Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Cardiology 79 (2022) 501–508

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Impact of serum lactate dehydrogenase on the short-term prognosis of COVID-19 with pre-existing cardiovascular diseases

Akiko Masumoto (MD)[a,b], Takeshi Kitai (MD, Ph.D)[a,c,*], Shingo Matsumoto (MD)[d], Shunsuke Kuroda (MD)[e], Shun Kohsaka (MD, PhD)[f], Ryo Tachikawa (MD, PhD)[g], Ryutaro Seo (MD)[h], Asako Doi (MD)[i], Keisuke Tomii (MD, Ph.D)[g], Taishi Yonetsu (MD)[j], Sho Torii (MD, Ph.D)[k], Issei Komuro (MD, Ph.D, FJCC)[l], Ken-ichi Hirata (MD, Ph.D, FJCC)[m], Koichi Node (MD, Ph.D, FJCC)[n], Yuya Matsue (MD, Ph.D)[o,p], Yutaka Furukawa (MD, Ph.D, FJCC)[a]

[a] Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan
[b] Division of Cardiovascular Medicine, Hyogo Brain and Heart Center, Himeji, Japan
[c] Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Medicine Center, 6-1 Kishibe-shinmachi, Osaka, Japan
[d] Department of Cardiovascular Medicine, Department of Internal Medicine, Toho University Faculty of Medicine, Tokyo, Japan
[e] Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH, United States
[f] Department of Cardiology, Keio University School of Medicine, Tokyo, Japan
[g] Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan
[h] Department of Intensive Care, Kobe City Medical Center General Hospital, Kobe, Japan
[i] Department of Infectious Diseases, Kobe City Medical Center General Hospital, Kobe, Japan
[j] Department of Interventional Cardiology, Tokyo Medical and Dental University, Tokyo, Japan
[k] Department of Cardiology, Tokai University School of Medicine, Isehara, Japan
[l] Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[m] Department of Internal Medicine, Division of Cardiovascular Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
[n] Department of Cardiovascular Medicine, Saga University, Saga, Japan
[o] Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan
[p] Cardiovascular Respiratory Sleep Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 18 September 2021
Revised 28 November 2021
Accepted 19 December 2021
Available online 28 December 2021

Keywords:
Coronavirus disease 2019
Serum lactate dehydrogenase
Cardiovascular disease
Severe acute respiratory syndrome coronavirus 2

ABSTRACT

Background: Patients with coronavirus disease 2019 (COVID-19) and underlying cardiovascular comorbidities have poor prognoses. Our aim was to identify the impact of serum lactate dehydrogenase (LDH), which is associated with mortality in acute respiratory distress syndrome, on the prognoses of patients with COVID-19 and underlying cardiovascular comorbidities.

Methods: Among 1518 patients hospitalized with COVID-19 enrolled in the CLAVIS-COVID (Clinical Outcomes of COVID-19 Infection in Hospitalized Patients with Cardiovascular Diseases and/or Risk Factors study), 515 patients with cardiovascular comorbidities were analyzed. Patients were divided into tertiles based on LDH levels at admission [tertile 1 (T1), <235 U/L; tertile 2 (T2), 235–355 U/L; and tertile 3 (T3); ≥356 U/L]. We investigated the impact of LDH levels on the in-hospital mortality.

Results: The mean age was 70.4 ± 30.0 years, and 65.3% were male. There were significantly more in-hospital deaths in T3 than in T1 and T2 [$n = 50$ (29.2%) vs. $n = 15$ (8.7%), and $n = 24$ (14.0%), respectively; $p < 0.001$]. Multivariable analysis adjusted for age, comorbidities, vital signs, and laboratory data including D-dimer and high-sensitivity troponin showed T3 was associated with an increased risk of in-hospital mortality (adjusted hazard ratio, 3.04; 95% confidence interval, 1.50–6.13; $p = 0.002$).

Conclusions: High serum LDH levels at the time of admission are associated with an increased risk of in-hospital death in patients with COVID-19 and known cardiovascular disease and may aid in triage of these patients.

ARDS, acute respiratory distress syndrome; CK, creatinine kinase; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; qSOFA, quick sequential organ failure assessment; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

* Corresponding author at: Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan.
E-mail address: t-kitai@kcho.jp (T. Kitai).

https://doi.org/10.1016/j.jjcc.2021.12.014
0914-5087/

Introduction

Severe acute respiratory distress syndrome (ARDS) caused by the coronavirus disease 2019 (COVID-19) has led to serious morbidity in hundreds of millions of individuals worldwide. Recent reports have identified that patients with COVID-19 and underlying cardiovascular morbidities face increased mortality compared with those without cardiovascular disease [1,2].

Lactate dehydrogenase (LDH) could be a useful marker of systemic inflammation, as it is a cytoplasmic enzyme that is widely expressed in tissues. It has been reported that serum LDH concentrations increase during the acute lung damage that occurs in interstitial lung disease and severe respiratory failure [3]. LDH level is also one of the biomarkers most strongly associated with ARDS mortality [4,5]. Of the various biomarkers that have been investigated for the prediction of the prognoses of patients with COVID-19, elevated LDH level is reported to be associated with increased mortality [6–10]. However, no previous study has focused on the significance of high LDH levels in patients with COVID-19 and underlying cardiovascular disease.

Thus, our aim of this study was to investigate the impact of LDH levels measured at the time of hospital admission on the prognoses of patients with COVID-19 and pre-existing cardiovascular comorbidities.

