

ORIGINAL ARTICLE

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Diagnostic value of lactate dehydrogenase in COVID-19: A systematic review and meta-analysis

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Abstract

Background: This meta-analysis outlines the role of elevated lactate dehydrogenase (LDH) levels in assessing the severity of coronavirus disease 2019 (COVID-19).

Methods: The current study was designed as a systematic review and meta-analysis. Embase, Pub-Med, Web of Science, Scopus and Cochrane Central Register of Controlled Trials were searched to identify the usefulness of LDH as a marker of COVID-19 severity. All extracted data were analyzed using RevMan V.5.4 or STATA V.14 software.

Results: A total of 264 records were selected for this meta-analysis. Pooled analysis showed that LDH levels were statistically significantly lower in the group of survivors compared to patients who died in hospital (standardized mean differences [SMD] = -3.10; 95% confidence interval [CI]: -3.40 to -2.79; $l^2 = 99\%$; p < 0.001). Lower LDH levels were observed in non-severe groups compared to severe course of COVID-19 (SMD = -2.38; 95% CI: -2.61 to -2.14; $l^2 = 99\%$; p < 0.001). The level of LDH was statistically significantly lower in the severe group compared to the critical group (SMD = -1.48; 95% CI: -2.04 to -0.92; $l^2 = 98\%$; p < 0.001). Patients who did not require treatment in the intensive care unit (ICU) showed significantly lower levels of LDH compared to patients who required treatment in the ICU (SMD = -3.78; 95% CI: -4.48 to -3.08; $l^2 = 100\%$; p < 0.001).

Conclusions: *This meta-analysis showed that elevated LDH was associated with a poor outcome in COVID-19.* (Cardiol J 2022; 29, 5: 751–758)

Key words: lactate dehydrogenase, LDH, marker, severity, COVID-19, SARS-CoV-2, meta-analysis

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has become a public health threat worldwide and have caused significant economic problems in many countries [1, 2]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogen and the disease caused by this virus, COVID-19, are not yet fully understood. In patients infected with SARS-CoV-2, there is a wide variation in the symptoms and forms of the disease, which depends on both patient-related factors, infection, and the virus itself. The main symptoms of infection with the new coronavirus include headache, elevated body temperature/fever, fatigue, cough, dyspnea, myalgia, and arthralgia [3, 4]. A severe course of the disease is observed in some cases, with a high risk of death associated with respiratory failure, circulatory failure, and multiple organ failure [5, 6].

After active infection with SARS-CoV-2 has resolved, up to 10% to as many as 30% of recovered patients may suffer from complaints in a symptom complex called long COVID-19. SARS-2 coronavirus infection also shows the potential to induce a generalized inflammatory response, which is directly related to the severity of the course of COVID-19 [7–9]. In addition to interleukin (IL)-6, whose role in inducing generalized inflammation is the most significant [10], increased levels of other inflammatory exponents were also observed, such as II-2, II-7, II-10, TNF, G-CSF, MCP1, MIP1, CXCL10, C-reactive protein, ferritin, D-dimer [11–20].

It is critical to rapidly identify factors contributing to the severity of the disease and indicators of a potentially severe course of COVID-19. In the clinical context, it has become essential to find markers that could predict the severity of the course of COVID-19. Determination of such a marker would allow early assessment of the course of COVID-19 and qualification of the patient for appropriate primarily therapeutic management [21]. It would also positively impact the monitoring of the COVID-19 patient's condition and extend medical supervision to patients who meet the criteria for severe COVID-19.

One potential biomarker whose elevated blood levels could herald the severity of COVID-19 is lactate dehydrogenase (LDH) — an intracellular enzyme that plays a role in energy production [22, 23]. An increased concentration of this enzyme in the blood was observed in tissue damage and subsequent cell death, hypoxia (in the course of respiratory failure), diseases of the hematopoietic and lymphatic systems, or inflammation of the lungs, pericardium, and pancreas. The highest concentrations are found in the heart, lungs, liver, and skeletal muscle. In many cases of severe COVID-19, an increase in LDH activity was observed, which may be due to cell damage as well as impaired blood flow and oxygen delivery.

This meta-analysis outlines the role of elevated LDH levels in assessing the severity of COVID-19. This analysis was based on recent studies, including those involving new virus variants, and included an extensive group of patients and a wide range of publications.

Methods

The present study was designed as a systematic review and meta-analysis, performed in accordance to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [24].

Data source and retrieval strategy

Two reviewers (B.F. and M.P.) comprehensively searched electronic databases (Embase, PubMed, Web of Science, Scopus and Cochrane Central Register of Controlled Trials) from their inception to April 2022. The following search terms were used: "lactate dehydrogenase" OR "LDH" AND "COVID-19" OR "SARS-CoV-2" OR "novel coronavirus".

Studies published in English, involving adult patients with COVID-19 were included in the study. Studies on the pediatric population, illustrative studies, meta-analyzes, editorials, also an inability to collect complete data or to get the full text were excluded.

Data extraction and literature quality evaluation

Two researchers (B.F. and M.P.) independently conducted literature screening and extraction to the inclusion and exclusion criteria. If there were different opinions, the matter was discussed and resolved through discussion with a third researcher (L.S.). Data were collected using a predesigned form. For each study, the following information was extracted: publication (last name of the first author, year of publication), LDH levels in predefined groups (survivor vs. non-survivor; non-severe vs. severe group; severe vs. critical group; non--intensive care unit [ICU] vs. ICU admission group).

The quality of each article was evaluated by the same researchers as above, using a previously piloted standardized form and the Newcastle--Ottawa scale [25].



Figure 1. Database search and selection of studies according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Statistical analysis

The STATA 14 software (StataCorp LP, College Station, USA) and RevMan 5.4 software (Cochrane Collaboration, UK) were used for data analysis in this meta-analysis. For dichotomous data, odds ratios (ORs) were used as the effect measure with 95% confidence intervals (CIs), and for continuous data, standardized mean differences (SMDs) with 95% CI were applied. When LDH values were reported as median and interquartile range, the estimated means and standard deviations using the formula described by Hozo et al. [26] were also utilized. Heterogeneity was assessed with the I² statistic, in which the results ranged from 0% to 100%. Heterogeneity was interpreted as not observed when $I^2 = 0\%$, low when $I^2 = 25\%$, medium when $I^2 = 50\%$, and high when $I^2 = 75\%$ [27]. For the meta-analysis, the random-effects model was used (assuming a distribution of effects across studies) to weight estimates of studies in proportion to their significance [28]. P < 0.05 was considered statistically significant.

