Lactate dehydrogenase and aspartate aminotransferase levels associated with the severity of COVID-19: A systematic review and meta-analysis

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Abstract. Lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) are important indicators of cardiovascular, muscle and liver lesions, and can be used as prognostic indicators for infectious diseases, such as coronavirus disease 2019 (COVID-19). The present systematic review and meta-analysis assessed the prognostic value of LDH and AST levels for COVID-19 severity. Ovid-Medline, PubMed, Embase and The Cochrane Library were used to search for articles, according to the inclusion and exclusion criteria, until July 2022. The meta-analysis was performed using Revman5.3 and Stata15.1. Standardized mean difference (SMD) and 95% confidence intervals (CIs) of LDH and AST concentrations were analyzed using a random-effects model. Heterogeneity was investigated using meta-regression and subgroup methods. A total of 4,342 patients with COVID-19 in 23 articles were included in the present study. LDH (SMD=1.21; 95% CI: 0.98, 1.44) and AST (SMD=0.68; 95% CI: 0.54, 0.81) were significantly higher in patients with severe COVID-19 compared with in those with non-severe COVID-19. Serum LDH and AST levels in critically ill patients with COVID-19 were increased, suggesting a correlation between the levels of LDH and AST and the severity of COVID-19. These findings may help to develop a risk-stratified approach to the care of patients with this disease.

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Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; WHO, World Health Organization; CVD, cardiovascular disease; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; 95% CI, 95% confidence interval

Key words: lactate dehydrogenase, aspartate aminotransferase, SARS-CoV infection, COVID-19, plasma biomarkers

Introduction

Coronavirus disease 2019 (COVID-19) has become a global pandemic; as of December 2022, over 600 million confirmed cases, including six million deaths, were reported to WHO (https://covid19.who.int/). COVID-19 is caused by SARS-CoV-2; the functional receptor for SARS-CoV is ACE-2, which is highly expressed in epithelial cells in the lung (1). These cause diffuse alveolar damage and acute respiratory distress syndrome. In addition to pneumonia and acute respiratory distress syndrome, a wide range of extra-pulmonary symptoms has been shown in COVID-19, including cardiac-related symptoms (2). The most common cardiac-related symptoms in patients with COVID-19 are increased risk of myocardial infarction, rapidly developing fulminant myocarditis with reduced left ventricular systolic function, arrhythmias, venous thromboembolism, and cardiomyopathy with STEMI-like presentation (2). Patients with cardiovascular disease (CVD) and COVID-19 may present with severe symptoms and a higher risk of death. Furthermore, 6~17% COVID-19 patients were found to develop cardiac arrhythmias and the patients in ICU had a higher prevalence (~44%) in ICU (3). 12~8% of COVID-19 patients were found to have acute cardiac injury complications (4). And the consequences of myocarditis in recovering COVID-19 patients have recently been found to be very serious and potentially fatal (5).

The population is generally susceptible to COVID-19, and some immunity can be improved after infection or vaccination against the new coronavirus (6). The WHO recommends the monoclonal antibody Sotrovimab for use in non-serious COVID-19 patients but only in those at the highest risk of hospital admission. And recommends corticosteroids in combination with the Janus kinase (JAK) inhibitor Baricitinib

to treat patients with severe or critically ill patients (7). However, these drugs are only sometimes effective against new variants constantly mutating. With limited access to treatment, testing laboratory biomarkers is less expensive, faster, and more readily available and is thought to provide a predictor of disease severity and prognosis (8).

Myocardial damage in COVID-19 patients is closely related to the severity of the disease and even the prognosis. Therefore, early monitoring of cardiac damage by biomarkers is recommended after hospitalization for COVID-19 infection in patients with pre-existing CVD. Lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) are traditional markers of myocardial injury. There have been several studies assessing the utility of biomarkers indicating severe COVID-19. Fialek *et al* (9) outlined the role of elevated LDH levels in assessing the severity of COVID-19 but only considered a single biochemical indicator rather than a multivariate assessment of multiple biochemical parameters. Most studies contained multiple indicators, but the indicators are too broad without a clear target organ. The study by Malik *et al* (10) involved indicators such as lymphocytes, platelets, D-dimer, LDH, AST, alanine aminotransferase, creatinine, procalcitonin and creatine kinase but did not target a particular organ. To our knowledge, there has been no meta-analysis of the association of dual indicators of cardiac enzyme profiles LDH and AST with COVID-19 prognosis. And the limitations of observational studies due to geographical location, single-center experience, and small cohorts prevent these findings from being generalized. Therefore, we conducted a comprehensive systematic review and meta-analysis to determine whether AST and LDH are associated with COVID-19 severity.

