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Infectious Medicine

Original Article

The liver-to-spleen ratio is a risk factor predicting oxygen demand in COVID-19 patients

Hiromasa Nakayasu*, Shogo Sakurai, Shuichi Sugiyama, Kotaro Shiratori, Kohei Okawa, Yoshihiro Kitahara, Shingo Takahashi, Toshihiro Masuda, Yutaro Kishimoto, Mika Saigusa, Akito Yamamoto, Taisuke Akamatsu, Satoru Morita, Kazuhiro Asada, Toshihiro Shirai

Department of Respiratory Medicine, Shizuoka General Hospital, 4-27-1 Kita-Ando, Aoi, 420-0805 Shizuoka, Japan

A B S T R A C T

Background: We aimed to investigate risk factors predicting oxygen demand in COVID-19 patients.
Methods: Patients admitted to Shizuoka General Hospital with COVID-19 from August 2020 to August 2021 were included. First, we divided patients into groups with and without oxygen demand. Then, we compared patients' clinical characteristics and laboratory and radiological findings to determine factors predicting oxygen demand.
Results: One hundred seventy patients with COVID-19 (aged 58±15 years, 57 females) were enrolled. Common comorbidities were cardiovascular diseases (47.6%), diabetes mellitus (28.8%), and dyslipidemia (26.5%). Elder age, higher body mass index, cardiovascular diseases, diabetes mellitus, lower lymphocyte count, albumin, hepatic attenuation value, and the liver-to-spleen ratio (L/S), higher D-dimer, aspartate aminotransferase, lactate dehydrogenase, troponin-T, C-reactive protein, KL-6, chest and abdominal circumference, and visceral fat were found in patients with oxygen demand. According to the multivariate logistic regression analysis, L/S, lymphocyte count, D-dimer, and abdominal circumference under the diaphragm were independent risk factors predicting oxygen demand in COVID-19 patients.
Conclusions: On admission, L/S, lymphocyte count, D-dimer, and abdominal circumference were predictive factors for oxygen demand. These factors may help in the appropriate triage of COVID-19 patients in the decision to admit them to the hospital.

1. Introduction

In late 2019, a novel coronavirus was identified as the cause of pneumonia, which spread rapidly, resulting in the global pandemic. The number of infections is increasing worldwide, and the clinical manifestations range from asymptomatic cases to patients with mild and severe symptoms, with or without pneumonia [1]. Among patients with COVID-19, 81.4% remained in mild disease, while 13.9% reported moderate disease and 4.7% progressed to severe disease [2]. However, with the rapid

increase in COVID-19 patients, most patients were treated at home rather than hospitalized in Japan. Therefore, it is crucial to appropriately triage patients who are most likely to become severe disease.

The risk of severe disease from COVID-19 is being studied. Many studies have examined risk factors for severe disease based on age, gender, comorbidity, and laboratory examination findings [3]. In comorbidity, cardiovascular diseases, diabetes, and hypertension have been associated with oxygen demand and death [4]. However, there are few studies on risk factors for severe disease related to computerized tomography (CT) im-

ages, and those analyses focused on lung field findings. Although some studies have focused on hepatic attenuation value and visceral fat, prognostic factors have been analyzed for hepatic attenuation value alone or visceral fat alone [5,6]. Therefore, we comprehensively analyzed age, gender, comorbidities, laboratory findings, and CT imaging findings such as hepatic attenuation value and visceral fat and examined factors that predict oxygen demand.