Results

Literature search results

The systematic search identified 3157 potential articles. As is shown in Figure 1, 294 reports met the inclusion criteria, and 30 were excluded for insufficient data after full text screening. A total of 264 records were selected for this meta-analysis. The Newcastle Ottawa Scale scores of the 264 included studies were ≥ 7 .

Meta-analysis results

One hundred and thirty studies reported LDH levels among survivor and non-survivor groups. Pooled analysis showed that LDH levels were statistically significantly lower in the group of survivors compared to patients who died in hospital (SMD = -3.10; 95% CI: -3.40 to -2.79; I² = 99%; p < 0.001; Fig. 2).

One hundred and two studies showed LDH levels in non-severe vs. severe COVID-19 patient group. Pooled analysis showed lower LDH levels in non-severe groups compared to severe course of COVID-19 (SMD = -2.38; 95% CI: -2.61 to -2.14; $I^2 = 99\%$; p < 0.001; Fig. 3).

Lactate dehydrogenase levels in the severe group compared with patients who had a critical course of COVID-19 were reported in 15 articles. The level of LDH was statistically significantly lower in the severe group compared to the critical group (SMD = -1.48; 95% CI: -2.04 to -0.92; $I^2 = 98\%$; p < 0.001; Fig. 4).

Patients who did not require treatment in the ICU showed significantly lower levels of LDH compared to patients who required treatment in the ICU (SMD = -3.78; 95% CI: -4.48 to -3.08; I² = 100%; p < 0.001; Fig. 5).