Methods

Patient characteristics

This study was a *post-hoc* analysis of the CLAVIS-COVID (Clinical Outcomes of COVID-19 Infection in Hospitalized Patients with Cardiovascular Diseases and/or Risk Factors) study. The design and primary results of the study have been reported elsewhere [11] with a unique description of the data of patients with COVID-19 and pre-existing or developing cardiovascular diseases or coronary risk factors. Briefly, the CLAVIS-COVID study was a multicenter retrospective observational study that included 1518 patients with COVID-19 who were hospitalized in participating institutions in Japan between January 1, 2020, and May 31, 2020. Patients under 20 years of age were excluded from the CLAVIS-COVID. For the present study, 938 patients without any pre-existing cardiovascular diseases and 65 patients without data on baseline serum LDH level at the time of hospital admission were excluded. Thus, a total of 515 patients with pre-existing cardiovascular disease on admission for COVID-19 were included. The patients were divided into three tertiles based on their serum LDH levels at the time of admission as follows: tertile 1 (T1, LDH $<$235 U/L), tertile 2 (T2, LDH, 235–355 U/L), and tertile 3 (T3, LDH $\geq$ 356 U/L).

The study protocol, including the use of an opt-out consent method, was approved by the local ethics committees of all participating institutions. This clinical study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (ID: UMIN000040598) before the first patient was enrolled, in accordance with the International Committee of Medical Journal Editors.

Diagnosis of COVID-19 and data collection

Patients were diagnosed with COVID-19 when a polymerase chain reaction detected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in their test samples [12]. The decision to hospitalize a patient was made by a physician based on the patient's clinical condition, age, and comorbidities. Upon hospital admission, baseline data on medical history, medication, vital signs, symptoms, and laboratory tests were obtained.

For the purpose of this study, cardiovascular disease was defined as a history or new diagnosis of at least one of the following diseases/conditions within 30 days of COVID-19 infection: hypertension, coronary artery disease, old myocardial infarction, cerebrovascular disease, peripheral vascular disease, heart failure, moderate or severe valvular heart disease, pulmonary hypertension, congenital heart disease, cardiomyopathy, myocarditis/pericarditis, arrhythmia, venous thromboembolism, aortic disease, cardiac transplant, cardiac arrest, and implantation of a left ventricular assist device or cardiac implantable electronic device.

Treatment

Patients with oxygen saturation under 92% were administered supplemental oxygen [13]. Mechanical ventilation was initiated when patients developed respiratory failure that could not be treated with oxygen therapy. Some patients underwent noninvasive ventilation with a high-flow nasal cannula or noninvasive positive pressure ventilation at the physician's discretion. Decisions regarding the initiation, duration, and dose of antibiotic therapy, antiviral therapy, anticoagulation with heparin, and steroid therapy were made by the physicians in each institution.

Clinical follow-up

The patients were followed up until the initial hospital discharge; their symptoms, in-hospital clinical events, type and date of in-hospital treatment, and laboratory data before discharge were recorded. The median follow-up duration was 18 days after admission. The primary outcome measure of this analysis was in-hospital mortality. The tertiles of serum LDH levels measured on admission were analyzed and compared.

Statistical analysis

Categorical variables were expressed as numbers and percentages and were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were expressed as either means and standard deviations or as medians and interquartile ranges and were compared using unpaired t-tests. Survival analysis was performed using Kaplan-Meier analysis, and differences among the three groups were assessed using a log-rank test. The Cox proportional hazards model was used to estimate the risk of variables to determine the predictors of the primary outcome. The following variables were selected *a priori*: age, sex, cardiovascular comorbidities (heart failure, coronary artery disease, old myocardial infarction, valvular heart disease, arrhythmia, cerebral infarction, hypertension, venous thromboembolism, aortic disease), non-cardiovascular comorbidities [dyslipidemia, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and end-stage renal disease with hemodialysis], patient's medication at the time of admission (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, beta-blocker, calcium channel blocker, mineralocorticoid receptor antagonist, statin, aspirin, warfarin, direct oral anticoagulant), vital signs measured at the time of admission (tachypnea, respiratory rate $\geq$ 22/min; hypoxia, SpO2 $<$ 92% or the need for oxygen therapy; tachycardia, heart rate $>$ 100 beats per minute; hypotension, systolic blood pressure $<$ 100 mmHg; and altered consciousness, Glasgow Coma Scale score $<$ 15), risk of sepsis [quick sequential organ failure assessment (qSOFA) score $\geq$ 2], and baseline laboratory data [white blood cell count, lymphocyte count, hemoglobin, LDH, creatinine kinase (CK), albumin, low-density lipoprotein (LDL) cholesterol, hemoglobin A1c (HbA1c), C-reactive protein (CRP), D-dimer, and high-sensitivity troponin levels]. Despite multiple possible confounders, the limited number of