2. Patients and methods

2.1. Study design and participants

This was a retrospective single-center study of adult patients. Patients included in the study had been diagnosed with COVID-19 and admitted to Shizuoka General Hospital from August 1, 2020, to August 31, 2021. Specific inclusion criteria were: (1) patients whose blood examinations had been performed; (2) patients whose computed tomography (CT) images could be analyzed using SYNAPSE VINCENT and (3) patients whose outcome was known. We set the target SpO_2 at 93–96% and started supplemental oxygen when the oxygen saturation was less than 93% at rest. Supplemental oxygen was adjusted to maintain this range. According to the oxygen demand on admission or during hospitalization, we divided patients into groups with and without oxygen demand (Fig. 1). Even if there was no oxygen demand at the time of admission, if oxygen demand emerged during hospitalization, the patient was included in the group with oxygen demand. In other words, the group without oxygen demand was defined as patients who did not require oxygen on admission and during hospitalization. Treatment was based on the severity of COVID-19 according to the guidelines issued by the Ministry of Health, Labour and Welfare (Japan).
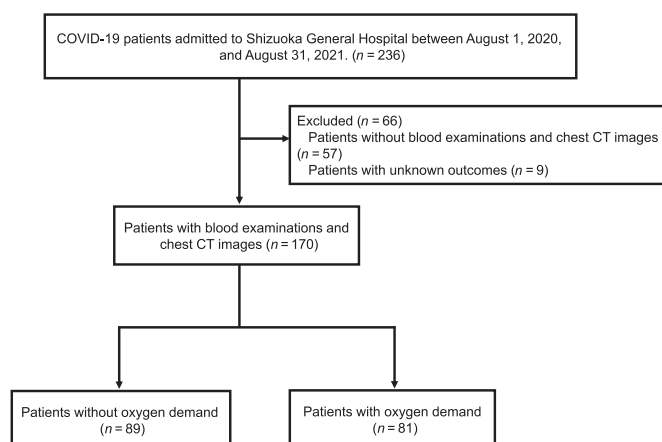


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┌─────────────────────────────────────────────────────────┐
│ COVID-19 patients admitted to Shizuoka General Hospital │
│ between August 1, 2020, and August 31, 2021. (n = 236)  │
└─────────────────────────────────────────────────────────┘
                          │
                          │        ┌──────────────────────────────────────────┐
                          ├───────▶│ Excluded (n = 66)                        │
                          │        │   Patients without blood examinations    │
                          │        │   and chest CT images (n = 57)           │
                          │        │   Patients with unknown outcomes (n = 9) │
                          │        └──────────────────────────────────────────┘
                          ▼
┌──────────────────────────────────────┐
│ Patients with blood examinations and │
│ chest CT images (n = 170)            │
└──────────────────────────────────────┘
            │
    ┌───────┴────────┐
    ▼                ▼
┌──────────────┐  ┌──────────────┐
│ Patients     │  │ Patients     │
│ without      │  │ with oxygen  │
│ oxygen demand│  │ demand       │
│ (n = 89)     │  │ (n = 81)     │
└──────────────┘  └──────────────┘
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Fig. 1. Patient flow through this study.

2.2. Data collection

We extracted patients' personal and clinical data included in the study from electronic medical records. Personal data included sex, age, body mass index (BMI), epidemiological history, history of smoking, and comorbidities (e.g., cardiovascular diseases, diabetes, dyslipidemia, respiratory disease, chronic renal failure, immunodeficiency, and malignancy). Clinical data included days from onset to hospitalization, respiratory support, laboratory data, CT images, treatment, and outcome.

2.3. Laboratory examinations and CT images

We performed laboratory examinations and chest CT images on admission. Laboratory examinations included complete blood count, coagulation profile, serum biochemical tests (including liver function, creatine kinase, lactate dehydrogenase, and electrolytes), myocardial enzymes, serum ferritin, immunoglobulin, KL-6, SP-D, and procalcitonin. CT was performed without contrast material, from lung apex to upper abdomen, and in a single breath at maximum inspiration after the patient received breathing instructions.

2.4. CT images analysis

CT images comprised 1 mm slice thickness throughout the entire lung. The chest CT images analyzed the visceral fat, subcutaneous fat, chest circumference, abdominal circumference, hepatic attenuation value, and splenic attenuation values. Hepatic and splenic attenuation values were measured using area region of interest (ROI) greater than 100 mm^2. Hepatic attenuation values were calculated by placing 2 ROIs greater than 100 mm^2 in the liver while excluding regions of nonuniform parenchymal attenuation, including hepatic vessels. Splenic attenuation was obtained by placing 1 ROI greater than 100mm^2 in the spleen. The liver-to-spleen ratio (L/S) was calculated by taking the average Hounsfield unit (HU) measurement of both hepatic ROIs and dividing it by the spleen HU value [7]. Additionally, we measured the visceral fat, subcutaneous fat, and abdominal circumference in CT cross-sections under the diaphragm and the subcutaneous fat and chest circumference at the fourth thoracic vertebra using the SYNAPSE VINCENT image analysis system (Fujifilm Inc., Tokyo, Japan). We set the lower and upper thresholds of visceral and subcutaneous fat analysis to −200 HU and −50 HU, respectively.