Materials and methods

Search strategy. Our work followed the PRISMA guidelines for reporting systematic reviews and meta-analyses (11). The checklist is presented in Appendix S1.We have searched Ovid-Medline (https://ovidsp.ovid.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/search/quick), and Cochrane library (https://www.cochranelibrary.com/advanced-search) for studies published up to July 2022. We used the following search terms and medical subject terms (MeSH): 'COVID-19', 'lactate dehydrogenase', 'aspartate aminotransferase', 'SARS-CoV-2', 'severity', 'mortality', and 'prognosis'. In the search process, MeSH keywords and Boolean operators were used. The PROSPERO registration number is CRD42022318819.

Study selection. Studies were included if they: i) Observational studies (cohort, case-control, cross-sectional); ii) Patients were diagnosed with COVID-19 by qPCR (quantitative real-time PCR); iii) Reported outcomes in the form of markers to LDH and AST; iv) Investigation of binary outcomes like ICU versus non-ICU admission, severe versus non-severe disease, in-hospital mortality versus discharged alive and survivors.

Exclusion criteria were: i) Lack of information on LDH and AST levels at the initial diagnosis or follow-up; ii) Studies investigated pregnant women or children; iii) No clear grouping of outcome indicators; iv) Letters, reviews, conference proceedings, guidelines, duplicate publications, or other unrelated topics are outside the scope of this review.

Data extraction. Two investigators (ZYH and RQY) independently reviewed the abstracts. A full-text review was conducted when a given abstract were considered potentially relevant. If there is a disagreement between investigators, the third author (SKY) gives suggestions. The two investigators (ZYH and RQY) reviewed whole papers independently against the inclusion criteria, and if necessary, any discrepancies were decided by the third author (SKY). Throughout the screening, the first author's name, publication date, the number of individuals enrolled, the nation or region, the patients' basic information (mostly gender and age), and the LDH and AST levels were separately collected by the two investigators from the included studies. To assess study quality, we used the Newcastle-Ottawa Scale (NOS), with a score above six considered high quality (12).

Statistical analysis. The forest plots of standard mean difference (SMD) were used to analyze the differences in LDH and AST concentrations between patients with severe and non-severe COVID-19. The raw data has been processed to the median and IQR values, making them acceptable for analysis (13). The I^2 statistic was used to assess inconsistency across studies. The I^2 statistic, more than 75 percent, shows high heterogeneity indicating a random-effects model to be used (14). The pooled SMD and associated 95% CIs were calculated. We also used the one-by-one elimination approach to assess the contribution of each study to the overall effect of the sensitivity analysis. Egger's test and funnel curves were used to represent publication bias. The heterogeneity across studies could be identified through meta-regression and subgroup analyses. In the meta-regression study, the following variables were investigated for heterogeneity: age, gender, region, publication year, and specified outcomes (severe, non-severe, survive, non-survive). Stata 15.1 (StataCorp, TX, USA) and RevMan 5.3 (Cochrane Collaboration, Oxford, UK) software were used for the statistical analysis.

Results

Study selection. A flowchart illustrating the filtering procedure is shown in Fig. 1, and 592 studies were initially identified. NoteExpress3.5.0 was used to remove the duplicated 38 studies. After carefully reading the titles and abstracts, we excluded 480 studies as they were all irrelevant. We further excluded 51 articles after a full-text review of the remaining 74 articles because they either did not report intended outcomes or intended groups. Finally, of the 4342 patients with COVID-19 in the 23 studies included in the meta-analysis, 3003 (54.0% male, mean age 52.1 years) had low severity and 1339 (67.3% male, mean age 64.2 years) had high severity or died.

Characteristics of included studies. Essential information included in the study is shown in Table I. The clinical endpoints for each study were split between severe vs. non-severe (15-25), survival or discharge vs. non-survival, or ICU (26-37). At the time of analysis, the non-survival and ICU patients were