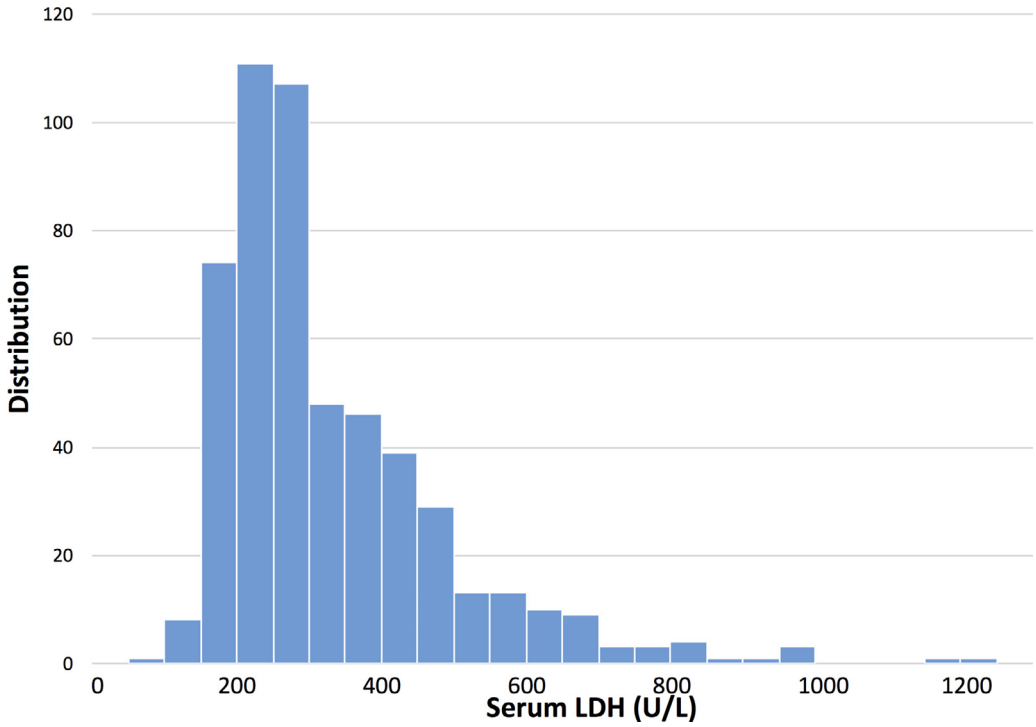


Fig. 1. Histogram of the distribution of serum lactate dehydrogenase (LDH) levels. The distribution of serum LDH level at the time of the hospital admission is shown. The median LDH level measured at the time of admission was 281 [interquartile range (IQR) 220, 402] U/L.

events led us to conduct two statistical models for the multivariable analyses, while variables were selected when they were reported to be associated with prognosis of COVID-19 patients or deemed clinically important and useful by the consensus of the authors. The multivariable analysis in Model 1 was conducted with adjustments for age, previous comorbidities, vital signs, and simplified laboratory data [estimated glomerular filtration rate (eGFR), white blood cell (WBC) count, lymphocyte count, D-dimer and LDH]. The multivariable analysis in Model 2 was conducted with adjustments for age, quick SOFA score, and general items in laboratory tests (eGFR, WBC count, lymphocyte count, D-dimer, LDH, hemoglobin, albumin, and CK). To test for effect modification, the interaction terms of age and sex and the primary outcome measure were evaluated with Cox regression models where they were included together. In all analyses, a p-value < 0.05 was considered significant. All statistical analyses were performed using SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Fig. 1 shows a histogram of the distribution of serum LDH levels measured at the time of admission; the median LDH level was 281 [interquartile range (IQR) 220, 402] U/L. Comparisons of patient background characteristics, data recorded on admission, and therapy administered during hospitalization for patients in each tertile of serum LDH levels are shown in Table 1. The mean age of the patients was 70.4 ± 30.0 years, and 336 patients (65.3%) were male. Age was not significantly different among the three tertiles. The prevalence of each cardiovascular comorbidity was similar among all tertiles. Regarding the vital signs measured on admission, more patients in T3 were tachypneic (T1, 22.2%; T2, 38.1%; T3, 52.2%; $p < 0.001$). More than 90% of patients in all tertiles were hypoxic (T1, 97.7%; T2, 99.4%; T3, 94.7%; $p = 0.027$). Patients in T3 were most likely to have altered consciousness (T1, 14.5%; T2, 15.7%; T3, 27.6%; $p = 0.004$). Regarding the risk of sepsis on admission, more patients in T3 had qSOFA ≥ 2 than in T2 and T1 (T1, 2.3%; T2, 9.3%; T3, 14.6%; $p < 0.001$). Regarding laboratory data recorded on admission, patients in T3 had significantly higher WBC counts, lower percentages of lymphocytes, higher CK levels, and higher D-dimer levels than the patients in T2 and T1. The levels of high-sensitivity troponin were similar among the three tertiles. Regarding the treatments, patients in T3 were most frequently administered antibiotic therapy (T1 vs. T2 vs. T3, 37.2% vs. 44.0% vs. 70.2%; $p < 0.001$), antiviral therapy (41.3% vs. 50.0% vs. 67.8%, $p < 0.001$), anticoagulation with heparin (9.3% vs. 15.1% vs 35.7%, $p < 0.001$), and steroids in any form (32.2% vs. 36.0% vs. 47.4%, $p = 0.011$). More patients in T3 underwent intubation during hospitalization than in T1 and T2 (10.5% vs. 13.4% and 42.1%, respectively; $p < 0.001$).

Outcomes

The median length of hospital stay was 18 (IQR 11, 28) days after admission to the hospital. The primary and secondary outcome measures recorded in each tertile of serum LDH level are shown in Fig. 2. There were significantly more in-hospital deaths in T3 than in the other tertiles (T1 vs. T2 vs. T3, 8.7% vs. 14.0% vs. 29.2%; $p < 0.001$). Fig. 3 shows the Kaplan-Meier curves of in-hospital mortality in each tertile of LDH levels. The in-hospital mortality 30 days after initial hospitalization in T1, T2, and T3 was estimated as 8.6%, 16.5%, and 27.8%, respectively ($p < 0.001$).

