D-dimer level and lymphocyte to white blood cell count ratio could be a predictor of mechanical ventilation therapy in patients with coronavirus disease 2019

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Abstract Some symptomatic patients with coronavirus disease 2019 (COVID-19) develop acute respiratory failure with mechanical ventilation support. Therefore, identifying patients who tend to experience respiratory deterioration is of great importance. We investigated blood markers upon hospital admission that could predict respiratory illness in patients with COVID-19. This retrospective observational study included 148 patients with COVID-19 admitted to our hospital. All blood marker levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, white blood cells (WBCs), and lymphocytes were measured on admission in 148 patients. Patients were divided into the severe group (SVG), requiring mechanical ventilation therapy, and the non-severe group (nSVG). The levels of CRP, LDH, D-dimer and WBC count were significantly higher, and the lymphocyte count and lymphocyte-to-WBC count ratio (LWR) were significantly lower in the SVG than in the nSVG. The area under the receiver operating characteristic curve for CRP, LDH, D-dimer and LWR were high in the SVG than in the nSVG. The area under the receiver operating characteristic curve for CRP, LDH, D-dimer and LWR showed high values of 0.69, 0.70, 0.70, and 0.74, respectively. The age-adjusted odds ratios of D-dimer and LWR were high (5.5 [1.9–15.9] and 5.6 [2.2–14.3], respectively). D-dimer level and LWR upon admission were highly predictive of mechanical ventilation support in patients with COVID-19.

Keywords novel coronavirus disease 2019, D-dimer, lymphocyte to white blood cell ratio, cytokine storm, respiratory failure

1. Introduction

The novel coronavirus disease 2019 (COVID-19) pandemic has produced a huge impact on public health and the socioeconomy. Many people suffer from this emerging infectious disease worldwide. While 30–60% of COVID-19 cases result in asymptomatic or mild infection, 5% of symptomatic cases develop acute respiratory failure requiring intensive care during the clinical course [1]. Therefore, identifying patients who are likely to experience respiratory deterioration is of great importance. Based on the pathophysiology of COVID-19, which includes a hyperinflammatory state and multiorgan dysfunction, some studies indicate that a couple of inflammatory and biochemical markers predict severe outcomes in patients with COVID-19 [2, 3]. The lymphocyte count can also be associated with a poor prognosis for COVID-19 [4]. However, there are some studies in which laboratory marker values are not evaluated upon hospital admission [5, 6]. Thus, it is insufficient to identify reliable blood markers to predict respiratory deterioration upon admission. In addition to some inflammatory markers, the lymphocyte to white blood cell count ratio (LWR), which consists of two markers similar to lymphocyte percentage, could predict respiratory distress more precisely than either of the markers. Investigating the beneficial laboratory marker upon admission for predicting severe outcome in patients with COVID-19 could contribute to an adequate decision on medical intervention. The study aimed to explore the predictive ability of laboratory markers, including LWR, upon admission for respiratory illness in patients with COVID-19.

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2. Materials and Methods

Study design and participants

This was a single-center retrospective observational study. This study was approved by the local ethics committee of the Otsu City Hospital (No. 70). A total of 308 patients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using real-time polymerase chain reaction (PCR) from a nasopharyngeal swab were admitted to our hospital between December 23, 2020 and August 31, 2021. Patients aged <18 years, with missing baseline and laboratory data, undergoing regular dialysis, with malignant cancer, infected by human immunodeficiency virus (HIV), or admitted only for receiving neutralizing monoclonal antibody treatment for COVID-19 were excluded. Patients undergoing regular dialysis and those with malignant cancer can often present with a high D-dimer level, which has been demonstrated by several studies [7, 8]. Also, the lymphocyte counts of patients with HIV infection can progressively decrease. Thus, patients with these diseases and those undergoing dialysis were excluded in this study. Ultimately, 148 patients were included in the final analysis.

Data collection

Information on the demographic characteristics, underlying comorbidities, laboratory findings, time from symptom onset to admission, time from admission to bronchial intubation or initiation of nasal high-flow oxygen therapy, and severity of COVID-19 was collected from the electronic medical records of the patients. For the patients transferred from other hospitals, the laboratory values measured at the time of admission to the previous hospital were collected. Laboratory values measured upon admission included C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer levels, white blood cell (WBC) count, and lymphocyte count. The severity of COVID-19 was defined into three categories in accordance with the diagnosis and treatment guidelines for novel coronavirus disease recommended by the Ministry of Health, Labor and Welfare of Japan: mild: light symptoms such as fever and fatigue without abnormality of chest computed tomography (CT) findings; moderate: respiratory symptoms including cough and shortness of breath with pneumonia CT images requiring supplemental oxygen therapy; and severe: tachypnea, percutaneous oxygen saturation (SpO2) ≤93% under rest state and respiratory failure requiring non-invasive or invasive mechanical ventilation therapy due to COVID-19 pneumonia. In this study, supplemental oxygen therapy was initiated when the patient’s SpO2 was less than 94%. In addition, high-flow oxygen therapy was initiated for patients whose SpO2 was less than 94% with an inspired oxygen (O2) amount of 5 L/min masks. When the respiratory condition deteriorated, for which a fraction of inspired oxygen ≥0.6 was needed to maintain the patient’s SpO2 more than 93% with tachypnea and forced breathing, invasive mechanical ventilation was initiated.

Laboratory analysis of blood samples

Blood samples were centrifuged at 3,000 rpm for 5 min. CRP and LDH levels were measured using a TBA-FX8 instrument (Canon Medical Systems, Tochigi, Japan) using latex turbidimetric and enzymatic reactions, respectively. D-dimer levels were determined using latex-enhanced photometric immunoassay using a CS2100i automatic coagulation analyzer (Sysmex, Kobe, Japan). WBC and lymphocyte counts were determined using a DHX 900 hematology analyzer (Beckman Coulter, Tokyo, Japan).

