Prognostic value of elevated lactate dehydrogenase in patients with COVID-19: a systematic review and meta-analysis

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ABSTRACT

Purpose This meta-analysis aimed to evaluate the prognostic performance of elevated lactate dehydrogenase (LDH) in patients with COVID-19.

Methods A systematic literature search was performed using PubMed, Embase and EuropePMC on 19 November 2020. The outcome of interest was composite poor outcome, defined as a combined endpoint of mortality, severity, need for invasive mechanical ventilation and need for intensive care unit care. Severity followed the included studies' criteria.

Results There are 10 399 patients from 21 studies. Elevated LDH was present in 44% (34%–53%) of the patients. Meta-regression analysis showed that diabetes was correlated with elevated LDH (OR 1.01 (95% CI 1.00 to 1.02), p=0.038), but not age (p=0.710), male (p=0.068) and hypertension (p=0.969). Meta-analysis showed that elevated LDH was associated with composite poor outcome (OR 5.33 (95% CI 3.90 to 7.31), p<0.001; I^2: 77.5%). Subgroup analysis showed that elevated LDH increased mortality (OR 4.22 (95% CI 2.49 to 7.14), p<0.001; I^2: 89%). Elevated LDH has a sensitivity of 0.74 (95% CI 0.60 to 0.85), specificity of 0.69 (95% CI 0.58 to 0.78), positive likelihood ratio of 2.4 (95% CI 1.9 to 2.9), negative likelihood ratio of 0.38 (95% CI 0.26 to 0.55), diagnostic OR of 6 (95% CI 4 to 9) and area under curve of 0.77 (95% CI 0.73 to 0.80). Elevated LDH would indicate a 44% posterior probability and non-elevated LDH would in indicate 11% posterior probability for poor prognosis. Meta-regression analysis showed that age, male, hypertension and diabetes did not contribute to the heterogeneity of the analyses.

Conclusion LDH was associated with poor prognosis in patients with COVID-19.

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INTRODUCTION

COVID-19 is one of the most common diseases, and the trend is rapidly increasing. It has infected 65.8 million people globally, resulting in over 1.5 million deaths.[1] Even though most of the patients with COVID-19 is only mildly symptomatic, a notable proportion of patients deteriorate remarkably, causing multiple organ failure that resulted in death.[2] Cost-effective biomarkers, especially those that are routinely tested, enable risk stratification to allow prudent resource allocation.[3]

Lactate dehydrogenase (LDH) catalyses the last step of aerobic glycolysis, the pyruvate to lactate conversion.[4] LDH has been shown to be a potential prognostic biomarker in patients with COVID-19.[5] Elevated LDH signifies tissue hypoperfusion indicates the extent of the disease, hence, may affect prognosis.[6 7] However, there are studies showing that LDH is not associated with poor prognosis.[8] This meta-analysis aimed to evaluate the prognostic performance of elevated LDH in patients with COVID-19.

MATERIAL AND METHODS

This meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

ELIGIBILITY CRITERIA

The inclusion criteria were letters and research articles reporting COVID-19 patients with information on LDH (dichotomous) along with mortality/severity/invasive mechanical ventilation (IMV)/critical care/intensive care unit (ICU) care. The exclusion criteria were preprint studies, conferences abstract, commentaries, letters containing no primary data, case reports and articles in a language other than English.

Search strategy and study selection

A systematic literature search was performed using PubMed, Embase and EuropePMC with keywords "2019-nCoV" OR "SARS-CoV-2" OR "COVID-19" AND "lactate dehydrogenase" OR "LDH" AND "Mortality" OR "non-survivor" OR "severity" OR "intensive care unit" OR "intubation" OR "invasive mechanical ventilation" on 19 November 2020. The PubMed (MEDLINE) search keywords was ((2019-nCoV) OR (SARS-CoV-2) OR (COVID-19) AND ((lactate dehydrogenase) OR (LDH)) AND (Mortality) OR (non-survivor) OR (severity) OR (intensive care unit) OR (intubation) OR (invasive mechanical ventilation)). Duplicates were removed from the initial record, and two individuals independently screened the title/abstract of the relevant studies.

DATA EXTRACTION

Extraction of data from the included studies was performed by two individuals independently using extraction forms that consisted of author, year, study design, age, gender, diabetes, hypertension, cardiovascular diseases, LDH cut-off points and outcome of interests.