2.5. Statistical analysis

Categorical variables were presented as numbers (percentages) and analyzed using Fisher's exact test. Contin-

uous variables were expressed as mean±standard deviation and analyzed using *t* test. The logistic regression model was used for univariate and multivariate analyses to identify oxygen demand associated variables. $p < 0.05$ was considered statistically significant. All analyses were performed with EZR software (version 1.27, Saitama Medical Center, Jichi Medical University, Saitama, Japan) [8].

2.6. Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Shizuoka General Hospital (SGHIRB#2022017).

3. Results

3.1. Baseline clinical characteristics

Table 1 indicates the subjects' clinical characteristics, comorbidity, and therapeutic drugs. This study included 170 patients, including 113 males and 57 females. The mean age and BMI were 58 and 24.7, relatively. Twenty-five patients were current smokers, 57 were ex-smokers, and 88 were never smokers. The most common comorbidity was cardiovascular diseases (81, 47.6%), followed by diabetes mellitus (49, 28.8%) and dyslipidemia (45, 26.5%). One hundred seventeen patients received dexam-

ethasone, and 73 patients received remdesivir. Twenty-nine patients with severe disease or a high likelihood of developing severe disease received tocilizumab or baricitinib.

3.2. Comparison of groups with and without oxygen demand

The comparisons of laboratory results and CT images between groups with oxygen demand and without oxygen demand are shown in Tables 1–3. Compared with a group without oxygen demand, the group with oxygen demand was older in age ($p = 0.002$) and had higher BMI ($p = 0.003$), had a higher prevalence of cardiovascular diseases ($p = 0.002$) and diabetes mellitus ($p = 0.028$) (Table 1). Also, a group with oxygen demand had lower lymphocyte count ($p = 0.031$) and albumin ($p < 0.001$), higher D-dimer ($p < 0.001$), aspartate aminotransferase (AST) ($p = 0.001$), lactate dehydrogenase ($p < 0.001$), troponin-T ($p = 0.046$), C-reactive protein (CRP) ($p < 0.001$), KL-6 ($p < 0.001$). The differences between the other parameters were not statistically significant ($p > 0.05$) (Table 2). In comparison to a group without oxygen demand, the group with oxygen demand was lower hepatic attenuation value ($p < 0.001$) and L/S ($p < 0.001$), higher chest circumference at the 4th thoracic vertebra, the visceral fat, visceral/subcutaneous fat ratio, and abdominal circumference under the diaphragm (Table 3).

Table 1
Clinical characteristics of the subjects.

	All $n = 170$	Oxygen demand (−) $n = 89$	Oxygen demand (+) $n = 81$	*p* value
Age, years	58.36±15.06	55.76±15.21	61.22±14.46	0.002
Sex, male/female	113/57	54/35	59/22	0.106
BMI, kg/m^2	24.71±4.82	23.94±4.07	25.55±5.43	0.003
Smoking history, never/ex/current smoker	88/57/25	48/24/17	40/33/8	0.082
Pack-years	13.92±22.10	10.81±17.20	17.33±26.15	0.054
Days from onset to hospitalization, days	6.54±3.03	6.48±3.18	6.61±2.88	0.792
Comorbidity (%)				
Cardiovascular diseases	81 (47.6)	32 (36.0)	49 (50.5)	0.002
Diabetes mellitus	49 (28.8)	19 (21.3)	30 (37.0)	0.028
Dyslipidemia	45 (26.5)	20 (22.4)	25 (30.9)	0.228
Respiratory diseases	24 (14.1)	9 (10.1)	15 (18.5)	0.128
Chronic kidney failure	24 (14.1)	14 (15.7)	10 (12.3)	0.660
Immunodeficiency	8 (4.7)	4 (4.5)	4 (4.9)	>0.999
Malignant tumor	5 (2.9)	2 (2.2)	3 (3.7)	0.670
Treatment (%)				
Dexamethasone	117 (68.8)	39 (43.8)	78 (96.3)	<0.001
Remdesivir	73 (42.9)	21 (23.6)	52 (64.2)	<0.001
Anticoagulant medicines	27 (15.9)	0 (0)	27 (33.3)	<0.001
Favipiravir	25 (14.7)	6 (6.7)	19 (23.5)	0.002
Baricitinib	19 (11.1)	0 (0)	19 (23.5)	<0.001
Ciclesonide	12 (7.1)	7 (7.9)	5 (6.2)	0.769
Tocilizumab	10 (5.9)	0 (0)	10 (12.3)	<0.001
Casirivimab and Imdevimab	5 (2.9)	5 (5.6)	0 (0)	0.060

Continuous variables were expressed as mean±SD and categorical variables were expressed as number (percentage). Data were compared using *t* test or Fisher's exact test.
BMI, body mass index.

