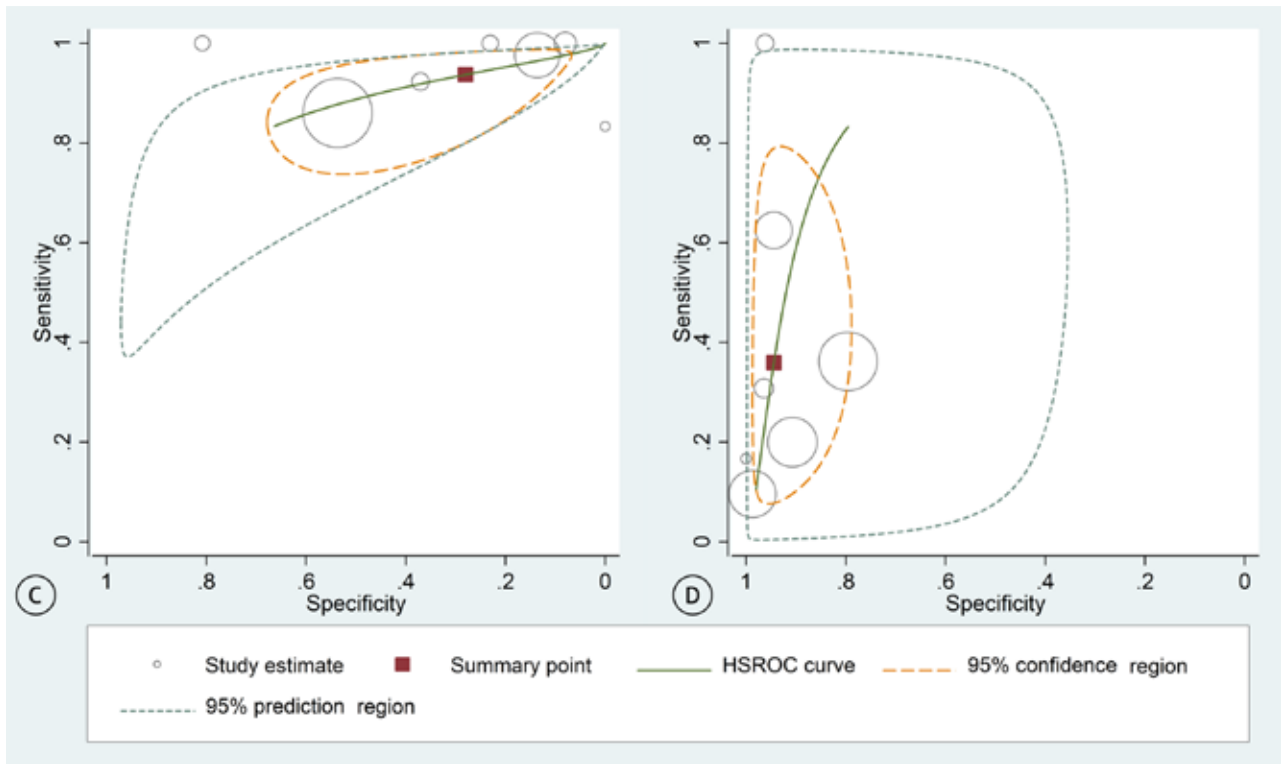


Figure 2. Evaluation of LDH and TnI for the prognosis of critical conditions: A) Forest plot for the sensitivity and specificity of LDH; B) Forest plot for the sensitivity and specificity of TnI; C) HSROC of LDH; and D) HSROC of TnI