In the univariable analysis outlined in Online Supplemental Table 1, older age (≥ 75 years), history of coronary artery disease, valvular heart disease, COPD, tachypnea, hypotension, altered consciousness, qSOFA score ≥ 2, use of aspirin on admission, high WBC counts, low lymphocyte percentages, low hemoglobin levels, low albumin levels, renal dysfunction, high creatinine kinase levels, and high D-dimer levels were significantly associated with an increased risk of the primary outcome. T3 was also associated with

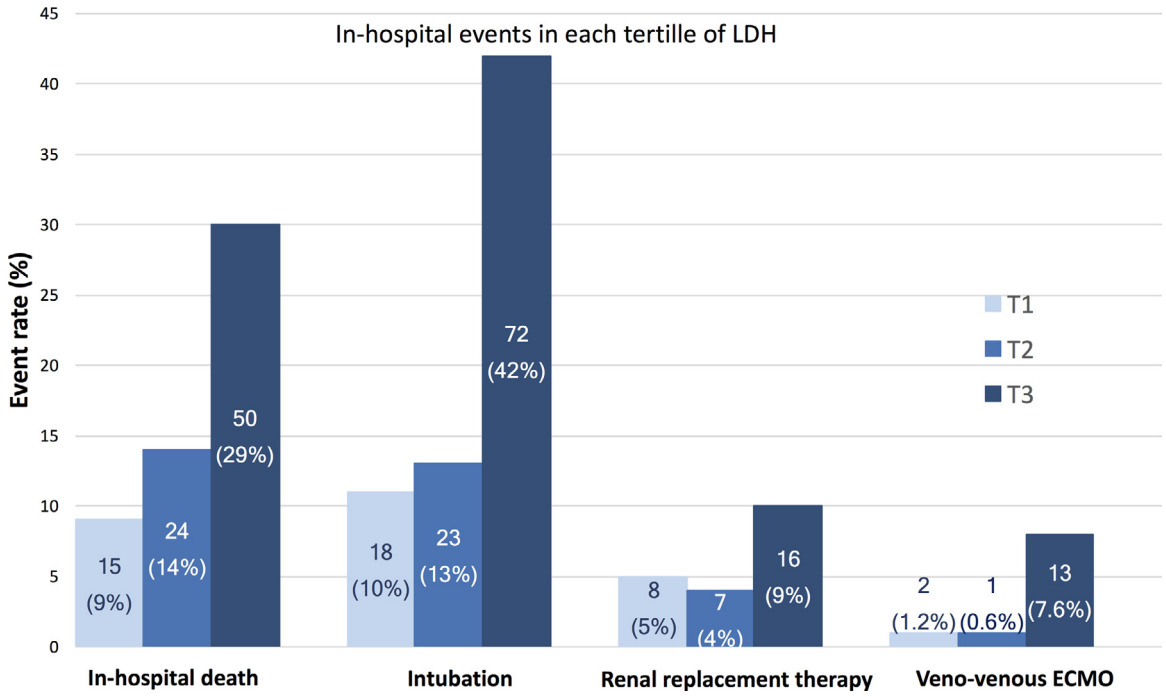
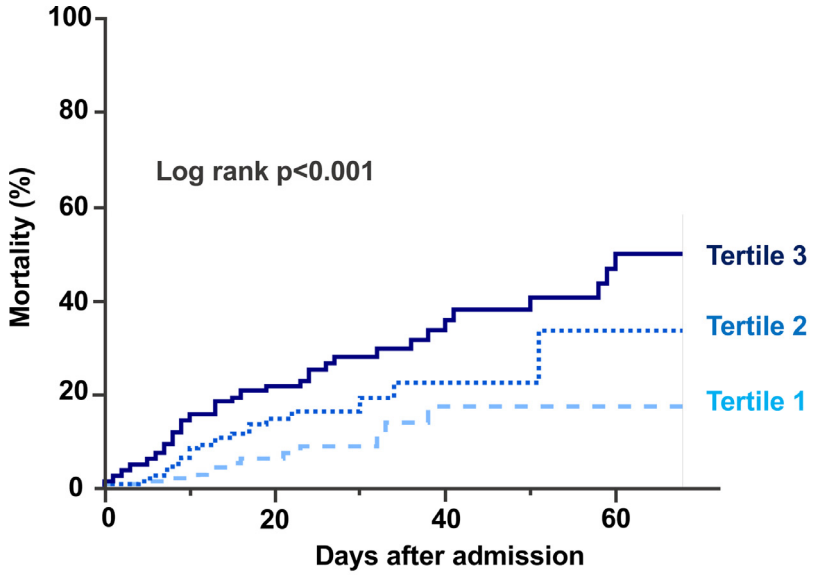


Fig. 2. In-hospital events in each tertile (T) of serum lactate dehydrogenase (LDH) levels. In-hospital events in each T of LDH are shown. There were significantly more in-hospital deaths in T3 than in the other tertiles (T1 vs. T2 vs. T3, 8.7% vs. 14.0% vs. 29.2%; $p < 0.001$). Patients in T3 underwent intubation (T1 vs. T2 vs. T3, 10.5% vs. 13.4% vs. 42.1%; $p < 0.001$), and veno-venous extracorporeal membrane oxygenation (ECMO) (T1 vs. T2 vs. T3, 1.2% vs. 0.6% vs. 7.6%; $p < 0.001$) more frequently.



	0	20 days	40 days	60 days
Tertile 1				
N of patients with events		8	13	13
N of patients at risk	172	82	24	13
Cumulative incidence (%)		6.0	17.2	17.2
Tertile 2				
N of patients with events		20	23	24
N of patients at risk	172	72	20	6
Cumulative incidence (%)		14.5	22.2	33.3
Tertile 3				
N of patients with events		33	42	47
N of patients at risk	171	84	32	18
Cumulative incidence (%)		21.4	35.6	49.7

Fig. 3. Kaplan-Meier curves of in-hospital mortality in each tertile (T) of serum lactate dehydrogenase (LDH) levels. The in-hospital mortality 30 days after initial hospitalization in T1, T2, and T3 was 8.6%, 16.5%, and 27.8%, respectively ($p < 0.001$).

