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Lactate dehydrogenase level as a COVID-19 severity marker



We read with great interest the article by Henry et al. [1] showed that elevated lactate dehydrogenase (LDH) values were associated with 6-fold increased odds of severe COVID-19 disease. Lactate dehydrogenase increases in the early stage of myocardial infarction as well as in states of hemolysis. It is most active in the liver, striated muscles, heart, kidneys, lungs, brain, and red blood cells (erythrocytes). In the case of cell damage, lactate dehydrogenase is released from inside them, its concentration and activity in the blood increase. High serum LDH activity is a negative prognostic factor in such patients. LDH is a marker of various inflammatory states, e.g., infections, malignancies, MI, sepsis, or cardio-pulmonary compromise. Denese et al. showed that lactate dehydrogenase is a potential marker of vascular permeability in immune-mediated lung injury [2]. Early data Henry et al. reported in COVID-19 patients have suggested significant differences in LDH levels between patients and without the severe disease [3].

A systematic review and meta-analysis were performed to verify the usefulness of using lactate dehydrogenase as a predictor of a patient's severity with COVID-19.

Two authors (M.P. and L.S.) searched electronic resources (Medline, EMBASE, and the Cochrane Central register from databases inception to 9 November 2020). A review of the bibliographies of the relevant articles was also performed. The retrieved articles were screened for relevance on title and abstract, followed by two independent investigators (L.S. and J.S.). The key search words were: "lactate dehydrogenase" OR "LDH" AND "COVID-19" OR "SARS-CoV-2".

All statistical analyses were performed with Review Manager Software 5.4 (The Cochrane Collaboration, Oxford, Copenhagen, Denmark). All results are presented with their 95% confidence interval (CI). When the continuous outcome was reported in a study as median, range, and interquartile range, we estimated means and standard deviations using the formula described by Hozo et al. [4]. The random-effects model was used for $I^2 > 50\%$. P < 0.05 was taken to show statistical significance. Statistical testing was two-tailed.

	9	Severe	Non-severe				Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chen G 2020	553.75	79.11	11	225.03	14.87	10	3.7%	328.72 [281.07, 376.37]	
Chen LD 2020	333.2	141.71	25	192.5	23.1	69	3.6%	140.70 [84.88, 196.52]	
Feng Z 2020	306.03	40.91	69	186.45	13.67	495	4.0%	119.58 [109.85, 129.31]	-
Gunder R 2020	415.25	213.35	50	290.5	83.3	172	3.5%	124.75 [64.32, 185.18]	
Han Y 2020	416.63	62.93	48	214.5	28.3	59	3.9%	202.13 [182.92, 221.34]	-
Hu J 2020	647.35	424.26	52	321.85	186.24	130	2.7%	325.50 [205.83, 445.17]	
Huang H 2020	356.9	204.6	21	209.2	52.2	43	3.1%	147.70 [58.81, 236.59]	
Huang R 2020	405.63	112.74	23	245.65	30.57	179	3.7%	159.98 [113.69, 206.27]	
Itelman E 2020	539.25	78.23	26	324.44	42.37	136	3.9%	214.81 [183.91, 245.71]	-
Lee J 2020	695.19	455.13	137	447.55	124.11	557	3.3%	247.64 [170.73, 324.55]	
Li Q 2020	408.25	47.06	26	227.5	13	296	4.0%	180.75 [162.60, 198.90]	-
Li Q 2020 (b)	475.5	40	122	204.25	16.17	1327	4.0%	271.25 [264.10, 278.40]	· · · · · · · · · · · · · · · · · · ·
Liu J 2020	462.4	190.6	13	221.5	71.2	27	2.8%	240.90 [133.87, 347.93]	
Liu J 2020 (b)	444.41	140.55	152	348.25	74.48	62	3.9%	96.16 [67.13, 125.19]	-
Lu Y 2020	425.33	132.62	9	284.7	109.62	44	3.1%	140.63 [48.13, 233.13]	
Popov GT 2020	774	371.6	45	453.2	201.2	95	2.7%	320.80 [204.93, 436.67]	
Schalekamp S 2020	421	251	168	317	1,340	188	1.7%	104.00 [-91.27, 299.27]	
Shang W 2020	302.75	40.5	139	213.5	13.75	304	4.0%	89.25 [82.34, 96.16]	
Sun Y 2020	325.77	132.83	19	220.07	67.95	44	3.5%	105.70 [42.69, 168.71]	
Wan S 2020	320.03	44.61	40	215.63	22.96	95	4.0%	104.40 [89.82, 118.98]	-
Wang F 2020	474.84	195.96	35	305.6	103.7	30	3.3%	169.24 [94.46, 244.02]	
Xie L 2020	418.4	19.14	51	168.8	21.5	322	4.0%	249.60 [243.85, 255.35]	· · · · ·
Xiong S 2020	285	47.93	55	235.38	34.51	61	4.0%	49.62 [34.28, 64.96]	÷
Xu Y 2020	422	72.18	25	286.5	34.65	44	3.9%	135.50 [105.41, 165.59]	-
Xue G 2020	358.19	45.38	58	258.06	34.86	56	4.0%	100.13 [85.31, 114.95]	-
Zeng Z 2020	367.31	102.22	224	240.13	12.42	93	4.0%	127.18 [113.56, 140.80]	-
Zhao K 2020	340.32	81.25	31	197	23.11	19	3.9%	143.32 [112.89, 173.75]	
Zheng F 2020	240.25	35.12	30	166.55	21.6	131	4.0%	73.70 [60.60, 86.80]	÷
Total (95% CI)			1704			5088	100.0%	165.13 [131.58, 198.68]	•
Heterogeneity: Tau ² = 7327.76; Chi ² = 2898.26, df = 27 (P < 0.00001); I ² = 99% -500 - 250 0 250									
Test for overall effect: $Z = 9.65$ (P < 0.00001) Severe Non-severe									

Fig. 1. Forest plot of lactate dehydrogenase level in sever vs. non-sever group. The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

Twenty-eight studies reported LDH levels in severe vs. non-sever groups. The level of LDH in the individual groups varied (MD = 154.49; 95% CI: 121.24, 191.73; P < 0.001, $I^2 = 99\%$; Fig. 1). A statistically significant higher level of LDH was also observed in terms of ICU vs. Non-ICU (MD = 272.98; 95% CI: 195.46, 350.51; p < 0.001; $I^2 = 99\%$), patients and in nonsurvival patients vs. survival patients (MD = 259.21; 95% CI: 166.91, 351.51; p < 0.001, $I^2 = 100\%$). Supplementary Digital Content, SDC). The full list of publications included in this meta-analysis is presented in SDC.

In conclusion, the current meta-analysis confirmed that lactate dehydrogenase level can be used as a COVID-19 severity marker and is a predictor of survival.

Declaration of Competing Interest

Authors don't declare any conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.ajem.2020.11.025.

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