The key exposure was elevated LDH, defined as level of LDH above specific cut-off points defined by each individual study. The outcome of interest

Table 1 Characteristics of the included studies

Authors	Design	Samples	Cut-off (U/L)	Age (years)	Male (%)	Hypertension (%)	Diabetes (%)	CAD/CVD (%)	Outcome	NOS
Chen *et al* 2020[9]	Retrospective Cohort	21	>300	56	81	23.8	14.3	–	Severity	7
Chen *et al* 2020[10]	Retrospective Cohort	635	>245	61	50	37.6	22.8	8.2 (CAD)	Severity	7
Colaneri *et al* 2020[11]	Retrospective Cohort	44	>300	–	72.7	34.9	15.9	25 (CVD)	Severity	7
Deng *et al* 2020[12]	Retrospective Cohort	65	>243	34	55.3	4.6	3	0	Severity	7
Guan *et al* 2020[13]	Retrospective Cohort	675	>250	47	58.1	15	7.4	2.5 (CAD)	ICU +IMV + Mortality	7
Hong *et al* 2020[14]	Retrospective Cohort	98	–	55.4	38.8	30.6	9.2	11.2 (CVD)	ICU	7
Huang *et al* 2020[5]	Retrospective Cohort	40	>245	49	73	15	20	15 (CVD)	ICU Care	7
Huang *et al* 2020[15]	Retrospective Cohort	614	>250	56	46.4	33.4	14.8	10.5 (CVD)	Mortality	9
Jang *et al* 2020[16]	Retrospective Cohort	110	>550	56.9	60.9	33.6	26.4	4.3 (CVD)	Severity	7
Khamis *et al* 2020[17]	Retrospective Cohort	63	>250	48	85	32	32	6.4 (CVD)	ICU	7
Li *et al* 2020[18]	Retrospective	113	>300	–	–	–	–	–	Mortality	6
Li 2020[19]	Retrospective Cohort	534	>250	60	50.9	30.3	15.1	6.2 (CAD)	Severity	9
Mikami *et al* 2020[20]	Retrospective Cohort	2126	>440	66	57.2	33	23.3	–	Mortality	9
Ramos-Rincon *et al* 2020[21]	Retrospective Cohort	2772	>500	86.3	49.4	75	25.6	30.8 (CVD)	Mortality	9
Wang *et al* 2020[22]	Prospective Cohort	65	–	57.1	57	–	–	–	Severity	5
Wang *et al* 2020[23]	Retrospective Cohort	252	>250	49	46.5	19.6	6.2	1.8 (CAD)	Severity	7
Wei *et al* 2020[24]	Retrospective Cohort	102	>250	51	56.2	17	5.1	4 (CAD)	Severity	7
Zhang *et al* 2020[8]	Retrospective Cohort	937	–	55.6	48.4	–	–	24.7 (CVD)	Mortality	7
Zhang S 2020	Retrospective Cohort	788	>250	44	51.6	16	7.2	1.4	Severity	7
Zheng *et al* 2020[26]	Retrospective Cohort	161	>225	45	49.7	13.7	4.3	2.5 (CAD)	Severity	7
Zhou *et al* 2020[27]	Retrospective Cohort	184	>245	56	62	30	19	8 (CAD)	Mortality	8

CAD, coronary artery disease; CVD, cardiovascular disease; ICU, intensive care unit; IMV, invasive mechanical ventilation; NOS, Newcastle-Ottawa Scale.

was composite poor outcome, defined as a combined endpoint of mortality, severity, need for IMV, and need for ICU care. Severity followed the included studies' criteria. The effect estimate was reported as OR. Sensitivity and specificity, positive and negative likelihood ratio (PLR and NLR), diagnostic OR (DOR) and area under curve (AUC) were generated for the diagnostic meta-analysis.

RISK OF BIAS ASSESSMENT

Newcastle-Ottawa Scale was used to facilitate the quality assessment of the included studies. The assessment was performed by two individuals independently, and arising discrepancies were resolved by discussion.