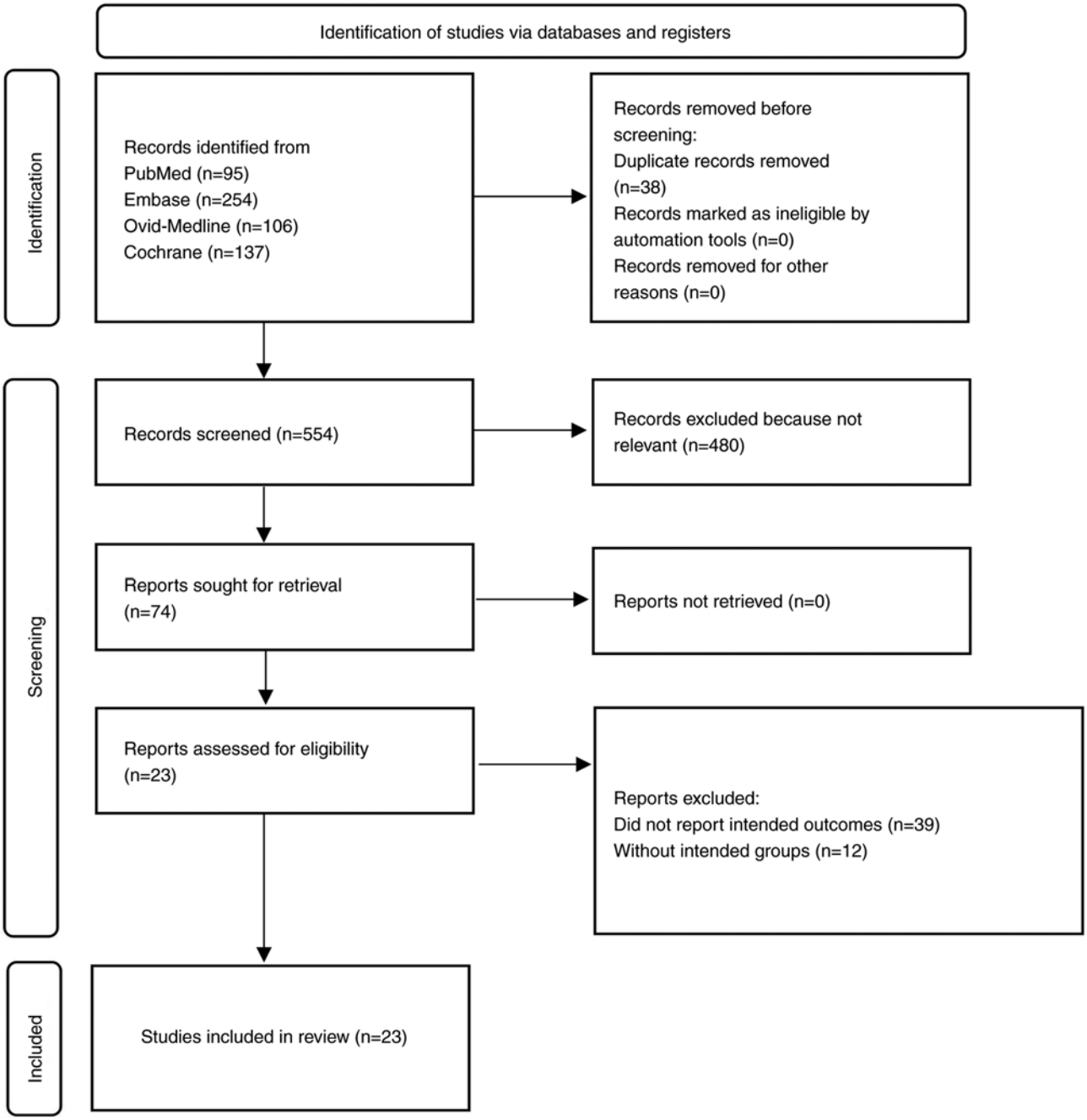

Figure 1. Flow diagram illustrating the filtering procedure according to PRISMA. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

classified as the severe group. In contrast, those patients after hospital discharge and the survival group were considered the non-severe group. Fifteen studies were conducted in Asia. Eleven of the studies were in China (15,22,23,25,29,30,32,33,35-37), one in Japan (31), one in India (19), one in Iran (28), and one in Pakistan (24); four studies were conducted in Europe, one in Georgia (21), one in Belgium (17), one in the Italian (18), one in Spain (34); two studies were performed in the Eurasian country of Turkey (16,26); one study was performed in African Morocco (27); one study was performed in North America Mexico (20). All studies were retrospective observation studies, except one was the case-control study (15). The disease severity in nine studies was diagnosed according to the 'Diagnosis and Treatment of Novel Coronavirus Pneumonia' developed by the National Health Care Commission of China (15,22,25,29,30,32,33,36,37); two studies were determined according to World Health Organization (WHO) criteria (27,31); five studies were determined based on clinical and radiological findings (21,23,24,26,35); seven studies were not clarified (16-20,28,34).

Analysis of disease prognosis. The LDH concentrations heterogeneity test results show high heterogeneity between studies (I^2=90%, P<0.001). Hence, we used the random-effects model to calculate the pooled SMD and 95% CIs. The meta-analysis forest plot showed that severe outcomes presented significantly

Table I. Baseline characteristics of COVID-19 patients from included studies.