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

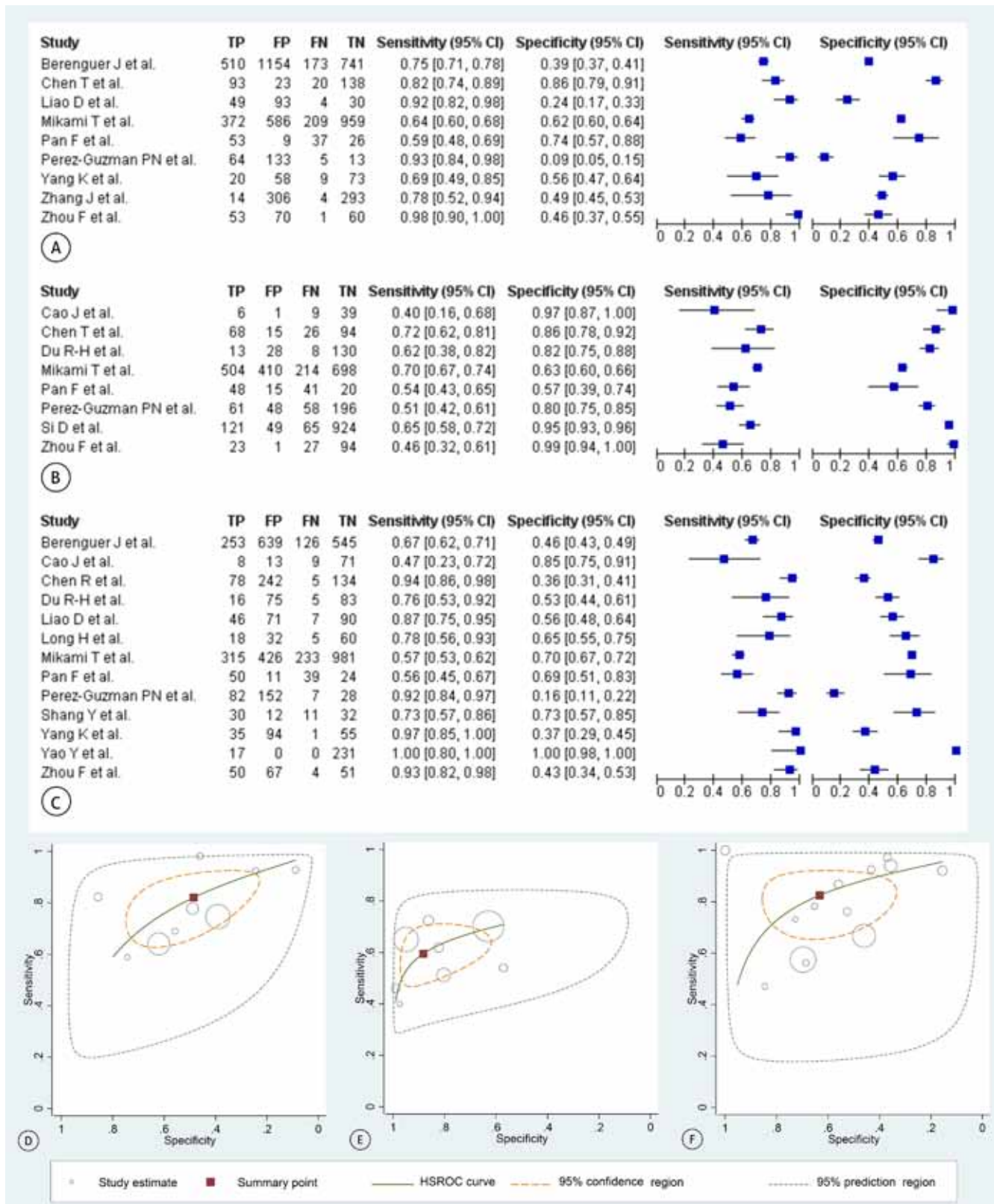


Figure 3. Evaluation of LDH, TnI, and D-dimer for the prognosis of mortality: A) Forest plot for the sensitivity and specificity of LDH; B) Forest plot for the sensitivity and specificity of TnI; C) Forest plot for the sensitivity and specificity of D-dimer; D) HSROC of LDH; E) HSROC of TnI; and F) HSROC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