itudy or Subgroup	Mean	urvivor SD	Total	Mean	n-survivor SD		Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
bbasi 2021 brishami 2021	587.5 382	55 23	206 83	865.5 640	127 132.2	56 17	0.8%	-3.64 [-4.07, -3.21] -4.46 [-5.28, -3.64]	-
hsan 2021 Ik 2021	305 278.9	223.5 100.5	131 453	568 374.5	419 325.1	34 22	0.8%	-0.95 [-1.34, -0.56] -0.80 [-1.23, -0.37]	-
khavizadegan 2021 killi 2021	487.4 336.63	142.9 139.1	56 547	587.1 421.6	161.8 221.96	56 35	0.8%	-0.65 [-1.03, -0.27] -0.58 [-0.93, -0.24]	-
Albalawi 2021 Alharthy 2021 Ajohani 2022	309.7 341.18 340	121.8 243.83 227.4	93 127 227	612.2 572.68 403	828.5 324.51 139.7	26 44 22	0.8% 0.8% 0.8%	-0.76 [-1.20, -0.31] -0.86 [-1.22, -0.51] -0.28 [-0.72, 0.15]	-
Ajonani 2022 Alkaabi 2021 Aloisio 2020	380.71	195.74	1346	605.8	291.22	196	0.8%	-0.28 [-0.72, 0.15] -1.07 [-1.22, -0.92] -9.24 [-9.91, -8.57]	
Noisio 2020 Archana 2021 Arslan 2021	345.8 366.2 259.35	28.2 148.2 4.36	332 287 654	688.8 455.5 459.42	59.5 215.4 47.79	89 15 59	0.8% 0.8% 0.8%	-9.24 [-9.91, -8.57] -0.59 [-1.11, -0.06] -14.00 [-14.78, -13.23]	
Arslan 2021 Asghar 2020 Avci 2022	259.35 495.62 316.8	4.36 279.68 161.1	263 643		47.79 1,398.56 451	101 230	0.8%	-14.00 [-14.78, -13.23] -0.50 [-0.73, -0.27] -0.77 [-0.93, -0.62]	
Wci 2022 Ay 2022 Ayhan 2021	409.8 324.45	161.1 142.3 217.26	643 26 67	430.7 487.52	451 146.5 435.64	230 27 22	0.8%	-0.77 [-0.93, -0.62] -0.14 [-0.68, 0.40] -0.57 [-1.05, -0.08]	_
Ayten 2021 Bag Soytas 2021	511.6	271.7 25.2	46	487.52 830.44 442.3	480.17 99.6	27	0.8%	-0.87 [-1.37, -0.37] -3.36 [-3.81, -2.92]	
lairwa 2021 lagi 2021	635.18	298.09 29.3	191 157	1,356	1,496.8	58	0.8%	-0.94 [-1.24, -0.63] -8.92 [-9.74, -8.09]	
lonetti 2020 lotero 2020	319.1	25 214	74	523.5 730	55 380	70 25	0.8%	-4.80 [-5.45, -4.15] -1.10 [-1.55, -0.66]	
Surhamah 2021 Cagnazzo 2021	515 287	209	55	745	348 118.7	78	0.8%	-0.77 [-1.12, -0.41] -3.21 [-3.86, -2.56]	
Castro-Castro 2022 Cen 2020	287 297.5	22 44	695 631	434 509.5	31.7 105.7	150 43	0.8%	-6.12 [-6.46, -5.78] -4.22 [-4.61, -3.84]	
Cena 2021 Chamorro-de-Vega 2021	708 312.3	67.7 28.5	129 76	824 459	111.5 81.7	58 54	0.8%	-1.38 [-1.72, -1.04] -2.56 [-3.03, -2.09]	
Chauhan 2021 Chen 2020	209.5 276.8	11.8 22.8	101 577	525.3 489.5	81.8 50	24 104	0.7%	-8.50 [-9.66, -7.34] -7.42 [-7.87, -6.97]	
Chen 2020 ((B) Chen 2021 (B)	266.7 270.23	17 102.86	161 195	568.9 649.66	47.5 347.17	113 163	0.7%	-9.09 [-9.89, -8.29] -1.54 [-1.77, -1.30]	
Chen 2021 (C) Cheng 2020	404.8 242	99.3 38.7	44 53	488.8 394.8	39.8 80	115 36	0.8% 0.8%	-1.35 [-1.73, -0.97] -2.57 [-3.14, -2.00]	
Chin 2021 Chowdhury 2021	264.37 271	128.66 102	70 193	482.8 642	195.78 341	10 162	0.8%	-1.57 [-2.27, -0.86] -1.53 [-1.77, -1.29]	-
Cortés-Tellés 2020 Covino 2021	641.3 276.3	47.8 29.2	123 162	947.8 329.5	79.8 46.3	77 77	0.8% 0.8%	-4.92 [-5.48, -4.36] -1.49 [-1.79, -1.19]	T -
Cruciata 2022 Cui 2020	271.3 281.3	22.2 21.5	384 637	393.3 501	41.2 49.7	110 199	0.8%	-4.42 [-4.77, -4.07] -7.16 [-7.54, -6.78]	_ T
Dolci 2021 Dong 2020	454 265.8	56.6 107.7	39 65	731 512.1	95.3 169	44 54	0.8%	-3.45 [-4.14, -2.76] -1.76 [-2.19, -1.34]	- J
I-Jawahri 2021 an 2020 arrari 2020	436.6 278.8	511.7 35.2	352	659.2 456.5	1,440.2 85.7	118	0.8%	-0.26 [-0.47, -0.05] -2.44 [-3.07, -1.81]	-]
Ferrari 2020 Fu 2020 Gan 2020	428.1 253.5	167.6 27.7	40	514.9 509.4	202.4 99.6	41 34	0.8%	-0.46 [-0.90, -0.02] -5.32 [-5.97, -4.68]	1
Jan 2020 Giacomelli 2020 Guan 2021	292.8 315 262.5	39.1 26.3 32.5	56 185 1198	492.3 477.8 447.8	102.5 97.3 77.2	39 48 72	0.8% 0.8% 0.8%	-2.74 [-3.32, -2.17] -3.26 [-3.70, -2.82] -5.08 [-5.39, -4.77]	_ _ _
ieber 2022 iernández-Cárdenas 2021	202.5 294 461.3	32.5 24.7 67.3	559 37	314.8 557.5	22.2 109.4	120 30	0.8%	-5.08 [-5.39, -4.77] -0.86 [-1.06, -0.65] -1.07 [-1.59, -0.56]	<u> </u>
iou 2021 iou 2021 iuang 2020 (C)	401.3 381.24 186.5	170.3 14.7	553 536	489.38 375.5	242.88 46	82 140	0.8%	-1.07 [-1.39, -0.36] -0.60 [-0.83, -0.36] -7.66 [-8.11, -7.21]	
lueda-Zavaleta 2021 lias 2021	703.5	57 88.9	232	863 481.9	60.3 124.9	119 36	0.8%	-2.74 [-3.04, -2.44] -0.77 [-1.14, -0.41]	
ncerti 2021 smail 2021	315.8 410.8	30.5	11495 269	412.1	45.4 39.3	2163	0.8%	-2.89 [-2.95, -2.83] -2.75 [-3.08, -2.42]	-
ang 2021 imenez-Solem 2021	530 279.4	61.2 26.6	39 3620	505 305.4	78 30.9	10 324	0.8%	0.38 [-0.32, 1.08] -0.96 [-1.08, -0.85]	·†
imeno 2021 (abootari 2022	570 525.5	82.5 44.3	68 395	727.6 766.5	146.7 76.3	47 165	0.8%	-1.38 [-1.80, -0.97] -4.32 [-4.64, -4.01]	
(aufmann 2021 i 2020 (B)	285.8 283	24.8 29.7	358 87	343.3 541	64.3 87.2	65 15	0.8%	-1.69 [-1.98, -1.40] -6.00 [-7.00, -4.99]	
i 2020 (C) i 2020 (D)	207.3 204.2	18.8 16.2	68 1327	373 474.5	151 40	25 122	0.8% 0.8%	-2.07 [-2.63, -1.52] -13.96 [-14.51, -13.42]	. –