		Severe group					Non-severe group						
First author (year)	Region	Number	Mean age, years (SD)	Male, %	Mean LDH level, U/l (SD)	Mean AST level, U/l (SD)	Number	Mean age, years (SD)	Male, %	Mean LDH level, U/l (SD)	Mean AST level, U/l (SD)	NOS	(Refs.)
Akdogan D (2021)	Turkey	57	51.6 (12.9)	NA	241.5 (82.4)	30.0 (14.9)	118	38.6 (11.9)	NA	191.4 (37.5)	27.2 (18.1)	6	(26)
Ayten O (2020)	Turkey	27	64.3 (12.0)	74.0	830.4 (480.2)	42.4 (26.3)	46	52.6 (12.2)	58.7	511.6 (271.7)	28.1 (14.2)	5	(16)
Kantri A (2021)	Morocco	45	65.0 (13.0)	77.8	327.3 (111.8)	36.5 (27.2)	89	42.3 (20.3)	42.7	210.3 (66.3)	20.7 (11.3)	7	(27)
Azizmohammadi S (2021)	Iran	63	59.8 (14.1)	74.6	311.3 (82.7)	33.3 (10.6)	176	43.9 (14.5)	48.9	213.7 (75.5)	27.0 (10.5)	6	(28)
Wang D (2020)	China	71	62.3 (12.1)	62.0	349.3 (162.7)	63.8 (32.9)	72	45.3 (21.2)	40.3	208.0 (78.7)	43.2 (20)	6	(29)
Sepulchre E (2022)	Belgium	60	66.5 (14.4)	71.7	510.3 (208.1)	66.7 (46.3)	138	60.3 (20.2)	52.2	342.7 (173.1)	42.0 (28.5)	8	(17)
Zheng F (2020)	China	30	56.5 (15.2)	46.7	244.9 (94.7)	35.6 (18.3)	131	40.3 (14.2)	50.4	168.0 (56.0)	23.7 (7.3)	5	(30)
Pan F (2020)	China	89	67.7 (9.0)	75.3	516.0 (108.1)	50.0 (23.4)	35	63.7 (21.6)	51.4	378.0 (195.6)	48.0 (35.6)	7	(15)
Fukushima K (2021)	Japan	41	67.3 (18.4)	90.2	467.7 (153.9)	53.7 (28.4)	193	44.0 (20.9)	60.6	232.8 (82.9)	28.0 (13.4)	7	(31)
Bonetti G (2020)	Italy	70	75.4 (15.0)	64.3	524.0 (166.0)	62.8 (29.5)	75	62.6 (15.0)	68.9	320.1 (111.8)	43.0 (25.7)	7	(18)
Wang H (2021)	China	24	55.7 (15.0)	62.5	267.5 (122.6)	32.4 (11.3)	37	51.0 (17.0)	43.2	181.2 (32.7)	22.0 (11.3)	8	(32)
Huang H (2021)	China	21	61.4 (16.4)	57.1	356.9 (204.6)	37.0 (30.2)	43	41.2 (15.7)	58.1	209.2 (52.2)	25.0 (6.9)	7	(33)
Kumar H (2021)	India	30	58.9 (13.2)	60.0	617.9 (389.4)	81.3 (51.1)	79	56.1 (16.6)	79.7	448.8 (185.9)	66.5 (33.6)	7	(19)
Gómez LC (2021)	Spain	166	76.0 (14.2)	n	377.3 (170.1)	31.0 (16.4)	376	64.0 (12.7)	n	276.8 (110.3)	31.0 (16.4)	9	(34)
Vidal-Cevallos P (2021)	Mexico	79	46.7 (25.7)	78.5	577.0 (269.6)	76.3 (80.0)	298	41.8 (22.7)	72.1	389.8 (191.8)	45.3 (22.7)	6	(20)
Mo P (2021)	China	85	60.7 (14.3)	64.7	306.7 (181.7)	29.0 (18.9)	70	45.0 (17.4)	44.3	259.0 (106.0)	22.7 (13.6)	9	(35)
Snipelisky D (2020)	Georgia	42	61.9 (15.5)	66.7	463.0 (224.0)	66.0 (48.0)	144	60.5 (17.7)	39.6	361.0 (242.0)	38.0 (22.0)	7	(21)
Qin W (2021)	China	23	69.3 (7.1)	43.5	458.4 (136.5)	37.9 (23.7)	239	61.3 (12.2)	47.3	245.0 (80.6)	25.3 (11.9)	7	(22)
Zhang W (2021)	China	16	51.2 (14.1)	68.8	759.7 (315.4)	31.1 (17.2)	49	43.6 (14.2)	53.1	438.3 (71.0)	23.7 (9.2)	5	(36)
Feng X (2020)	China	20	69.2 (11.1)	65.0	665.7 (388.6)	62.8 (68.0)	94	62.8 (13.7)	61.7	285.3 (127.1)	40.6 (23.5)	6	(37)
Zhu Y (2020)	China	29	72.6 (13.2)	65.5	785.5 (274.4)	51.0 (50.0)	73	62.2 (13.6)	53.4	352.1 (140.9)	32.0 (13.0)	8	(23)
Yousaf MN (2022)	Pakistan	135	56.5 (16.3)	n	702.0 (375.0)	49.0 (37.0)	251	52.7 (16.0)	n	498.0 (348.0)	41.0 (21.0)	9	(24)
Wang Z (2020)	China	116	72.7 (12.0)	56.0	475.5 (203.4)	42.0 (23.3)	177	49.6 (22.2)	41.2	231.3 (71.2)	26.3 (10.5)	9	(25)

LDH, lactate dehydrogenase; AST, aspartate aminotransferase; NA, not available; NOS, Newcastle-Ottawa Scale. Data presented as mean (SD).