Table 2

Laboratory results of the subjects.

	Oxygen demand (−) $n = 89$	Oxygen demand (+) $n = 81$	*p* value
WBC, $\times 10^2/\mu$L	57.66 ± 25.48	58.20 ± 26.96	0.894
Hb, g/dL	14.51 ± 1.78	14.76 ± 1.88	0.364
Neutrophil count, $/\mu$L	4284.80 ± 2455.02	4540.38 ± 2639.49	0.515
Lymphocyte count, $/\mu$L	1052.49 ± 382.46	919.26 ± 412.38	0.031
D-dimer, μg/mL	0.93 ± 0.38	1.40 ± 1.07	<0.001
Albumin, g/dL	3.76 ± 0.42	3.49 ± 0.43	<0.001
Total cholesterol, mg/dL	166.38 ± 30.49	162.67 ± 31.27	0.485
HDL cholesterol, mg/dL	48.68 ± 17.62	46.73 ± 12.61	0.462
Neutral fat, mg/dL	117.81 ± 45.92	122.44 ± 44.28	0.542
AST, IU/L	39.65 ± 33.17	56.21 ± 32.61	0.001
ALT, IU/L	39.16 ± 40.49	44.23 ± 29.17	0.355
LDH, IU/L	299.45 ± 84.53	411.21 ± 155.32	<0.001
BNP, pg/mL	59.23 ± 171.22	86.40 ± 411.00	0.574
Troponin T, ng/mL	0.011 ± 0.012	0.018 ± 0.032	0.046
CRP, mg/dL	4.56 ± 5.73	7.99 ± 6.53	<0.001
IgG, mg/dL	1209.59 ± 270.86	1169.52 ± 322.83	0.428
IgA, mg/dL	267.04 ± 101.14	240.48 ± 84.11	0.091
IgM, mg/mL	86.76 ± 40.13	77.94 ± 36.63	0.172
Procalcitonin, ng/mL	0.12 ± 0.26	0.30 ± 1.06	0.169
Ferritin, ng/mL	684.57 ± 763.12	698.00 ± 1141.51	0.928
HbA1c, %	6.23 ± 1.01	6.36 ± 0.92	0.527
KL-6, IU/mL	227.90 ± 77.43	346.93 ± 211.51	<0.001
SP-D, ng/mL	47.19 ± 60.40	32.89 ± 26.47	0.068

The variables were expressed as mean±SD and compared using *t* test.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic hormone; CRP, C-reactive protein; Hb, hemoglobin; HDL, high-density lipoprotein; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; WBC, white blood cell.

Table 3

Image findings of the subjects.

	Oxygen demand (−) $n = 89$	Oxygen demand (+) $n = 81$	*p* value
Hepatic attenuation value, HU	52.65 ± 10.99	45.12 ± 13.72	<0.001
Splenic attenuation value, HU	50.40 ± 3.45	49.94 ± 3.10	0.364
The liver-to-spleen ratio	1.05 ± 0.22	0.91 ± 0.29	<0.001
The subcutaneous fat of the 4th thoracic vertebra, cm^2	115.15 ± 65.61	135.73 ± 77.28	0.062
Chest circumference of the 4th thoracic vertebra	94.17 ± 12.50	97.71 ± 8.52	0.034
The subcutaneous fat area under the diaphragm	80.19 ± 49.98	88.71 ± 54.12	0.287
The visceral fat area under the diaphragm	109.71 ± 72.97	144.98 ± 88.37	0.005
The visceral/subcutaneous fat ratio under the diaphragm	1.63 ± 1.08	2.10 ± 1.56	0.022
abdominal circumference under the diaphragm	89.27 ± 9.67	93.94 ± 9.34	0.002

The variables were expressed as mean±SD and compared using *t* test.

HU, Hounsfield unit.

3.3. Univariate and multivariate analyses of risk factors predicting oxygen demand in COVID-19 patients

3.3.1. Univariate analysis

On univariate analysis, the following characteristics were associated with an increased odds of oxygen demand: age of patients (odds ratio (OR) 1.03, CI 1.00–1.05), BMI (OR 1.08, CI 1.01–1.16), diabetes mellitus (OR 2.17, CI 1.10–4.27), cardiovascular diseases (OR 2.73, CI 1.47–5.08), D-dimer (OR 5.52, CI 2.18–14.00), abdominal circumference under the diaphragm (OR 1.05, CI 1.02–1.09), the visceral fat area under the diaphragm (OR 1.01, CI 1.00–1.02). On the other hand, the following factors were associated with decreased odds ratios: L/S (OR 0.10, CI 0.27–0.39), lymphocyte count (OR 0.999, CI 0.998–1.000) (Table 4).