i 2021 i 2021 (B)	252.2 248.7	22.9 43	390 58	484.9 423.9	80.5 92.7	34 39	0.8%	-7.38 [-7.99, -6.77] -2.58 [-3.13, -2.03]	
iu 2020 (8) .ore 2021 .u 2021	145.3 350.9 230.43	8.3 38.6 105	194 89 140	208.2 484.3	10 55.7 199.05	31 22 99	0.7% 0.8% 0.8%	-7.33 [-8.11, -6.55] -3.12 [-3.75, -2.50] -1.72 [-2.02, -1.42]	-
u 2021 Aachado 2021 Aahendra 2021	230.43 325 788.1	105 10.67 681.62	140 126 254	491.21 384 866.39	199.05 22.72 558.52	99 71 306	0.8% 0.8% 0.8%	-1.72 [-2.02, -1.42] -3.66 [-4.12, -3.19] -0.13 [-0.29, 0.04]	-
Manendra 2021 Marimuthu 2021 Masetti 2020	788.1 378.9 303	29.3 113	254 186 196	584.4 395	558.52 124 246	306 35 33	0.8%	-0.13 [-0.29, 0.04] -3.67 [-4.17, -3.17] -0.66 [-1.03, -0.28]	
Aikami 2020 Aontrucchio 2021	396.3 749	32.8 196	2014	540.5 923	62.7 295	806 31	0.8%	-3.31 [-3.43, -3.20] -0.67 [-1.21, -0.14]	·
Aorell-Garcia 2021 Auhammad 2021	308 352	143 177	179 155	418 561	186 330	20 45	0.8%	-0.74 [-1.21, -0.27] -0.94 [-1.29, -0.60]	
laqvi 2021 licholson 2021	317.8 384.9	29.6 11.45	221 829	669.9 503.4	78.4 80.72	27 211	0.7%	-9.27 [-10.19, -8.36] -3.14 [-3.34, -2.94]	÷ .
liu 2021 Dba 2021	203.9 322.6	10.3 73.1	119 34	406.4 397.5	104.6 40.7	31 140	0.8% 0.8%	-4.20 [-4.82, -3.58] -1.53 [-1.94, -1.13]	
Dbeidat 2021 Dmore 2021	234.55 464.6	34.22 51.1	99 152	383.56 675	54.11 56.3	64 83	0.8% 0.8%	-3.44 [-3.93, -2.95] -3.96 [-4.41, -3.51]	-
an 2020 Paranjpe 2020	281.8 353.5	73 29.3	35 419	516.8 540.3	39.8 64.2	89 134	0.8%	-4.56 [-5.25, -3.86] -4.60 [-4.93, -4.26]	-
Peiro 2021 Ponsford 2022	274.5 379.8	23.7 46.6	159 278	349 389.7	58.9 35.1	37 113	0.8%	-2.24 [-2.66, -1.81] -0.23 [-0.45, -0.01]	
Portacci 2021 Iya 2021	65.6 253.7	12.8	101 205	439 403.5	70.4 68.7	39 34	0.7%	-9.64 [-10.85, -8.44] -4.45 [-4.99, -3.90]	-
Pérez 2021 Pérez-García 2021	355 261 244	160 20	79 988	662 362.8	504 35.8	17 212	0.8%	-1.20 [-1.75, -0.65] -4.32 [-4.55, -4.09]	
)in 2021)uiroga 2021 Jamírez-Plascencia 2022	244 203.3 374.4	18 29.2 129	239 12 13	457.3 412.3	49.9 128.5 122	23 4 66	0.7%	-9.44 [-10.36, -8.52] -3.05 [-4.71, -1.39]	
tamirez-Plascencia 2022 tashedi 2021 tastad 2020	374.4 673.4 451.5	129 291.56 32.7	403 2656	514 877.55 579.3	466.33 52.5	101 301	0.8%	-1.12 [-1.74, -0.50] -0.61 [-0.83, -0.39] -3.63 [-3.78, -3.48]	
todriguez-Gonzalez 2021 Rozenbaum 2021	451.5 259 291.5	19.7 23.8	2050 940 648	328 409.8	34	268	0.8%	-3.03 [-3.78, -3.48] -2.92 [-3.10, -2.74] -4.50 [-4.80, -4.20]	- *
ialacup 2021 ierin 2020	372.5 261.3	46.3	190 1457	520 443.9	71.6	52 60	0.8%	-2.79 [-3.19, -2.39] -1.34 [-1.61, -1.08]	
iheng 2021 ingh 2021	245.4 414.9	65.3 193.96	144	571.5 467.91	73 265.69	88 73	0.8%	-4.76 [-5.27, -4.25] -0.25 [-0.51, 0.00]	
ioltani 2022 iong 2021	770.7 416.1	494.1 36.1	52 1365	1,008.2 518.8	612.2 46.6	40 470	0.8% 0.8%	-0.43 [-0.85, -0.01] -2.63 [-2.76, -2.49]	
urve 2021 weeney 2021	434.3 459.3	42.4 63.5	18 91	596.4 531.8	50.4 43.5	26 90	0.7% 0.8%	-3.36 [-4.31, -2.41] -1.33 [-1.65, -1.00]	
filch 2021 Tomacruz 2021	303 282	11 148	32 51	523 396	27 274	18 17	0.5% 0.8%	-11.81 [-14.29, -9.33] -0.60 [-1.16, -0.05]	-
Jmeh 2021 Jan Halem 2020	339.05 307.5	443.13 28.3	626 238	581.04 383.8	626.22 32.5	238 81	0.8% 0.8%	-0.48 [-0.63, -0.33] -2.59 [-2.91, -2.26]	- 1
/iana-Llamas 2021 /idal-Cevallos 2021	345 387.5	29.3 42.9	481 298	435.8 566.8	44.2 59.5	128 79	0.8% 0.8%	-2.75 [-3.00, -2.50] -3.82 [-4.19, -3.45]	-
Vang 2020 (C) Vang 2020 (E)	280.9 312.95	22.6 12.54	101 45	396.5 381.94	75.6 43.23	15 16	0.8%	-3.39 [-4.09, -2.69] -2.80 [-3.57, -2.03]	-
Wang 2021 (C) Wu 2020	179.5 352.1	11.7 35.4	100 40	325.43 471.9	80.3 62.8	56 44	0.8%	-2.97 [-3.44, -2.50] -2.30 [-2.86, -1.74]	
Gong 2022 (ang 2021	230.8 286.3	15.3 26.8	182 145	349.8 488.8	31.8 74.3	105	0.8%	-5.22 [-5.71, -4.72] -4.42 [-4.95, -3.89]	-
(ang 2021 (B) (ousaf 2022	169.1 498	8.8 348	1437	218.9	17.9 375	625 135	0.8%	-4.05 [-4.21, -3.90] -0.57 [-0.78, -0.36]	-
Cemlin 2022 Chang 2021 (B)	601 208.5	144.3 15.5	28 410	783.6	93.7 103.9	54 22	0.8%	-1.60 [-2.12, -1.08] -7.21 [-7.85, -6.56]	
theng 2020 thou 2020	165.7 261 262	41.4	52 137	197.2 518.5	50.9 88.3 266.8	28 54	0.8% 0.8% 0.8%	-0.69 [-1.17, -0.22] -5.25 [-5.87, -4.64]	-]
(hou 2020 (C) (hu 2021 (inellu 2020	262 244.49 277.8	249.8 93.19 25.8	67 68 77	453.4 584.47 387	266.8 460.36 57	51 15 28	0.8%	-0.74 [-1.12, -0.36] -1.61 [-2.22, -1.00] -2.96 [-3.55, -2.36]	
Cinellu 2020 Zou 2020	277.8	25.8 29	107	387 430.5	57 115.3	28 14	0.8%	-2.96 [-3.55, -2.36] -2.98 [-3.65, -2.30]	
			53850			13475	100.0%	-3.10 [-3.40, -2.79]	•
Fotal (95% CI) leterogeneity: Tau ² = 3.08;	Chi ² - 17			(P < 0.00	001)-12 - 4	996			-10 -5 0 5 10