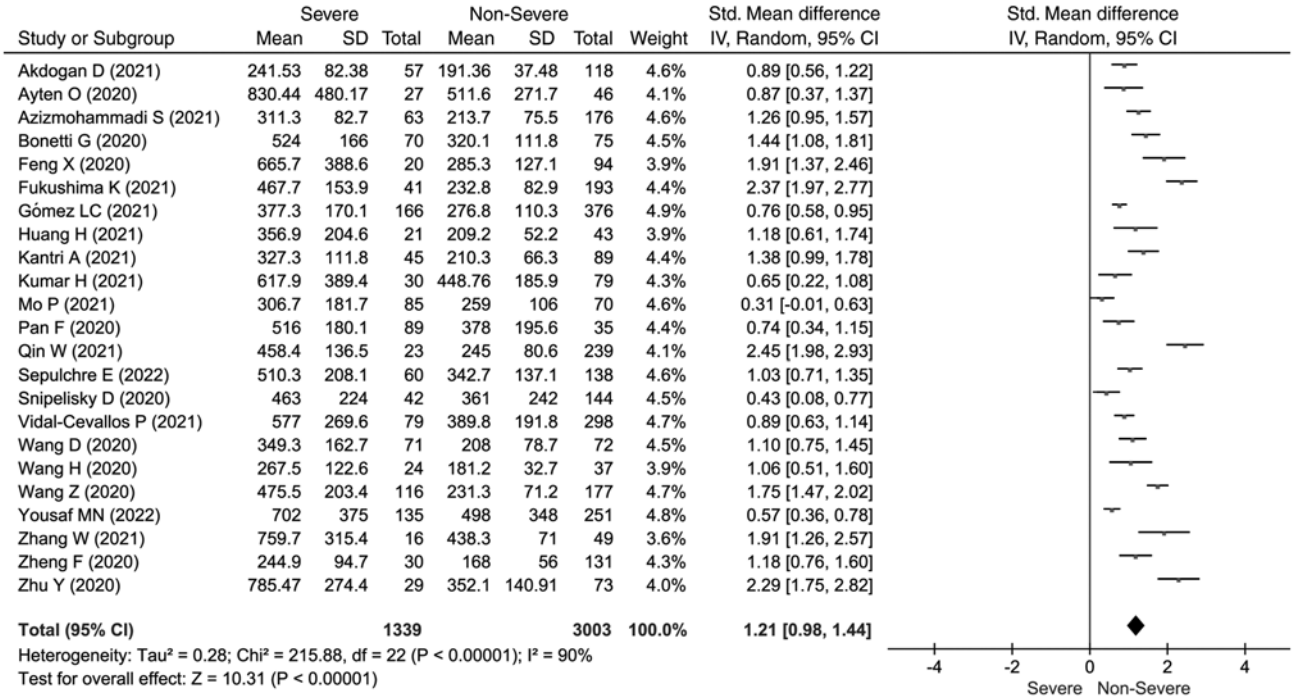

Figure 2. Forest plots depicting different LDH concentrations in the severe group vs. the non-severe group. The diamond represents the point estimate and CIs after combining and averaging all individual studies. LDH, lactate dehydrogenase; SD, standard deviation; Std. Mean Difference, standardized mean difference; IV, inverse variance; CI, confidence interval; df, degree of freedom.