3.3.2. Multivariable analysis

Multivariate analysis indicated that L/S (OR 0.14, CI 0.02–0.93), lymphocyte count (OR 0.999, CI 0.998–1.000), D-dimer (OR 4.46, CI 1.60–13.40), abdominal circumference under the diaphragm (OR 1.09, CI 1.01–1.18) were risk factors predicting oxygen demand in COVID-19 patients (Table 4).

4. Discussion

This study described abdominal circumference under the diaphragm, L/S, lymphocyte count, and D-dimer as independent risk factors predicting oxygen demand in COVID-19 patients.

Previous meta-analyses have reported that high D-dimer and low lymphocyte counts are poor prognostic

Table 4

Univariate and multivariate linear regression analysis of factors predicting oxygen demand in COVID-19 patients.

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age, years	1.03	(1.00, 1.05)	0.020	1.02	(0.99, 1.05)	0.223
Sex, male	1.74	(0.91, 3.32)	0.095			
BMI, kg/m^2	1.08	(1.01, 1.16)	0.034	0.95	(0.84, 1.06)	0.348
Smoking history, yes	1.20	(0.66, 2.19)	0.553			
Diabetes mellitus	2.17	(1.10, 4.27)	0.026	0.93	(0.38, 2.27)	0.869
Cardiovascular diseases	2.73	(1.47, 5.08)	0.002	1.72	(0.76, 3.90)	0.191
The liver-to-spleen ratio	0.10	(0.27, 0.39)	<0.001	0.14	(0.02, 0.93)	0.042
Lymphocyte count, /μL	0.999	(0.998, 1.00)	0.003	0.999	(0.998, 1.00)	0.045
D-dimer, μg/mL	5.52	(2.18, 14.00)	<0.001	4.64	(1.60, 13.40)	0.043
Abdominal circumference under the diaphragm, cm	1.05	(1.02, 1.09)	0.003	1.09	(1.01, 1.18)	0.024
The visceral fat area under the diaphragm, cm^2	1.01	(1.00, 1.02)	0.007	0.99	(0.99, 1.00)	0.340

BMI, body mass index.

factors [9–11]. This known finding is consistent with our study. The postulated mechanisms for lymphocytopenia in patients with severe COVID-19 include inflammatory cytokine storms such as TNF-α and IL-6 [12], cell exhaustion due to COVID-19 infection [13], infection of T cells with the SARS-CoV-2 [14], and downregulation of genes involved in T cell activation and function due to SARS-CoV-2 infection [15]. This study did not examine inflammatory cytokines such as IL-6 and TNF-α or T-cell counts. However, CRP is a nonspecific acute-phase protein induced by IL-6 [16], and CRP was significantly higher in the group with oxygen demand in this study. Therefore, it is highly likely that inflammatory cytokines are involved in the appearance of oxygen demand.

Liver injury is a well-known pathologic feature of COVID-19, with systematic reviews reporting the incidence of elevations in AST from 2.5% to 50.0% and alanine aminotransferase from 2.5% to 61.1% [17]. According to a previous report, a liver biopsy specimen from a patient who died due to severe COVID-19 showed hepatic steatosis, mild lobular and portal inflammation [18,19]. Concerning liver injury in COVID-19, immune-mediated damage as a result of the severe inflammatory response following SARS-CoV-2 infection [20], direct cytotoxicities as a result of active viral replication in hepatic cells [21], and anoxia [22] are thought to be involved. A previous report showed that L/S was reduced in cases that led to severe disease than in those that did not [23]. Therefore, it is possible that a decreased L/S indirectly reflects that hepatic steatosis and mild lobular and portal inflammation result from liver damage due to the above. On the other hand, underlying preexisting liver disease is a risk factor for increased severity of COVID-19 [24]. In our study, L/S before SARS-CoV-2 infection was not evaluated, and it is unclear whether the decrease in L/S was present before SARS-CoV-2 infection. The relationship between L/S and oxygen demand is not a clear conclusion, but the decrease in L/S is an objective indicator of the presence of fatty liver. Chang et al. demonstrated that fatty liver was positively asso-

ciated with an increased risk of severe COVID-19, requiring mechanical ventilation, admission to the intensive care unit (ICU), and high-flow oxygen therapy [25]. Moreover, a previous study reported increased hepatic expression of the SARS-CoV-2 entry points angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) in individuals with fatty liver [26]. Therefore, it has been noted that more ACES and TMPRSS2 in patients with fatty liver may facilitate SARS-CoV-2 entry into cells and lead to the progression to severe COVID-19. Hence, we should consider the possibility of progression to severe disease in patients with decreased L/S.