Table 1
Patient background characteristics, data collected on admission, and therapy during hospitalization for each tertile of serum lactate dehydrogenase levels.

LDH tertile	T1 (N = 172)	T2 (N = 172)	T3 (N = 171)	p-value
Age, years	71.2 ± 16.6	70.9 ± 15.0	69.2 ± 13.3	0.40
Male	102 (59%)	113 (66%)	121 (71%)	0.08
BMI ≥ 25 kg/m^2	50 (35%)	50 (36%)	66 (48%)	0.06
Cardiovascular comorbidity				
Heart failure	23 (13%)	17 (10%)	17 (10%)	0.50
Coronary artery disease	27 (16%)	19 (11%)	20 (12%)	0.48
Old myocardial infarction	9 (5%)	7 (4%)	11 (6%)	0.62
Valvular heart disease	7 (4%)	5 (3%)	6 (4%)	0.84
Cerebral infarction	14 (8%)	13 (8%)	18 (11%)	0.59
Hypertension	146 (85%)	159 (92%)	150 (88%)	0.09
Venous thromboembolism	0 (0%)	4 (2%)	4 (2%)	0.13
Aortic disease	4 (2%)	6 (4%)	6 (4%)	0.77
Other comorbidities				
Dyslipidemia	66 (38%)	53 (31%)	62 (36%)	0.32
Diabetes mellitus	51 (30%)	51 (30%)	69 (40%)	0.052
COPD	8 (5%)	8 (5%)	11 (6%)	0.69
Hemodialysis	5 (3%)	3 (2%)	6 (4%)	0.59
Liver cirrhosis	1 (1%)	0 (0%)	0 (0%)	0.37
Vital signs at admission				
Max temperature (°C)	37.9 ± 0.9	37.9 ± 0.8	38.2 ± 0.9	<0.001
Asymptomatic	21 (12%)	14 (8%)	2 (1%)	<0.001
Respiratory rate ≥22 /min	28 (22%)	53 (38%)	70 (52%)	<0.001
SpO2 ≤ 92% or oxygen	168 (98%)	171 (99%)	162 (95%)	0.03
Heart rate ≥ 100	23 (13%)	36 (21%)	54 (32%)	<0.001
Systolic BP ≤ 100 mmHg	3 (2%)	11 (6%)	11 (6%)	0.07
Glasgow Coma Scale <15	24 (15%)	26 (16%)	43 (28%)	0.004
Quick SOFA≥2	4 (2%)	16 (10%)	25 (15%)	<0.001
Medication at admission				
ACE inhibitor	10 (6%)	10 (6%)	9 (5%)	0.97
ARB	68 (40%)	76 (44%)	71 (42%)	0.68
Beta blocker	43 (25%)	21 (12%)	31 (18%)	0.009
CCB	76 (44%)	83 (48%)	77 (45%)	0.73
MRA	10 (6%)	7 (4%)	7 (4%)	0.68
Statin	61 (36%)	46 (27%)	50 (29%)	0.20
Aspirin	26 (15%)	15 (9%)	19 (11%)	0.18
Warfarin	4 (2%)	4 (2%)	5 (3%)	0.92
DOAC	16 (9%)	10 (6%)	10 (6%)	0.35
Laboratory data				
WBC (/μL)	5400 [4100–7100]	5300 [4290–7150]	6300 [4900–8625]	<0.001
Lymphocytes (%)	21.6 [14.8–29.0]	16.0 [11.0–25.1]	12.3 [8.5–17.9]	<0.001
Hemoglobin (g/dL)	13.1 [11.4–14.5]	13.6 [11.7–14.9]	13.6 [12.0–14.8]	0.011
Albumin (mg/dL)	3.5 [3.1–4.1]	3.3 [2.9–3.7]	3.1 [2.7–3.4]	<0.001
LDH (U/L)	209 [184–227]	284 [261–320]	451 [389–557]	–
CK (U/L)	65 [43–98]	86 [54–132]	111 [57–249]	0.003
Creatinine (mg/dL)	0.77 [0.61–0.93]	0.84 [0.68–1.06]	0.90 [0.68–1.12]	0.27
eGFR (mL/min/1.73m2)	91.3 [72.9–110.7]	85.3 [66.5–106.4]	81.7 [59.0–101.0]	0.012
Total bilirubin (mg/dL)	0.5 [0.4–0.7]	0.6 [0.4–0.8]	0.6 [0.5–0.8]	0.06
LDL cholesterol (mg/dL)	88 [73–115]	92 [75–122]	82 [61–104]	0.07
HbA1c (%)	6.2 [5.7–6.6]	6.3 [5.9–7.0]	6.5 [6.0–7.3]	0.012
CRP (mg/dL)	2.2 [0.4–5.7]	5.2 [2.1–10.0)	10.5 [6.1–16.2]	<0.001
D-dimer (mg/dL)	1.1 [0.65–2.38]	1.3 [0.7–2.5]	2.0 [1.2–4.8]	0.006
High-sensitivity troponin (ng/mL)	0.03 [0.01–0.04]	0.01 [0.01–0.04]	0.02 [0.01–0.04]	0.04
Medication during hospitalization				
Antibiotics	64 (37%)	76 (44%)	120 (71%)	<0.001
Antiviral therapy	71 (41%)	86 (50%)	116 (68%)	<0.001
Heparin	16 (9%)	26 (15%)	61 (36%)	<0.001
Steroid in any form	55 (32%)	62 (36%)	81 (48%)	0.011

BMI, body mass index; COPD, chronic obstructive pulmonary dissease; °C, degrees Celsius; BP, blood pressure; SOFA, sequential organ failure assessment; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid receptor antagonist; DOAC, direct oral anticoagulant; WBC, white blood cell; LDH, lactate dehydrogenase; CK, creatinine kinase; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; CRP, C-reactive protein.

an increased risk of the primary outcome [hazard ratio (HR) 3.18; 95% confidence interval (CI) 1.78–5.66; $p < 0.001$].