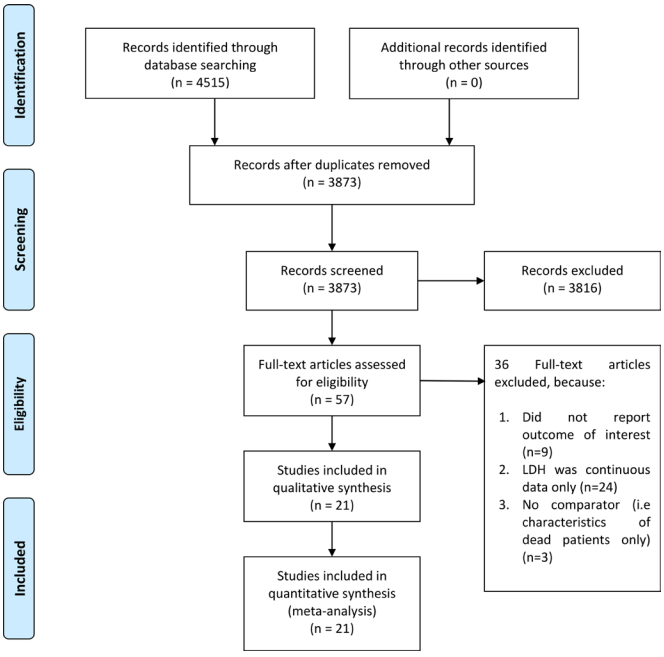

Figure 1 PRISMA flow chart. LDH, lactate dehydrogenase; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

STATISTICAL ANALYSIS

STATA V.16 (StataCorp) was used to perform statistical analysis. Meta-analysis of proportion was used to the incidence of poor composite outcome and elevated LDH. DerSimonian and Laird method random-effects model was used to calculate ORs. A $p<0.05$ was considered as statistically significant. Inter-study heterogeneity was assessed using theI^2 and Cochran Q test; a value of <50% or $p<0.10$ indicates significant heterogeneity. Restricted-maximum likelihood random effects meta-regression analysis was performed with age, gender, diabetes mellitus and hypertension as covariates, for the prevalence of elevated LDH and the association between elevated LDH and composite poor outcome. Funnel plot and Egger't test were performed to assess publication bias. Trim-and fill analysis was performed to account for the asymmetrical funnel plot. Pooled sensitivity and specificity, summary receiver operating characteristic curve, Fagan's nomogram and Deek's asymmetry test were performed. Univariate meta-regression and subgroup analyses were performed for age, male, hypertension and diabetes.

RESULTS

Study selection and baseline characteristics

There are 10 399 patients from 21 studies included in the qualitative and quantitative synthesis (figure 1).[5 8–27] Baseline characteristics and risk of bias assessment of the included studies are displayed in table 1. The incidence of composite poor outcome was 25%.

LDH and Poor Prognosis

Elevated LDH was present in 44% (34%–53%) of the patients. Meta-regression analysis showed that diabetes was correlated with elevated LDH (OR 1.01 (95% CI 1.00 to 1.02), p=0.038), but not age (p=0.710), male (p=0.068) and hypertension

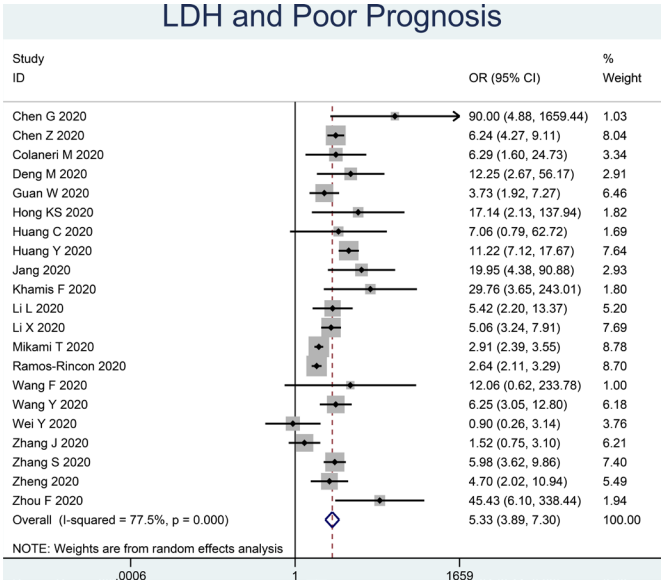

Figure 2 Forest-plot for lactate dehydrogenase and composite poor outcome. LDH, lactate dehydrogenase.