Figure 2. Forest plot of lactate dehydrogenase levels among survivors vs. non-survivors COVID-19 groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizonal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

Study or Subgroup		oderate	Tetal	Maar	Severe	Tetal		Std. Mean Difference	Std. Mean Difference
tudy or Subgroup	Mean 268	SD 95.57	Total 380	Mean 344.9	SD 180.6	Total 95	Weight 1.0%	IV, Random, 95% CI -0.65 [-0.88, -0.42]	IV, Random, 95% CI
Akdogan 2021	191.36	37.48	118	241.53	82.38	57	1.0%	-0.89 [-1.22, -0.56]	-
Al Harbi 2022 Alsharidah 2021	259.76 429.5	120.62 39.3	8669 155	310.1 504.3	182.5 60.5	721	1.0%	-0.40 [-0.47, -0.32] -1.57 [-1.88, -1.26]	- '
Az 2021	218.3	13.7	221	284.8	37.5	320	1.0%	-2.20 [-2.42, -1.99]	-
Azizmohammadi 2021	210.8	16.8	176	307.3	31.5	63	1.0%	-4.45 [-4.94, -3.95]	-
Bats 2021 Bennouar 2020	291.3 330	22.5 132	106 187	408 623	30.7 422	97 143	1.0%	-4.35 [-4.86, -3.84] -0.99 [-1.22, -0.76]	-
Betti 2021	526.5	44.3	89	766	66.8	82	1.0%	-4.24 [-4.79, -3.70]	-
Cai 2021	197.3	12.2	307	273.3	24.8	125	1.0%	-4.51 [-4.87, -4.14]	-
Cen 2020 Chen 2020 (C)	305.9 192.5	33.4 23.1	409 69	318.9 333.2	106.9 141.7	265 25	1.0%	-0.18 [-0.34, -0.03] -1.86 [-2.39, -1.33]	- 1
Chen 2021	235	23.1	33	465.3	97.3	26	0.9%	-3.41 [-4.22, -2.59]	
Chen 2021 (C)	180.1	11.3	158	255.3	48.3	43	1.0%	-3.08 [-3.53, -2.62]	-
Chen 2021 (D)	255.8	27	63	328.5	90	4	0.8%	-2.20 [-3.28, -1.12]	
Chen 2021 (E) Deng 2021	210 185.3	22 13.2	70 149	324 289.9	67.6 49	43 17	1.0% 0.9%	-2.51 [-3.02, -2.01] -5.26 [-6.02, -4.50]	
Dubey 2021		303.21	25	913.55	443.42	50	1.0%	-0.70 [-1.19, -0.21]	-
Emsen 2021	231.2	71.2	26	316	110.8	15	0.9%	-0.95 [-1.62, -0.28]	
Feng 2020 Feng 2020 (B)	244.5 186.5	20.3 13.7	352 495	354.7 306	68.7 40.9	124 69	1.0%	-2.81 [-3.09, -2.54] -6.23 [-6.67, -5.78]	
Fukuda 2021	195.8	27.1	50	470.1	104.8	22	0.9%	-4.40 [-5.29, -3.50]	
Gaber 2022	593.9	100	18	737.3	456.5	48	1.0%	-0.36 [-0.90, 0.19]	-
Gharib 2021 Gogu 2021	354	135.1 290.39	100	726 677.92	36.88 775.23	50 26	1.0%	-3.29 [-3.80, -2.78] -0.69 [-1.15, -0.23]	
Gong 2020	179.8	11.8	161	300.5	58.9	28	0.9%	-4.83 [-5.46, -4.19]	(<u></u>)(
Guervilly 2021	284.3	19.5	73	376.8	52.3	38	1.0%	-2.67 [-3.21, -2.14]	-
Guner 2020	290.5	83.3	172	415.3	213.4	50	1.0%	-1.00 [-1.33, -0.67]	
Gómez 2021 Hachim 2021	283.4 268.7	20.2 287.6	354 189	372.1 482.2	37.9 310.6	158 352	1.0%	-3.29 [-3.57, -3.01] -0.70 [-0.89, -0.52]	
Han 2020	214.5	28.3	59	416.5	62.9	48	0.9%	-4.26 [-4.96, -3.57]	-
He 2020	229.7	16	530	349.8	38.8	501	1.0%	-4.09 [-4.30, -3.87]	-
Hosseinzadeh 2022 Hu 2020		191.51 186.24	599 130	666.98 647.35	290.98 424.26	132 52	1.0%	-0.94 [-1.14, -0.75] -1.18 [-1.52, -0.83]	-
Hu 2020 Huang 2020 (B)	245.7	30.6	179	405.6	424.26	23	1.0%	-3.37 [-3.92, -2.83]	-
Huang 2021	269.8	24.2	142	406	34	86	1.0%	-4.80 [-5.32, -4.28]	-
telman 2020 ang 2020	324.4 527.7	42.4 171.9	136 87	539.3 996.7	78.2 497.3	26 23	0.9%	-4.30 [-4.93, -3.67] -1.71 [-2.23, -1.20]	
ang 2020 I 2021	214.6	47.1	18	292.1	497.3	23	1.0%	-1.36 [-2.25, -0.47]	
ia 2021	178.8	5.8	2071	185.5	8.1	2071	1.0%	-0.95 [-1.02, -0.89]	
in 2022	202.94	63.87	114 89	299.35	68.82	26	1.0%	-1.48 [-1.94, -1.02]	
Kantri 2021 Khamis 2021	211.5 403	14.7 302.5	163	328 534.1	42.1 463.8	45 839	0.9%	-4.27 [-4.90, -3.64] -0.30 [-0.46, -0.13]	
Kojima 2021	293.3	25.2	385	449.3	49.4	65	1.0%	-5.21 [-5.64, -4.78]	-
Kurahara 2021	304.7	60.3	332	430.6	55	63	1.0%	-2.11 [-2.42, -1.80]	-
Lee 2020 Liu 2020	447.55 221.5	124.11 71.2	557 27	695.19 462.4	455.13 190.6	137 13	1.0%	-1.07 [-1.27, -0.88] -1.93 [-2.73, -1.13]	
Liu 2021	248.3	35.5	43	403.7	31.3	79	0.9%	-4.70 [-5.41, -4.00]	
Liu 2021 (B)	214.5	125	202	320.9	22.1	92	1.0%	-1.02 [-1.28, -0.76]	-
Liu 2021 (C)	242.5	16.7	329	342	75.1	56	1.0%	-3.07 [-3.42, -2.71]	-