Multivariable analysis was conducted to determine whether the serum LDH level measured at the time of admission was related to in-hospital death. The multivariable analysis in Model 1 was adjusted for age, history of coronary artery disease, valvular heart disease, COPD, vital signs, renal function, and laboratory data (**Table 2**). The results also showed that T3 was associated with an increased risk of the primary outcome (adjusted HR 3.04, 95% CI 1.50–6.13, $p = 0.002$). In addition, age ≥ 75 years, history of COPD, and chronic kidney disease (stage 4 or 5) were independently associated with an increased risk of the primary outcome. Another multivariable analysis was conducted in Model 2 with adjustments for age, qSOFA scores, renal function assessed on admission, WBC counts, lymphocyte counts, D-dimer, hemoglobin, albumin, CK, and LDH levels on admission (**Table 2**). The results of that analysis showed that T3 was associated with an increased risk of in-hospital death (adjusted HR 2.60; 95% CI 1.24–5.42, $p = 0.011$).

Table 2
Multivariable Cox regression analysis of the risk factors associated with in-hospital death.

	Adjusted hazard ratio (95% CI)	*p*-value
Model 1*		
LDH levels <235 U/L	Reference	–
LDH levels 235–355 U/L	1.02 (0.45–2.36)	0.96
LDH levels >355 U/L	3.04 (1.50–6.13)	0.002
Model 2**		
LDH levels <235 U/L	Reference	–
LDH levels 235–355 U/L	0.94 (0.41–2.15)	0.88
LDH levels >355 U/L	2.60 (1.24–5.42)	0.01

COPD, chronic obstructive pulmonary disease; LDH, lactate dehydrogenase; SOFA, sequential organ failure assessment.

* Model 1 was adjusted by age, history of coronary artery disease, valvular heart disease, COPD, vital signs (respiratory rate, SpO2, heart rate, systolic blood pressure, Glasgow Coma Scale, and quick SOFA score), estimated glomerular filtration rate (eGFR), white blood cell (WBC) count, lymphocyte count, D-dimer, and LDH.

** Model 2 was adjusted by age, quick SOFA score, eGFR, WBC count, lymphocyte count, D-dimer, LDH, hemoglobin, albumin, and creatinine kinase levels.

In addition, decreased renal function (adjusted HR 2.352, 95% CI 1.161–4.766, $p = 0.018$) and increased age (adjusted HR 4.738, 95% CI 2.523–8.900, $p < 0.001$) were each associated with an increased risk of in-hospital death. The results remained significant with no effect modification by age and sex (p-interaction > 0.05 for both).

Discussion

In the present study, we investigated the impact of serum LDH level measured at the time of hospital admission on the prognoses of high-risk COVID-19 patients with pre-existing cardiovascular comorbidities. Our results showed that elevated serum LDH level on hospital admission was associated with an increased risk of in-hospital death in patients with COVID-19 and underlying cardiovascular comorbidities. LDH has been reported to predict severe respiratory failure and mortality in patients with COVID-19; however, no study has been conducted to clarify its significance in patients with COVID-19 and cardiovascular comorbidities.

Patients with COVID-19 and underlying cardiovascular disease have poor prognoses [2,14]. Pre-existing cardiovascular disease seems to be associated with worse outcomes and increased risk of death in patients with COVID-19. The overall case fatality rate of COVID-19 reported by the Chinese Center for Disease Control and Prevention as of February 11, 2020, was 2.3% (1023 deaths among 44,672 confirmed cases) [1]. The individual case fatality rate for patients with cardiovascular disease was 10.5% [1]. In a report of 1591 patients with COVID-19 who were admitted to an intensive care unit in Italy, 49% of the patients had pre-existing hypertension, 21% had cardiovascular disease, and 17% had diabetes [15]. COVID-19 not only causes viral pneumonia but also triggers cardiovascular disorders, such as myocardial injury, arrhythmias, acute coronary syndrome, and thromboembolism [16–21]. The mechanism by which SARS-CoV-2 affects the heart is not clear. Some researchers have suggested that the myocardial injury is secondary to systemic causes, whereas others demonstrated direct viral infection of the heart and subsequent viral myocarditis [22–25]. Although physicians fear that patients with COVID-19 who have concomitant cardiovascular diseases would have poor prognoses, no criteria that focus on the risk stratification of these patients upon hospital admission have yet been identified. In this study, significantly more patients in the lowest tertile of LDH presented with hypoxia than the patients with higher LDH. As patients with high LDH followed worse prognosis, initial lower percentage of hypoxia was not met with the reasonable explanation. However, since CLAVIS-COVID comprises patients hospitalized for COVID-19, the premise of the study is inclusion of patients with more severe condition than the general population of COVID-19. The percentage of hypoxic patients in the whole study calculates as high as 97.3%, demonstrating inclusion of patients with severe disease.