(p=0.969). Meta-analysis showed that elevated LDH was associated with composite poor outcome (OR 5.33 (95% CI 3.90 to 7.31), p<0.001; I^2: 77.5%, p<0.001) (figure 2). Based on meta-regression, the effect estimate was found to not significantly vary with age (p=0.223), male (p=0.117), hypertension (0.445) and diabetes (p=0.583). The funnel-plot analysis showed an asymmetrical shape and Egger's test demonstrates small-study effects (p=0.005). Trim-and-fill analysis was performed, and the addition of 6 imputed studies on the left side, the OR became 4.31 (95% CI 3.00 to 6.20]. Subgroup analysis showed that elevated LDH increased mortality (OR 4.22 (95% CI 2.49 to 7.14), p<0.001; I^2: 89%, p<0.001).

Diagnostic meta-analysis

Elevated LDH has a sensitivity of 0.74 (95% CI 0.60 to 0.85), specificity of 0.69 (95% CI 0.58 to 0.78) (figure 3), PLR of 2.4 (95% CI 1.9 to 2.9), NLR of 0.38 (95% CI 0.26 to 0.55), DOR of 6 (95% CI 4 to 9) and AUC of 0.77 (95% CI 0.73 to 0.80) (figure 4). Elevated LDH would indicate a 44% posterior probability and non-elevated LDH would in indicate 11% posterior probability for poor prognosis (figure 5). Deek's asymmetry test was significant (p=0.004). Meta-regression analysis showed that age, male, hypertension and diabetes did not contribute to the heterogeneity of the analysis. Figure 6 shows the univariate meta-regression and subgroup analyses.

DISCUSSION

Elevated LDH was associated with poor prognosis in patients with COVID-19, indicating 37% posterior probability for 'composite poor outcome' with AUC of 0.77, sensitivity of 74%, and specificity of 69%.

The incidence of LDH was associated with presence of diabetes, this phenomenon might be due to reduced glycogen synthesis, change in glucose oxidative metabolism and elevated whole-body rate of non-oxidative glycolysis.[28–31] These mechanisms cause elevated lactate in patients with insulin resistance compared with those without. LDH has been found to affect the prognosis of various diseases, including cancers.[32] LDH elevation in patients with COVID-19 indicates lung and tissue injuries.[19] COVID-19 may lead to inadequate tissue perfusion and multiple organ failure due to various mechanisms, including thrombosis, which lead to LDH elevation.[2 33] Thus, high LDH serves as a biomarker of the disease extent. This study indicated that the association between LDH elevation and poor prognosis was not affected by age, gender, hypertension or diabetes; these factors were known to increase COVID-19 severity and its associated mortality, thus, may confound the association .[3 34–37] Three studies reported that elevated LDH was independently

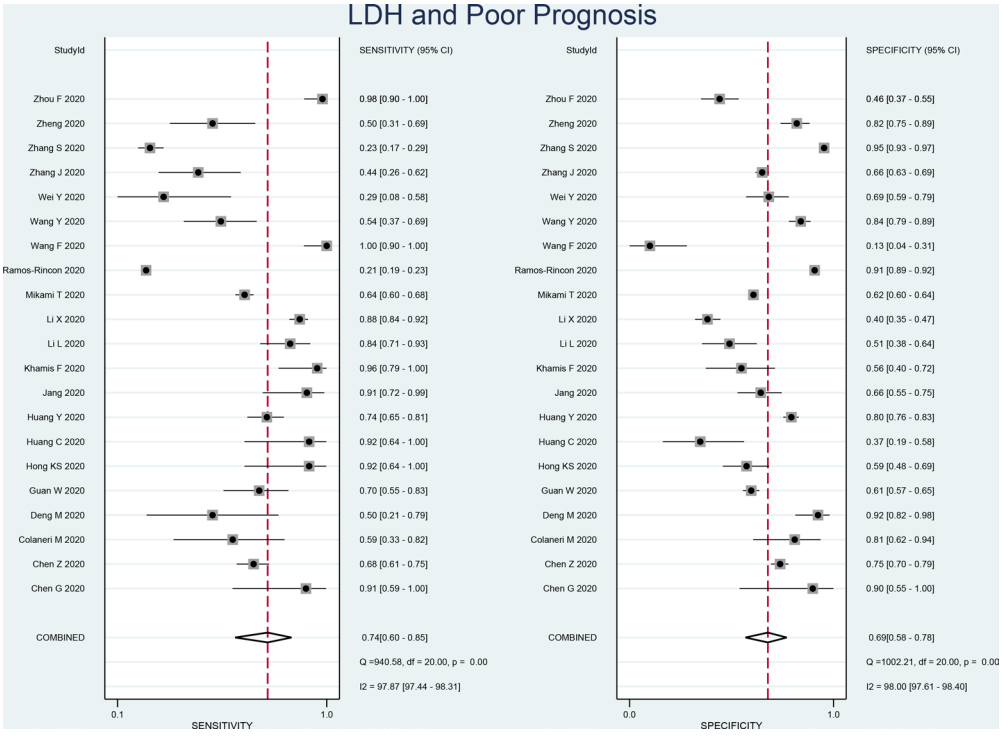

Figure 3 Pooled sensitivity and specificity. LDH, lactate dehydrogenase.