Abdominal circumference was also an independent predictor of oxygen demand in this present study. Obesity has been a risk factor for severe disease in previous studies [27,28], and abdominal circumference is an objective value that reflects obesity. However, it is noteworthy that the group with oxygen demand had significantly more visceral fat than those without oxygen demand. Previous studies have reported that visceral fat, but not subcutaneous fat, is a factor in the severity of COVID-19 [29–31], which is consistent with the results of this study. Furthermore, visceral fat was more strongly correlated with COVID-19 severity than BMI and subcutaneous fat [6,32], suggesting that visceral fat has some relationship to COVID-19 severity. In obese patients, visceral adipocytes secrete IL-6 and increase the production and release of leptin, which enhances the pro-inflammatory state [33,34]. Conversely, subcutaneous fat produces and secretes adiponectin, which acts against inflammatory conditions by suppressing the secretion of IL-6 and TNF-α and increasing the production of anti-inflammatory cytokines [35]. It is known that adiponectin decreases as visceral fat increases, and furthermore, it has been reported that adiponectin is decreased in COVID-19 compared to healthy controls, even when BMI matched [36]. Therefore, high visceral fat may be one of the key triggers for the underlying exacerbated inflammatory state associated with severe COVID-19.

It should be noted here that the present study measured visceral fat under the diaphragm. Previous studies were measured between the third and fourth lumbar vertebrae or at the first lumbar vertebrae. However, visceral fat remained significantly associated with metabolic syndrome regardless of measurement sites between T10–T11 and L5–S1 [37]. Thus, there is a certain validity to the association between visceral fat under the diaphragm and oxygen demand.

Managing all COVID-19 patients in the hospital is impossible, and we need to triage patients progressing to severe disease appropriately. In this study, patients with oxygen demand had larger abdominal circumference under the diaphragm and D-dimer, lower L/S and lymphocyte count. Therefore, if those patients are infected with COVID-19, they are more likely than those without to experience the emergence of oxygen demand. Consequently, they should be managed with pharmacotherapeutic intervention or strictly inpatient management from earlier when there is no oxygen demand.

This study has several limitations. First, this is a retrospective design and a small number of patients, leading to biased results. Thus, a large-scale multicenter survey with additional researchers is required. Second, since the study was limited to inpatients and outpatients were excluded, the proportion of severe patients and fatality rates may differ from the total infected population. Third, we did not evaluate the thoracic imaging characteristics of COVID-19. Fourth, we only assessed CT images on admission. The previous report demonstrated the changes in hepatic attenuation during the course of the disease in COVID-19 patients [23]. Therefore, the CT attenuation value may have changed with the time elapsed since the onset of the disease, which may have affected the results.

5. Conclusion

L/S, lymphocyte count, D-dimer, and abdominal circumference may predict the appearance of oxygen demand. Therefore, paying attention to L/S as well as laboratory examinations and comorbidities may be possible to extract patients with the more severe disease with greater accuracy.

Funding

Author contributions

H.N.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft; S.S (Shogo Sakurai): Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing; S.S (Syuichi Sugiyama): Data curation. K.S.: Data curation. K.O.: Data curation. Y.K. (Yoshihiro Kitahara): Conceptualization, Data curation. S.T.: Conceptualization, Data curation. T.M.: Conceptualization, Data curation. M.S.: Conceptualization, Data curation. A.Y.: Conceptualization, Data curation. T.A.: Conceptualization, Data curation, Formal analysis, Methodology. S.M.: Conceptualization, Data curation. K.A.: Conceptualization, Data curation, Formal analysis, Methodology. T.S.: Conceptualization, Supervision, Writing - review & editing.

Data available statement

Research data are not shared.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Shizuoka General Hospital (SGHIRB#2022017).

Informed consent

The Board waived patient approval or informed consent because the study was a retrospective review of patient records.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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