As LDH is a cytoplasmic enzyme that is widely expressed in tissues, it could be a useful marker of systemic inflammation. The enzyme converts pyruvate, which is the final product of glycolysis, to lactate when oxygen is in short supply. LDH is present in five separate isozymes (LDH-1 in cardiomyocytes, LDH-2 in the reticuloendothelial system, LDH-3 in pneumocytes, LDH-4 in the kidneys and pancreas, and LDH-5 in the liver and striated muscles) [26,27]. As it is present in most body cells, LDH is a general indicator of acute or chronic tissue damage and is considered an inflammatory marker [28]. Historically, LDH was first used for the diagnosis of myocardial infarction, as it reflects necrosis of cardiomyocytes. LDH serum concentrations have been reported to increase during the acute lung damage that occurs in interstitial lung disease and severe respiratory failure [3]. It is also one of the biomarkers most strongly associated with ARDS mortality [4,5]. In a study of 67 patients with severe ARDS during the epidemic in 2003, multivariate analyses showed that elevated LDH levels (odds ratio 8.4, 95% CI 1.9–36.9) at the time of admission was an independent predictor of ARDS [29].

LDH has been reported to predict mortality in severe and critically ill patients with COVID-19 [6]. In a pooled analysis of nine published studies that included 1532 patients with COVID-19, elevated LDH levels were associated with a 6-fold increase in the odds of developing severe disease and a 16-fold increase in the odds of mortality [30]. In a multicenter nested case-control study, advanced age and high LDH level were independent risk factors for deterioration in patients with mild COVID-19 [7]. LDH is also independently associated with one-month mortality in older inpatients with COVID-19 [8] and is a predictor of respiratory failure in hospitalized patients with COVID-19 [9]. A previous study has also shown that elevated LDH level on admission is an independent risk factor for severe COVID-19 [10].

In the present study, a very high LDH level (LDH > 355 U/L) at the time of hospital admission was associated with an increased risk of in-hospital death in patients with COVID-19 and cardiovascular comorbidities. LDH could reflect damage to pneumocytes due to severe respiratory failure and damage to the myocardium and other organs. Measurement of a specific LDH isozyme in future studies would help reveal which tissue is more extensively affected by COVID-19. In the present study, neither high-sensitivity troponin nor D-dimer levels were significantly associated with an increased risk of the primary outcome in the multivariable analysis. On the other hand, as serum LDH level was an independent risk factor for in-hospital death in patients with coexisting cardiovascular diseases, it seemed to be a reliable marker. In addition, since measurement of LDH is generally included in the initial laboratory tests performed on hospital admission and the data can easily be obtained from outpatient clinics and emergency departments, serum LDH level could widely aid physicians in predicting the clinical course of the patients with COVID-19 at the time of admission. The results of the present study have shown the significance of serum LDH level in the assessment of patients with COVID-19 and cardiovascular comorbidities.

Study limitations

First, owing to the retrospective nature of the study, decisions regarding the hospitalization of patients and subsequent initiation of treatment were made by the physicians in the participating medical centers. Because this study was conducted in the early period of the pandemic, medication usage of steroids, antiviral drugs, and immuno-suppressants might differ from the cur-

rent practice. At the time of the study in early 2020, genetic variants of SARS-CoV-2 had not been as widely observed as in year 2021, which might therefore lead to different results if conducted in the circumstances where most of the infections are caused by genetic variants. Second, only hospitalized patients with COVID-19 were included in the CLAVIS-COVID study. Since only 252 patients had data on brain natriuretic protein (BNP) or N-terminal (NT)-proBNP measured at initial hospitalization, it was not feasible to determine whether BNP or NT-proBNP was a risk factor for the primary outcome. In this observational study, data were collected on the patients' vital signs at admission and flow rate of oxygen administered. However, neither the fraction of inspired oxygen (FiO2) nor type of oxygen delivery device were collected, so it was not possible to calculate PaO2/FiO2, which is commonly used to determine severity of COVID-19. Third, since the primary outcome was in-hospital death, patients were not followed up after discharge; therefore, the long-term prognoses of the patients were not known. Finally, specific LDH isozymes were not evaluated; thus, it is not possible to draw conclusions on which organ was the primary source of tissue damage.

Conclusions

In summary, high serum LDH level measured at the time of admission is associated with an increase in the risk of in-hospital death in patients with COVID-19 and underlying cardiovascular disease. Since measurement of serum LDH is generally included in the initial laboratory tests, the results could aid physicians in predicting the clinical course of patients with COVID-19 and cardiovascular comorbidities.

Sources of funding

None

Disclosures

Dr Taishi Yonetsu belongs to endowed departments of Abbott Vascular Japan, Boston Scientific Japan, Japan Lifeline, WIN International, and Takeyama KK. Dr Yuya Matsue is affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi, received an honorarium from Otsuka Pharmaceutical Co. and Novartis Japan, received consultant fee from Otsuka Pharmaceutical Co., and joint research funds from Otsuka Pharmaceutical Co. and Pfizer inc. Dr Koichi Node has received honoraria from Astellas, AstraZeneca, Boehringer Ingelheim Japan, Daiichi Sankyo, Eli Lilly Japan, Mitsubishi Tanabe Pharma, MSD, Ono Pharmaceutical, Otsuka, Takeda Pharmaceutical; research fundings from Asahi Kasei, Astellas, Boehringer Ingelheim Japan, Mitsubishi Tanabe Pharma, Teijin Pharma, Terumo; scholarship from Bayer Yakuhin, Daiichi Sankyo, Medtronic, Takeda Pharmaceutical, Teijin Pharma. Dr Issei Komuro, Dr Ken-ichi Hirata, and Dr Koichi Node are members of *Circulation Journal*'s editorial team.

IRB

The study protocol, including the use of an opt-out consent method, was approved by the

Ethics Committee of Toho University Omori Medical Center (No. M20253) and the local ethics committees of all participating institutions.

Acknowledgments

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2021.12.014.