Lu 2020 Ma 2020	231.1 388.2	13.9 35.2	243 64	369.5 496.5	46.8 67	22 20	0.9%	-7.35 [-8.12, -6.58] -2.40 [-3.03, -1.78]	
Maksane 2021	923	281	50	1,427	693.7	50	1.0%	-0.95 [-1.36, -0.53]	-
Mao 2020	335.1	150.9	126	371.6	146.3	88	1.0%	-0.24 [-0.52, 0.03]	-
Mutashar 2021 Mutinelli-Szymanski 2021	267.53 246	152.68 54	45 34	444.36 291	200.53 72	45 28	1.0%	-0.98 [-1.42, -0.55] -0.71 [-1.22, -0.19]	-
Naqvi 2021	313.6	73.1	201	432.6	94.3	47	1.0%	-1.53 [-1.88, -1.19]	-
Nizami 2021	256.4	127.53	75	542.2	249.6	34	1.0%	-1.63 [-2.09, -1.16]	-
Okuma 2021 Okuyan 2021	292 248.7	134.2 27.6	60 70	392.86 316.3	243.25 67.6	40 38	1.0%	-0.54 [-0.95, -0.13] -1.47 [-1.91, -1.03]	
Dtoshi 2021	234.3	76.9	254	303.1	123.5	46	1.0%	-0.80 [-1.12, -0.48]	-
Popov 2020	453.2	201.2	95	774	371.6	43	1.0%	-1.20 [-1.59, -0.81]	-
Rashedi 2021 Rastogi 2021		329.96 201.65	132 6484	745.28 420.7	340.94 243.2	372 38876	1.0%	-0.36 [-0.56, -0.17] -0.28 [-0.31, -0.26]	-
Ren 2020	191.8	13.8	89	420.7	129.3	40	1.0%	-3.39 [-3.96, -2.83]	-
Rosenberger 2021	253.1	30.6	201	409	76.2	59	1.0%	-3.45 [-3.87, -3.03]	-
Sana 2022 Shabbir 2021		118.85	81	395.7	116.17	69	1.0%	-0.38 [-0.70, -0.05]	_ ~
Shabbir 2021 Shang 2020	426.88 213.5	251.9 13.8	318 304	928 302.8	437.4 40.5	177 139	1.0%	-1.51 [-1.72, -1.31] -3.51 [-3.82, -3.21]	-
Sheng 2021	213.5	15.7	102	491.2	137.7	130	1.0%	-2.67 [-3.03, -2.31]	-
5hi 2021	185.6	18.1	88	243.5	27.7	46	1.0%	-2.63 [-3.11, -2.16]	
5hi 2021 (B) 5un 2020	229 220.1	10.3 67.9	151 44	357 325.7	47.4	45 19	1.0% 1.0%	-5.24 [-5.86, -4.62] -1.13 [-1.71, -0.56]	
Tahtasakal 2020	380	135.3	398	728.5	366.7	136	1.0%	-1.59 [-1.81, -1.38]	-
Taj 2021	254.8	155.9	73	497.8	476.2	28	1.0%	-0.86 [-1.31, -0.40]	-
Tang 2021 Teima 2022	160.5 239.2487	10.7	195 538	211.2 363.4	28.3 54.6	33	1.0%	-3.47 [-3.96, -2.98] -2.04 [-2.21, -1.87]	
Turan 2021	246.8	31.3	618	360.4	85.3	242	1.0%	-2.17 [-2.35, -1.98]	-
Vaira 2021	296.5	29.7	26	304.8	34.1	17	1.0%	-0.26 [-0.87, 0.36]	+
Wan 2020 Wang 2020 (B)	215.6 179.9	13.3 12.3	95 37	320 264.1	44.6 44.9	40 24	1.0%	-3.90 [-4.50, -3.30] -2.80 [-3.53, -2.08]	
Wang 2020 (D)	181	11.7	230	281.3	66.7	45	1.0%	-3.47 [-3.90, -3.04]	-
Wang 2020 (F)	284.9	40.5	46	367.8	78.2	39	1.0%	-1.35 [-1.83, -0.88]	-
Wang 2020 (G) Wang 2021	305.6 182.5	103.7 12	30 236	474.8 305.8	195.9 52	35 36	1.0%	-1.04 [-1.57, -0.52] -5.64 [-6.23, -5.04]	
Wang 2021 Wang 2021 (B)	207.3	13.1	236	261.5	46.8	36	1.0%	-5.64 [-6.23, -5.04] -1.90 [-2.37, -1.43]	-
Wu 2021	206	11.5	113	295.3	49.1	45	1.0%	-3.19 [-3.69, -2.70]	-
Kie 2020	169.3	20.6	38	216.9	36.1	24	1.0%	-1.70 [-2.30, -1.11]	
Ku 2020 Kue 2020	286.5 258.1	34.6 34.9	44 56	422 358.4	72.2 45.1	25 58	0.9%	-2.61 [-3.27, -1.94] -2.47 [-2.96, -1.97]	
ramamoto 2021	205.7	40.4	144	476.3	119.2	9	0.9%	-5.62 [-6.54, -4.69]	
Yan 2021	213	72.9	482	343.4	152.6	128	1.0%	-1.37 [-1.58, -1.16]	-
rang 2020 re 2021	257.5 281.17	21 65.74	103 152	370 314.75	64.1 85.28	33 44	1.0%	-3.08 [-3.62, -2.54] -0.47 [-0.81, -0.14]	
Zhang 2020	281.17	20.5	166	431.5	85.28	55	1.0%	-4.55 [-5.08, -4.03]	-
Zhang 2020 (B)	207.5	16.9	710	249.7	46.3	78	1.0%	-1.95 [-2.20, -1.70]	-
Zhang 2020 (B)	240.1	12.4	93	367.4	100.3	224	1.0%	-1.50 [-1.77, -1.23]	-
Zhang 2021 Zhang 2021 (C)	441.3 196.3	26.8 11.6	49 72	746.5 379.5	112 73.9	16 6	0.8%	-5.07 [-6.13, -4.01] -8.24 [-9.80, -6.67]	
Zhao 2020 Zhao 2020	196.3	23.1	19	379.5	81.2	31	0.7%	-2.15 [-2.87, -1.43]	
Zhao 2021	182.8	65.9	29	272.8	159.7	36	1.0%	-0.70 [-1.21, -0.20]	-
Zhu 2021	207.98	80.97			267.9143	58	1.0%	-0.51 [-0.98, -0.03]	_ ~
Zou 2020	246.5	33	69	413.4	90.8	52	1.0%	-2.57 [-3.06, -2.08]	-
Total (95% CI)			33916		10000 miles		100.0%	-2.38 [-2.61, -2.14]	•
Heterogeneity: Tau ² = 1.43	; Chi ² = 103	47.78, df	= 102 (P < 0.000	01); $I^2 = 99$	%			-10 -5 0 5
Test for overall effect: Z = 1									