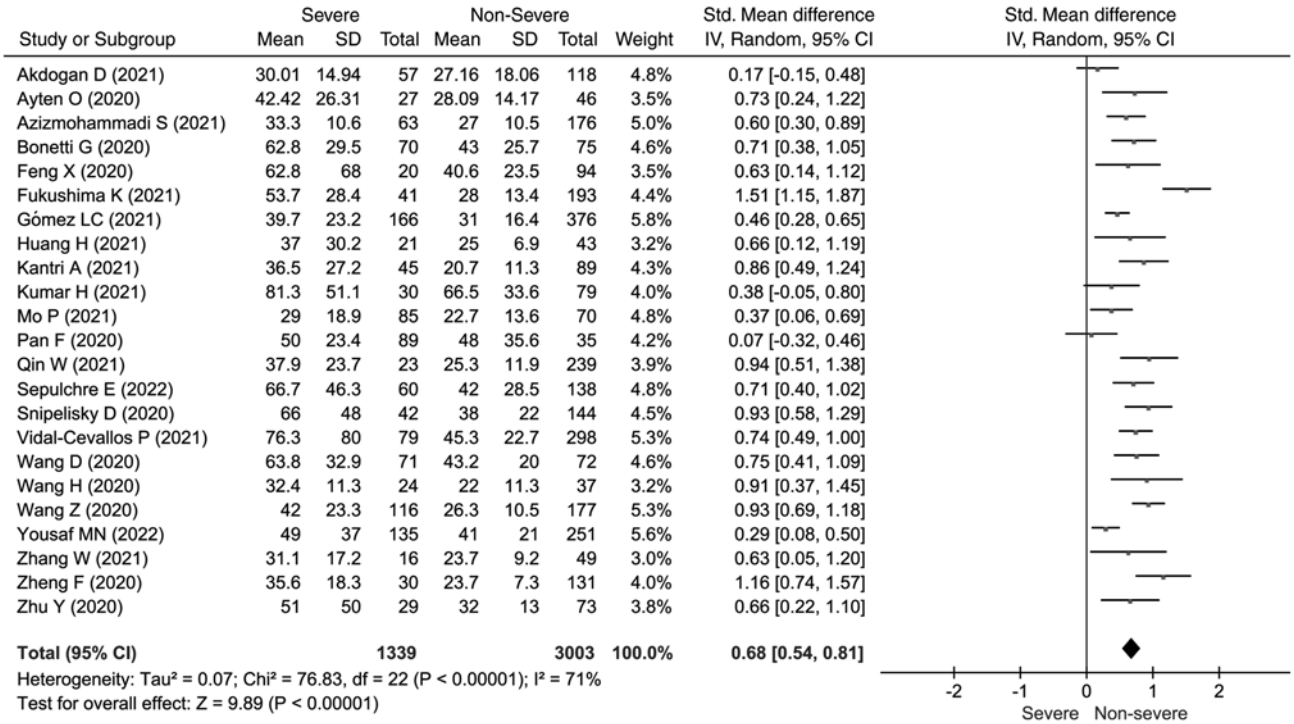

Figure 3. Forest plots depicting different AST levels in the severe group vs. the non-severe group. The diamond represents the point estimate and confidence intervals after combining and averaging all individual studies. AST, aspartate aminotransferase; SD, standard deviation; Std. Mean Difference, standardized mean difference; IV, inverse variance; CI, confidence interval; df, degree of freedom.

elevated LDH concentrations (SMD=1.21; 95% CI: 0.98, 1.44) (Fig. 2). Elevated AST concentrations were also found to be concerned with a severe outcome (SMD=0.68; 95% CI: 0.54, 0.81; I^2=71%; P<0.001) (Fig. 3).

Sensitivity analysis. We did a sensitivity analysis and applied the leave-one-out method to evaluate each study's influence. The heterogeneity was found to be considered regardless of whatever study was omitted. Both LDH and AST sensitivity

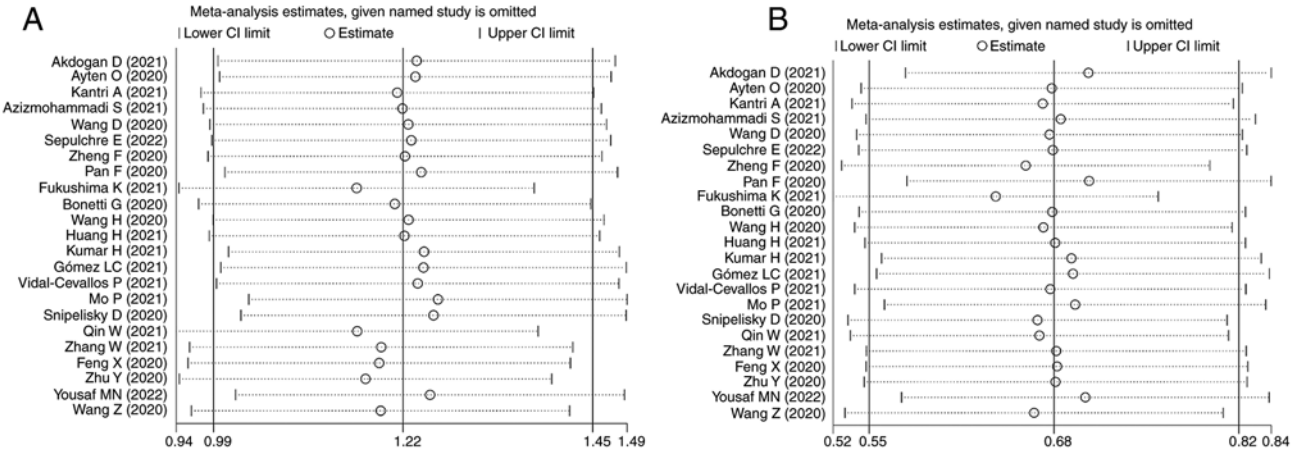

Figure 4. Sensitivity analysis for (A) LDH and (B) AST and coronavirus disease 2019 severity. The hollow circles represent the pooled SMD when the given named study is omitted from the meta-analysis. The middle vertical axis indicates the overall SMD and the two vertical axes indicate the 95% CIs. AST, aspartate aminotransferase; CI, confidence interval; LDH, lactate dehydrogenase; SMD, standardized mean difference.