References

[1] The Novel Coronavirus Pneumonia Emergency Response Epidemiology TeamVital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)-China, 2020. China CDC Weekly 2020;2:113–22.
[2] Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol 2020;17:543–58. doi:10.1038/s41569-020-0413-9.
[3] McFadden RG, Oliphant LD. Serum lactate dehydrogenase in interstitial lung disease. Chest 1991;100:1182. doi:10.1378/chest.100.4.1182-b.
[4] Terpstra ML, Aman J, van Nieuw Amerongen GP, Groeneveld AB. Plasma biomarkers for acute respiratory distress syndrome: a systematic review and meta-analysis*. Crit Care Med 2014;42:691–700. doi:10.1097/01.ccm.0000435669.60811.24.
[5] Hoeboer SH, Oudemans-van Straaten HM, Groeneveld AB. Albumin rather than C-reactive protein may be valuable in predicting and monitoring the severity and course of acute respiratory distress syndrome in critically ill patients with or at risk for the syndrome after new onset fever. BMC Pulm Med 2015;15:22. doi:10.1186/s12890-015-0015-1.
[6] Dong X, Sun L, Li Y. Prognostic value of lactate dehydrogenase for in-hospital mortality in severe and critically ill patients with COVID-19. Int J Med Sci 2020;17:2225–31. doi:10.7150/ijms.47604.
[7] Shi J, Li Y, Zhou X, Zhang Q, Ye X, Wu Z, et al. Lactate dehydrogenase and susceptibility to deterioration of mild COVID-19 patients: a multicenter nested case-control study. BMC Med 2020;18:168. doi:10.1186/s12916-020-01633-7.
[8] Bousquet G, Falgarone G, Deutsch D, Derolez S, Lopez-Sublet M, Goudot FX, et al. ADL-dependency, D-Dimers, LDH and absence of anticoagulation are independently associated with one-month mortality in older inpatients with Covid-19. Aging 2020;12:11306–13. doi:10.18632/aging.103583.
[9] Poggiali E, Zaino D, Immovilli P, Rovero L, Losi G, Dacrema A, et al. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients. Clin Chim Acta 2020;509:135–8. doi:10.1016/j.cca.2020.06.012.
[10] Han Y, Zhang H, Mu S, Wei W, Jin C, Tong C, et al. Lactate dehydrogenase, an independent risk factor of severe COVID-19 patients: a retrospective and observational study. Aging 2020;12:11245–58. doi:10.18632/aging.103372.
[11] Matsumoto S, Kuroda S, Sano T, Kitai T, Yonetsu T, Kohsaka S, et al. Clinical and biomarker profiles and prognosis of elderly patients with coronavirus disease 2019 (COVID-19) with cardiovascular diseases and/or risk factors. Circ J 2021;85:921–8.
[12] Centers for Disease Control and Prevention. *CDC's Diagnostic test for COVID-19 Only and Supplies*. COVID-19. [online] Available at: <https://www.cdc.gov/coronavirus/2019-ncov/lab/virus-requests.html.> Accessed: 1 January 2022.
[13] National Institute of Health.*Oxygenation and ventilation.* NIH COVID-19 Treatment Guidelines. [online] Available at: <https://www.covid19treatmentguidelines.nih.gov/critical-care/oxygenation-and-ventilation/.> Accessed: 1 January 2022.
[14] Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol 2020;5:831–40. doi:10.1001/jamacardio.2020.1286.
[15] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020;323:1574–81. doi:10.1001/jama.2020.5394.
[16] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13. doi:10.1016/S0140-6736(20)30211-7.
[17] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62. doi:10.1016/S0140-6736(20)30566-3.
[18] Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet 2020;395:1014–15. doi:10.1016/S0140-6736(20)30633-4.
[19] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934–43. doi:10.1001/jamainternmed.2020.0994.
[20] Tomidokoro D, Hiroi Y. Cardiovascular implications of the COVID-19 pandemic. J Cardiol 2021 S0914-5087(21)00243-4[Elsevier: Please update]. doi:10.1016/j.jjcc.2021.09.010.
[21] Mai F, Del Pinto R, Ferri C. COVID-19 and cardiovascular diseases. J Cardiol 2020;76:453–8. doi:10.1016/j.jjcc.2020.07.013.
[22] Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol 2020;311:116–21. doi:10.1016/j.ijcard.2020.03.087.
[23] Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail 2020;22:911–15. doi:10.1002/ejhf.1828.

[24] Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med 2020;173:268–77. doi:10.7326/M20-2003.
[25] Schaller T, Hirschbühl K, Burkhardt K, Braun G, Trepel M, Märkl B, et al. Postmortem examination of patients with COVID-19. JAMA 2020;323:2518–20. doi:10.1001/jama.2020.8907.
[26] Feron O. Pyruvate into lactate and back: from the Warburg effect to symbiotic energy fuel exchange in cancer cells. Radiother Oncol 2009;92:329–33. doi:10.1016/j.radonc.2009.06.025.
[27] Glick JH. Serum lactate dehydrogenase isoenzyme and total lactate dehydrogenase values in health and disease, and clinical evaluation of these tests by means of discriminant analysis. Am J Clin Pathol 1969;52:320–8. doi:10.1093/ajcp/52.3.320.
[28] Rubba P, Gentile M, Panico S, Pauciullo P. Nutrition, metabolism, and cardiovascular disease. Chichester, UK: Wiley-Blackwell; 2011. p. 149–58.
[29] Chen CY, Lee CH, Liu CY, Wang JH, Wang LM, Perng RP. Clinical features and outcomes of severe acute respiratory syndrome and predictive factors for acute respiratory distress syndrome. J Chin Med Assoc 2005;68:4–10. doi:10.1016/S1726-4901(09)70124-8.
[30] Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: a pooled analysis. Am J Emerg Med 2020;38:1722–6. doi:10.1016/j.ajem.2020.05.073.