Figure 3. Forest plot of lactate dehydrogenase levels among moderate vs. severe COVID-19 groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizonal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

		Severe			Critical		3	Std. Mean Difference		S	td. Mean Difference	2	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		1	V, Random, 95% CI		
Az 2021	276.5	20.7	290	365.3	61.5	30	6.8%	-3.27 [-3.72, -2.82]			-		
Cen 2020	266.5	20.3	200	480.1	104.4	65	6.8%	-3.91 [-4.35, -3.48]		-	-		
eng 2020	310.8	49.9	54	388.5	62	70	6.9%	-1.35 [-1.75, -0.96]					
achim 2021	418.1	186.9	203	569.5	409.7	149	7.1%	-0.50 [-0.72, -0.29]			-		
tikhar 2020	643.06	391.48	79	724.25	420.43	62	7.0%	-0.20 [-0.53, 0.13]			-		
lizami 2021	476.7	157.9	18	615.9	312.9	16	6.4%	-0.56 [-1.25, 0.13]					
amirez-Hinojosa 2021	467.68	273.48	37	515.15	267.72	21	6.7%	-0.17 [-0.71, 0.36]					
astogi 2021	365.77	196.79	25849	529.81	286.05	13027	7.1%	-0.71 [-0.73, -0.69]					
un 2020	279.7	84.36	10	376.89	161.55	9	5.9%	-0.73 [-1.67, 0.20]					
Faj 2021	463.5	487.5	20	583.5	466.8	8	6.2%	-0.24 [-1.06, 0.58]					
(an 2021	329.9	146	95	382.2	166.5	33	6.9%	-0.34 [-0.74, 0.06]			-		
Zeng 2020 (B)	313.8	23.8	167	524.3	68.8	57	6.6%	-5.22 [-5.79, -4.64]			-		
(hang 2020 (B)	231.9	32.4	661	313.4	28.9	17	6.7%	-2.52 [-3.02, -2.02]					
Zhao 2020	293.3	50.5	18	405.5	70.4	13	6.1%	-1.84 [-2.70, -0.97]					
Zhu 2021	247.5	85.09	26	389	341.87	32	6.7%	-0.54 [-1.06, -0.01]					
Fotal (95% CI)			27727			13609	100.0%	-1.48 [-2.04, -0.92]			•		
Heterogeneity: $Tau^2 = 1.1$	5: Chi ² =	651.54.	df = 14	(P < 0.0	0001); I ²	= 98%			-			+	
est for overall effect: Z =									-10	-5	0 Severe Critical	5	1

Figure 4. Forest plot of lactate dehydrogenase levels among severe vs. critical COVID-19 groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizonal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