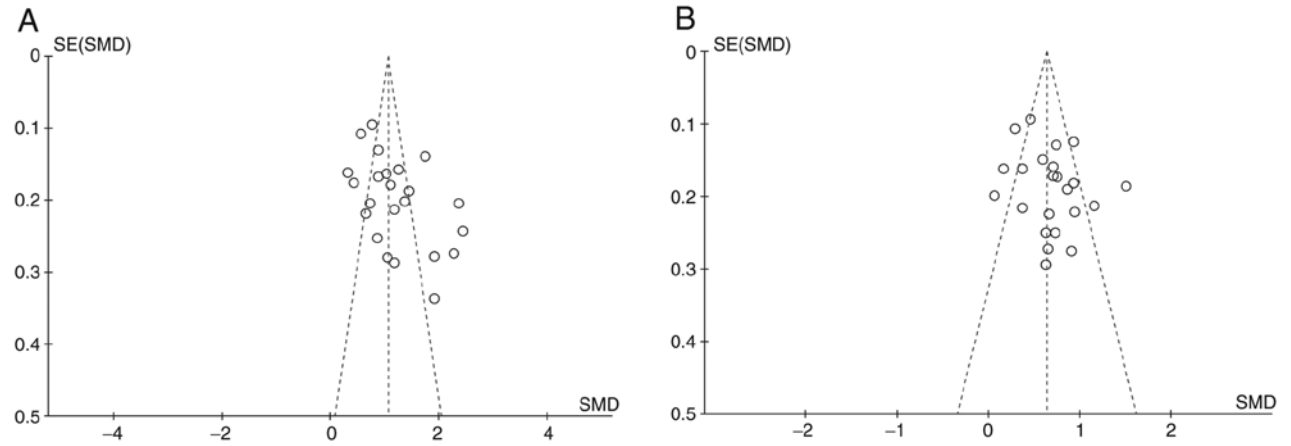

Figure 5. Funnel plot for the study evaluating the relationship between (A) lactate dehydrogenase and (B) aspartate aminotransferase concentrations with coronavirus disease 2019 severity status. SMD, standardized mean difference.

analyses revealed no significant differences between studies. The pooled SMD values did not change after the sequential removal of individual studies (Fig. 4).

Publish bias analysis. We used funnel plots and Egger's tests to evaluate publication bias. Using Egger's test, no significant publication bias was found for all included AST studies (P=0.155), but LDH has (P=0.015). The funnel plot also showed the difference between the two groups (Fig. 5).

Meta-regression. The effect estimate did not differ substantially with outcomes (LDH P=0.909, AST P=0.851), publication year (LDH P=0.383, AST P=0.977), region (LDH P=0.261, AST P=0.533), and age (LDH P=0.301, AST P=0.716) according to meta-regression (Table II).

Subgroup analysis. A higher proportion of men with severe COVID-19 was found in the subgroup analysis (RD 0.21; 95% CIs: 0.06, 0.35; P<0.001) (Fig. S1). COVID-19 patients with a high severity are also older (SMD 0.70; 95% CIs: 0.53, 0.88; P<0.001) (Fig. S2). We also performed outcomes, published years, and areas subgroup analyses to see whether there were any correlations between the groups (Figs. S3 and S4). LDH and AST levels were higher in the experimental group, according to the subgroup analysis of uncombined outcomes. The rise in the severe vs. non-severe group was more significant than in the death vs. discharge group. About half of the studies were conducted in China, so we separated the studies into two groups, conducted in China or other countries. The year of publication, as well as the region, revealed a slight variance in subgroup analysis. Meta-regression and subgroup analysis failed to identify the cause of the heterogeneity.

Discussion

LDH catalyzes the conversion of pyruvate (the end product of glycolysis) to lactate, reversing the liver's Cori cycle when hypoxia or insufficient supply occurs (38). Multiple organ injury, severe infections, reduced oxygenation, and activation of the glycolytic pathway can cause LDH concentration increases. LDH has many isoenzymes, and LD1 high activities are found in the heart; since the 1960s, LDH has long been a conventional indicator of cardiac injury (39). A pooled analysis indicated that patients with elevated LDH had a

Table II. Meta-regression analysis in different subgroups.