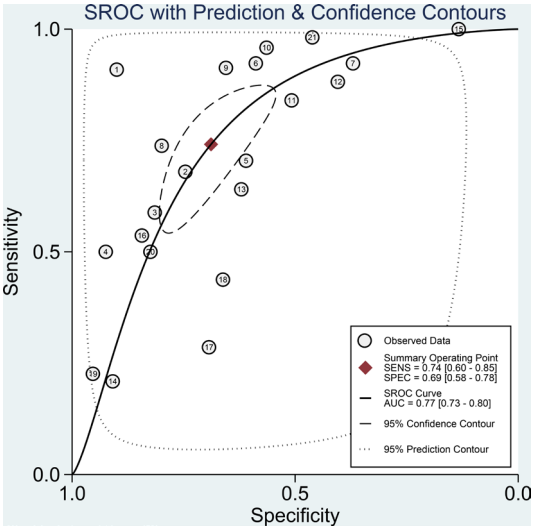

Figure 4 Summary receiver operating characteristics (SROC) curve . AUC, area under curve; SROC, summary receiver operating characteristic

associated with poor prognosis (HR 1.01, HR 2.00 and OR 1.63).[15 19 21] One study reported that elevated LDH was lost its statistical significance after adjustment.[20]

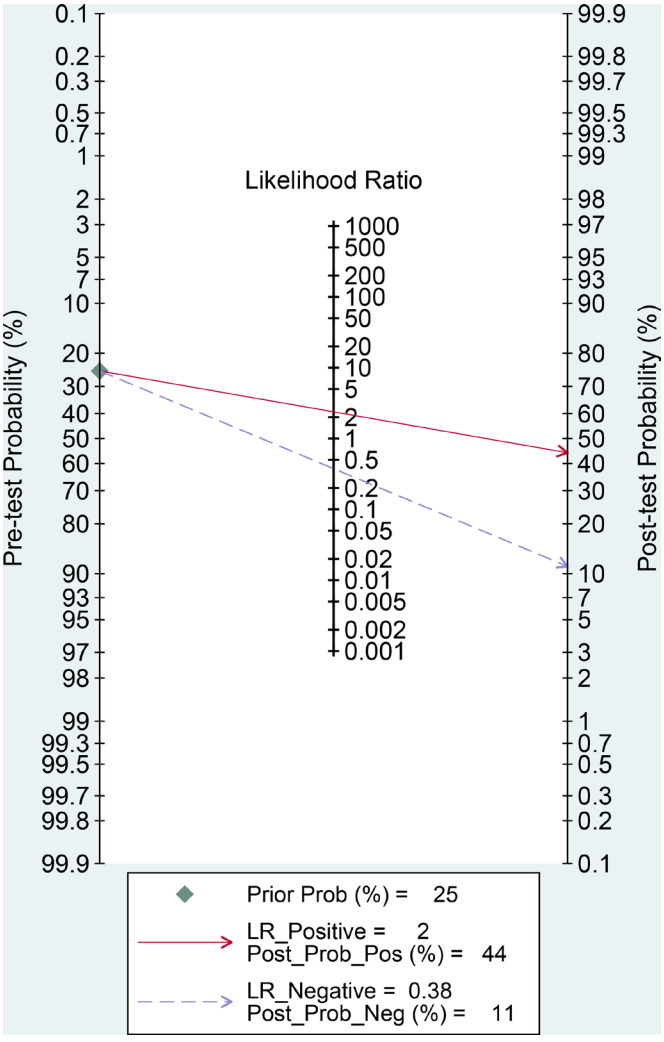

Figure 5 Fagan's normogram. LR, likelihood ratio.