	N	on-ICU			ICU			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Abbasi 2021	363	33	374	695	102.2	47	2.8%	-7.20 [-7.78, -6.63]	-
Akman 2021	331.3	31.7	342	397.5	95.6	58	2.9%	-1.42 [-1.71, -1.12]	-
Alhumaid 2021	14.2	18.7	809	22.6	24.2	205	2.9%	-0.42 [-0.58, -0.27]	*
Antinori 2020	406.3	35.5	17	558.8	65.5	18	2.7%	-2.81 [-3.77, -1.84]	
Bastug 2020	279.5	65	145	358	125.9	46	2.9%	-0.93 [-1.28, -0.59]	-
Burian 2020	394.1	529.3	35	487.6	277.7	24	2.8%	-0.21 [-0.73, 0.31]	-+
Carlino 2020	189.94	51.89	18	748.7	543.8	10	2.8%	-1.68 [-2.59, -0.77]	
Dheir 2021	273	51.9	47	461.5	62.9	40	2.8%	-3.27 [-3.92, -2.61]	-
El Aidaoui 2020	211.5	14.7	89	328.3	36.3	45	2.8%	-4.81 [-5.49, -4.12]	-
Ena 2022	359.5	197.1	14868	501.5	365	1420	2.9%	-0.65 [-0.71, -0.60]	
Ferguson 2020	345	55.4	51	420.3	64.4	21	2.8%	-1.28 [-1.83, -0.73]	
Garzon-Chavez 2021	443.8	304.9	47	502.5	227.2	17	2.8%	-0.20 [-0.76, 0.35]	-+
Güngörer 2021	220.1	14.8	847	330.3	31.6	158	2.9%	-5.96 [-6.27, -5.65]	-
Hachim 2021	355.9	248.5	388	553.4	410.7	153	2.9%	-0.65 [-0.84, -0.46]	
Hong 2020	555.5	184	85	1,272.6	542.1	13	2.8%	-2.76 [-3.47, -2.06]	-
Huang 2020	288	35.8	28	425.3	73.6	13	2.8%	-2.66 [-3.56, -1.77]	
imenez-Solem 2021	268.6	22.8	1178	440.5	32.7	181	2.9%	-7.06 [-7.37, -6.75]	+
Khamis 2020	288	35.8	39	4,745	79.7	24	0.2%	-77.90 [-91.95, -63.84]	•
Lacap 2022	320.3	32.2	172	518.8	44.5	141	2.8%	-5.18 [-5.64, -4.71]	-
Lei 2020	209.3	11.3	19	213.5	12.1	15	2.8%	-0.35 [-1.03, 0.33]	
Li 2020	338.5	29.3	837	449.3	43.5		2.9%	-3.32 [-3.52, -3.13]	-
Lore 2021	334.5	35.7	75	512.5	88.3		2.8%	-3.05 [-3.62, -2.48]	
Machiraju 2021	371.3	45.6	63	498.8	52.8		2.8%	-2.62 [-3.16, -2.07]	
Mazzitelli 2021	334.8	49.6	48	640			2.8%	-3.51 [-4.32, -2.70]	
Morell-Garcia 2021	303	147	175	413	225		2.9%	-0.69 [-1.13, -0.26]	-
Ortiz-Brizuela 2020	275.9	22.2	111	469.5	72.7		2.8%	-5.03 [-5.75, -4.31]	
Pore 2021	629.8	68.2	360	10,033	72.2			-134.57 [-142.26, -126.87]	•
Samuel 2020	391	235	593	677	425		2.9%	-0.91 [-1.06, -0.77]	
Statsenko 2021		80.08	488		267.95	72	2.9%	-2.17 [-2.45, -1.89]	-
Velazquez 2021	516.3	33.2	2069	703.3	66.5		2.9%	-5.04 [-5.25, -4.83]	-
Veyrenche 2022	318.9	63.3	24	399.5	54.3	58	2.8%	-1.40 [-1.92, -0.88]	
Wang 2020	257.6	15.7	14	572.3	126.7	14	2.7%	-3.38 [-4.59, -2.17]	
Weikert 2021		148.5	98	406.8	144	22	2.8%	-0.90 [-1.38, -0.43]	-
Yang 2020 (B)	222.8	15.2	171	353.3	60.1	29	2.8%	-4.88 [-5.51, -4.26]	
Zangeneh 2021		110.3	54	639.5	275.7	52	2.9%	-1.30 [-1.72, -0.88]	-
Zeng 2020	175.1	11.9	406	277.5	45	55	2.9%	-5.36 [-5.81, -4.92]	
Zhou 2020 (B)	161.9	10.7	156	231.9	37.4	45	2.8%	-3.49 [-3.97, -3.02]	-
Total (95% CI)			25340			4135	100.0%	-3.78 [-4.48, -3.08]	•
Heterogeneity: $Tau^2 =$	4.43: Chi ²	2 = 7448		= 36 (P <	0.00001				
Test for overall effect:					0.0000				′−10 −′5 o 5 : Non−ICU ICU

Figure 5. Forest plot of lactate dehydrogenase levels among non-intensive care unit (ICU) vs. ICU COVID-19 groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizonal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

Discussion

Lactate dehydrogenase plays a vital role in biochemical processes; it takes part in the interconversion of pyruvate, the final product of glycolysis to lactate without sufficient oxygen supply [29, 30]. Elevated LDH activity indicates a lack or deficiency of oxygen in biochemical processes, tissue oxygen deficiency, or multi-organ failure [31]. Increased LDH activity may be indicative of cellular damage, hypoxia or death. It should also be considered that elevated LDH activity may be associated with other conditions, including those associated with cardiac ischemia and pathological processes involving the lungs, renal cortex, liver, muscle, and red blood cells. Elevated LDH activity is also found in various malignant neoplasms.

Because of the clinical benefit of early identification of patients at risk for severe COVID-19, identification of markers of severe disease is of practical importance [32–33]. Several factors have been investigated to predict COVID-19 severity, including C-reactive protein, alanine aminotransferase, D-dimers, ferritin, Il-6, creatine kinase, aspartate aminotransferase, among others [34–36]. Recently, several studies have been undertaken to assess the utility of various markers indicative of severe COVID-19. One of these markers is elevated LDH activity. Several studies have shown elevated LDH activity in severe COVID-19 respiratory failure, COVID-19-related lung injury, and COVID-19-related multi-organ failure.

A problem that has been highlighted in studies investigating the association between COVID-19 severity and elevated LDH activity has been the small sample size and often retrospective nature of the analyses [22]. This meta-analysis addresses these methodological issues by including many new and extensive studies.

Herein, the usability of blood LDH determination in patients with COVID-19 was analyzed. 264 studies were included in a meta-analysis and changes in blood LDH concentrations were observed in patients with COVID-19 disease (**Suppl. material:** [S1-S264]). The clinical utility of blood LDH assay was then evaluated to differentiate the severity of SARS-CoV-2 infection.

This meta-analysis highlights the potential use of LDH as a biomarker for early determination of COVID-19 severity. LDH is released from cells following cell injury and death [37]. Often, this process is caused by hypoxia due to the disproportionate transfer of oxygen to the cells, the cause of which is, among others, SARS-CoV-2 infection. The vast majority of studies evaluated in the meta-analysis presented a significant difference between LDH levels in patients with severe COVID-19 compared to patients who did not meet the criteria for severe disease. A study by Henry et al. [38] demonstrated a 6-fold increased likelihood of severe COVID-19 in patients with elevated LDH levels.

In the analyzed studies, elevated blood LDH levels were observed in a group of patients with severe COVID-19. LDH was a negative predictor of COVID-19 complications and death from the disease. The present study estimates that elevated blood LDH levels may be a biomarker that increases the likelihood of a severe course of COVID-19. These meta-analysis results indicate a strong relationship between elevated LDH activity with COVID-19 severity and increased patient mortality.

Determining the significance of LDH activity in the severity of COVID-19 is of clinical importance. However, given that many other biochemical parameters have been shown to be associated with mortality and severity of COVID-19, a multivariate analysis including a variety of biochemical parameters should be considered, which may further correlate with clinical course.

Limitations of the present analysis are due to the nature of the studies analyzed and the associated biases, mainly related to the retrospective nature of the analyses. The next step is a multivariate evaluation considering several biochemical parameters rather than a single biochemical indicator.

Conclusions

This meta-analysis showed that elevated LDH was associated with a poor outcome in COVID-19.

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