	LDH			AST		
Subgroup	Coef	Std. Err.	*P*>|*z*|	Coef	Std. Err.	*P*>|*z*|
Outcomes	-.0371399	.3256605	0.909	-.0333406	.1769221	0.851
Publication year	.5294593	.6070254	0.383	.0099645	.3463723	0.977
Region	-.367411	.3268494	0.261	-.1122298	.1800766	0.533
Age	.3303795	.31914	0.301	-.0628999	.1726357	0.716

LDH, lactate dehydrogenase; AST, aspartate aminotransferase; Coef, coefficient; Std. Err., standard error. *P*>|*z*|< 0.05 was considered statistically significant.

16-fold higher mortality rate and a more than 6-fold increased probability of developing severe COVID-19 illness (40). Meanwhile, according to a recent study, COVID-19 patients' LDH and C-reactive protein levels may predict respiratory failure. LDH and CRP should be viewed as helpful tests for the early detection of individuals who need more aggressive supportive therapy and tighter respiratory monitoring to avoid poor prognosis (41).

The time-dependent concentration of AST also has strong sensitivity and specificity to acute myocardial injury. A multi-center retrospective study showed that the mortality rate of AST abnormalities in COVID-19 patients was higher than that of other patients. This result recommended using AST to monitor COVID-19 patients immediately (42). Interestingly, not all studies showed that AST abnormalities were associated with higher in-hospital mortality. For example, Aloisio and Panteghini thinks the practical significance of AST in COVID-19 patients is affected by data sources, lack of standardization of commercial assays, and interference from unqualified specimens (43). AST and LDH are both markers of myocardial injury, and whether they simultaneously increase and interact with each other in COVID-19 patients is ambiguous. In a Chinese cohort study, it has been observed that the increased AST has a dependence on the LDH of hospitalized COVID-19 patients (44). A systematic review found that elevated AST and LDH were independently associated with the risk of adverse clinical outcomes for COVID-19 patients (10). Our findings were consistent with the meta-analysis published by Battaglini *et al* (45) and the review by Stegeman *et al* (46). Battaglini's group researched the possibility of multi-organ impaired in COVID-19 patients and Stegeman explored the accuracy of routine laboratory tests (including hematological, inflammatory, and other laboratory biomarkers) to diagnose COVID-19, they both found that LDH and AST were increased in COVID-19 patients. Hence, the study adds to the existing knowledge of biomarkers that can be used as a predictor in the risk stratification model of severe COVID-19.

It is worth noting that both LDH and AST have widespread activities in numerous body tissues, and they are also typical markers of sepsis. What is certain is that they are indeed elevated in patients with severe COVID-19. The potential causes of cardiac injury in COVID-19 patients are diverse, such as direct viral damage to cardiomyocytes, cytokines and interferon-induced inflammation, myocardial interstitial fibrosis, T-cell responses, disruption of ACE-2 receptors. Moreover, the lung injury may cause damage to cardiac muscle cells due to hypoxia, and continued disruption of endothelial function negatively affect the thrombotic/fibrinolytic balance (47). Additionally, numerous studies have demonstrated that COVID-19 infections and severe symptoms are more frequent in individuals with cardiovascular disease (48-50). The study aimed to investigate the prognostic role of conventional myocardial enzyme profiles in COVID-19. LDH and AST are characterized by their long duration at the time of myocardial injury and better reflect COVID-19 severity. The study also tested the simultaneous detection of LDH and AST, which is more dominant than a single indicator indicating myocardial injury. The study also has certain limitations, including the following. Firstly, there were considerable discrepancies in effect size estimates due to differences in the number of included studies and sample sizes. Second, since no RCTs were published, only observational retrospective studies were included, which conduct a high risk of bias. In the future, more randomized controlled studies should be included. Despite the considerable heterogeneity between studies, the sensitivity analysis was unaffected by deleting each study. The explanations for the large to extreme heterogeneity between studies may be: i) As an emerging infectious disease, the studies included in this meta-analysis lack a single criterion for grading COVID-19 severity, which could impact the final results. ii) Because of the varying severity of COVID-19 individuals included in this study and the considerable age gap between them, there is a significant difference in the prognostic index values of patients of different age groups, which could be a source of high heterogeneity. iii) This is likely owing to a lack of standardization of analytical methodologies, including various measurement methods. More standardized diagnostics and test studies, including RCTs, are needed in the future.

The systematic review and meta-analysis showed that LDH and AST serum concentrations were considerably higher in COVID-19 patients with severe disease than in non-severe. These findings show that LDH and AST could be employed as possible predictors of prognosis and risk of death in patients with COVID-19. However, as most of the studies in the current review were retrospective and had significant heterogeneity, bigger sample sizes and high-quality prospective cohort studies are required to confirm this finding.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SKY, LZ and FZ conceptualized and designed the study. ZYH and RQY collected data and drafted the manuscript. JSL, HBD and YLZ analyzed and interpreted data. SKY gave final approval of the version to be published. ZYH and RQY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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