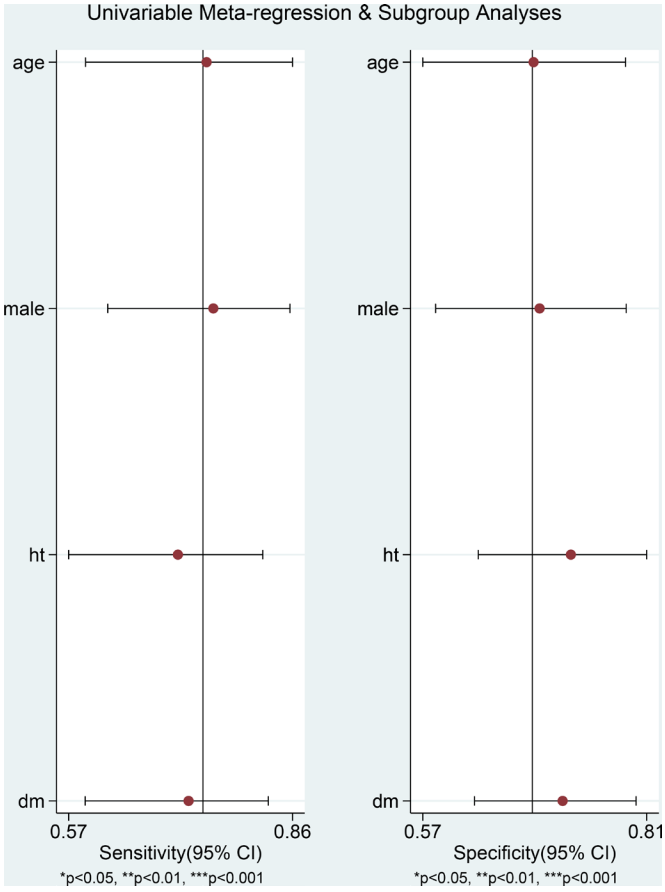

Figure 6 Univariable meta-regression and subgroup analyses.

The heterogeneity might be due to different cut-off points, lab references and diagnostic tools. Another possible explanation was due to the very different methods by which patients with COVID-19 get the attention of medical services. Nevertheless, most of the studies demonstrate that elevation of LDH for at least >250 U/L was associated with poor prognosis. Funnel-plot analysis and Egger's test indicate small study effect in the pooled estimate. Trim-and-fill analysis was performed to evaluate whether the adjustment to publication bias will cause the effects estimate to become non-significant. With the imputation of six hypothetical studies the OR was only reduced slightly (OR 4.31 vs 4.22), indicating the robustness of the effect estimate. Thus additional studies are unlikely to nullify the prognostic performance of this meta-analysis

The pooled result is that LDH has poor predictive performance; and might be similar to other metabolic marker of physiological distress (Troponin, C reactive proteins, white cell count, d-dimer, brain natriuretic peptide (BNP) and others),[38 39] thus, it should be studies further and integrated into a risk prediction model rather used alone. This result adds to the literature that elevated LDH is associated with poor outcome, whether they are discriminatory requires further investigation with large sample size.

This systematic review's limitation was mainly due to retrospective studies, which have a higher potential for bias. Additionally, different cut-off points may cause high heterogeneity. Future studies are suggested to use single cut-off points for prognostic purposes. Drugs associated with comorbidities, such as metformin and renin–angiotensin–aldosterone system

inhibitor, may affect LDH[40 41]; the studies inadequately report these.

CONCLUSION

LDH was associated with poor prognosis in patients with COVID-19.

Main messages

- Elevated lactate dehydrogenase (LDH) has a sensitivity of 74% and specificity of 69%.
- Elevated LDH would indicate a 44% posterior probability and non-elevated LDH would in indicate 11% posterior probability for poor prognosis.
- Meta-regression analysis showed that age, male, hypertension and diabetes did not contribute to the heterogeneity.

Current research question

- Future studies are suggested to use a single cut-off point for prognostic purposes.
- Integrating lactate dehydrogenase into a model may enhance prognostication.
- More prospective studies are required for a higher quality of evidence.

What is already known on the subject

- Lactate dehydrogenase (LDH) catalyses the last step of aerobic glycolysis, the pyruvate to lactate conversion.
- Elevated LDH signifies tissue hypoperfusion indicates the extent of the disease, hence, may affect prognosis in COVID-19.
- There are studies showing that elevated LDH was associated with mortality, and some studies did not.

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Competing interests None declared.

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