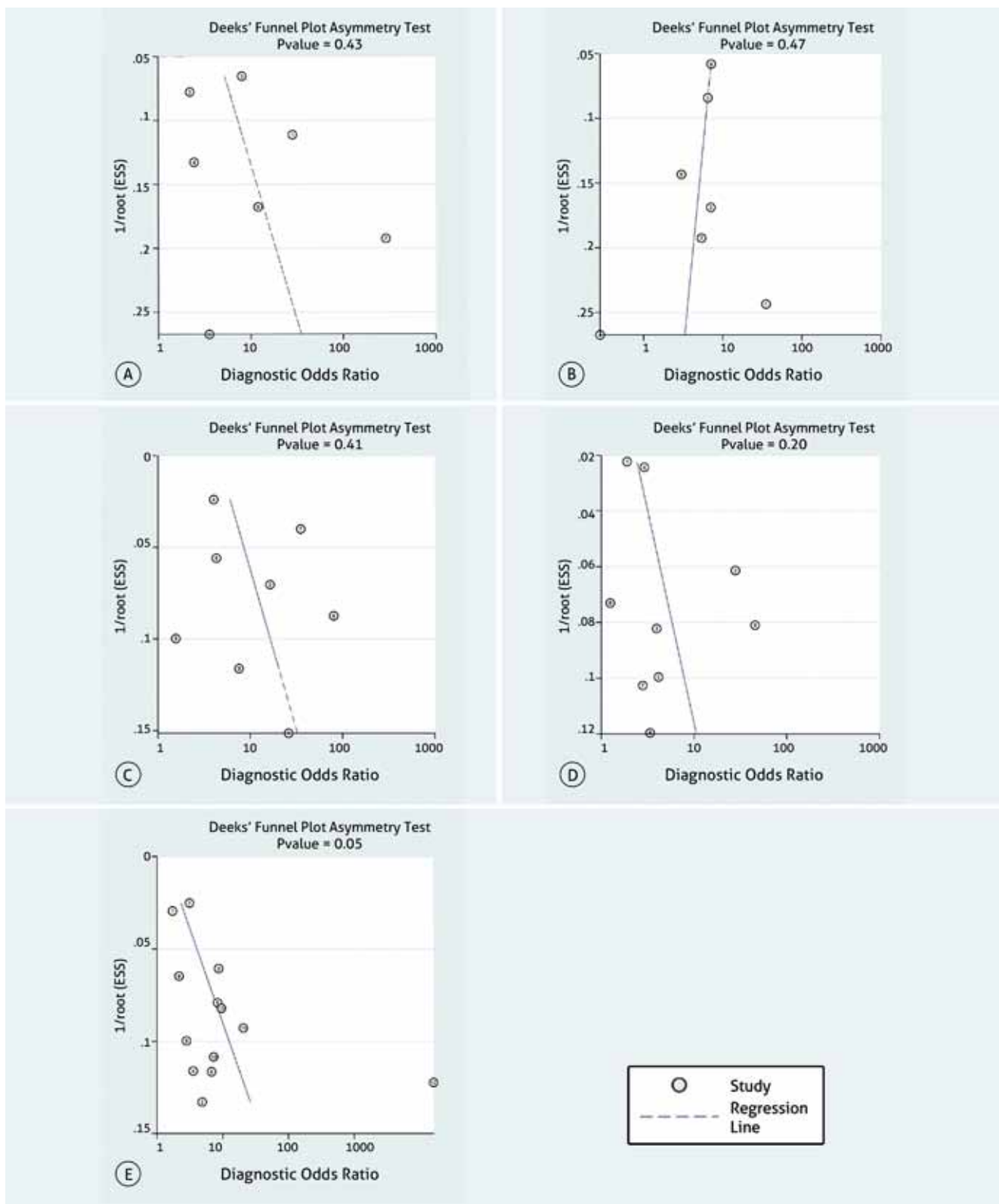


Figure 4. Deeks funnel plot of publication bias: A: Troponin I in the critical outcome group (P=0.435); B: Lactate dehydrogenase in the critical outcome group (P=0.472); C: Troponin I in the mortality outcome group (P=0.413); D: Lactate dehydrogenase in the mortality outcome group (P=0.205); and E: D-dimer 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 ($AUC_{HSROC}\geq 0.80$ 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.

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