Statistical analysis

Categorical variables were presented as frequency and percentage, and the χ² test or Fisher’s exact test was used to compare the differences among the groups. Normal and non-normally distributed continuous variables were expressed as mean ± standard deviation and median (interquartile range) and were analyzed using the t-test and Mann-Whitney U-test, respectively. Statistical significance was set at P < 0.05. The predictive value was evaluated by measuring the area under the curve (AUC). The optimal cut-off point was determined using the Youden index. Odds ratios (ORs) were estimated using logistic regression analysis. Statistical analyses were performed using the R software package (version 4.0.3, R Core Team. R: Language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Patient characteristics

Among the 308 eligible patients, those lacking laboratory data (n = 91), younger than 18 years (n = 21), undergoing regular dialysis treatment (n = 7), with malignant cancer (n = 8), infected with human immunodeficiency virus (n = 1), and admitted only for receiving neutralizing monoclonal antibody therapy for COVID-19 (n = 32) were excluded. In total, 148 patients were included in this study (Figure 1).

Twenty-five patients were assigned to the severe group (SVG), and 123 patients (mild: 76 patients, moderate: 47 patients) were allocated to the non-severe group (nSVG). In the SVG, 23 patients required invasive mechanical ventilation, whereas the remaining two patients demanded a type of non-invasive mechanical ventilation, nasal high-flow oxygen therapy. The median age was 55 years (range,
44–69 years) among 148 patients and was significantly higher in the SVG than in the nSVG (P = 0.04, Table 1). There were no significant differences in sex or body mass index between the two groups. The most common comorbidity was hypertension (31.8%), which was more frequently observed in the SVG than in the nSVG (P = 0.002, Table 1). None of the patients were diagnosed with deep-vein thrombosis or pulmonary embolism on admission or had a past medical history of these conditions. Regarding the medications prior to admission to the hospital, one patient used anticoagulant medications and nine patients used antiplatelet medications. There was no significant difference in the prevalence rates of anticoagulant and antiplatelet medications prior to admission observed between the two groups (Table 1). Furthermore, none of the patients were administered steroids or anti-viral drugs for COVID-19 prior to admission. No significant difference in the median time from onset to admission was found between the two groups (Table 1). More patients in the SVG were transferred to our hospital from other hospitals than in the nSVG (P < 0.001; Table 1). The median time from admission to bronchial intubation or initiation of nasal high-flow oxygen therapy was 4 days (Table 1). In the SVG, six patients required invasive mechanical ventilation on the day of admission to the hospital. The mean arterial partial pressure of oxygen/fraction of inspired oxygen (P/F ratio) immediately before mechanical ventilation in the SVG was 149.

Laboratory parameters in patients with COVID-19

The hematological characteristics of patients are shown in Table 2. The levels of CRP, LDH, D-dimer, lymphocytes, WBC, and LWR, were significantly different between the two groups.

ROC analysis was performed to assess the diagnostic value of these parameters for severe conditions. The AUC value of CRP, LDH, D-dimer, and LWR showed a high value of 0.69 [0.58–0.80], 0.70 [0.58–0.81], 0.70 [0.59–0.82] and 0.74 [0.63–0.84] with the cut-off point of 3.6, 290, 1.2, and 0.15, respectively (Table 3).

To evaluate the association with the outcome in this study, the OR value of each marker for the optimal cut-off point was calculated. The crude ORs of D-dimer and LWR were high (5.8 [2.3–14.7] and 5.5 [2.2–13.8], respectively). There was a significant difference in the median ages of the two groups. Thus, the adjusted OR of each marker for age was evaluated. The adjusted ORs of D-dimer and LWR were also high (Table 4).
Table 1 Clinical characteristics between the two groups.

| Baseline characteristics          | Total (n = 148) | Severe Case |
|-----------------------------------|----------------|-------------|
| Median age, y (IQR)               | 55 [44–69]     | 65 [52–72]  |
| Male sex, n (%)                   | 88 (59.5%)     | 18 (72.0%)  | 0.186 |
| Median BMI, kg/m² (IQR)           | 24.4 [21.5–26.8] | 26.3 [22.3–29.3] | 0.113 |

Comorbidities

| Hypertension, n (%)               | 47 (31.8%)     | 15 (60.0%)  | 0.002 |
| Coronary artery disease, n (%)    | 3 (2.0%)       | 2 (8.0%)    | 0.074 |
| Diabetes mellitus, n (%)          | 29 (19.6%)     | 8 (32.0%)   | 0.100 |
| Chronic obstructive pulmonary disease, n (%) | 8 (5.4%)     | 1 (4.0%)    | 1.000 |
| Bronchial asthma, n (%)           | 6 (4.1%)       | 0 (0%)      | 0.590 |
| Chronic kidney disease (excluded end-stage renal disease), n (%) | 6 (4.1%)     | 2 (8.0%)    | 0.267 |

Medications prior to admission

| Anticoagulant, n (%)              | 1 (0.7%)       | 0 (0%)      | 1.000 |
| Antiplatelet, n (%)               | 9 (6.1%)       | 3 (12%)     | 0.178 |

Median time from onset to admission, days (IQR)

| Median time from admission to bronchial intubation or initiation of high-flow oxygen therapy, days (IQR) | 4 [1–5] |

Categorical variables were presented as frequency and percentage. Non-normal distributed continuous variables were showed as median and interquartile range, respectively. P < 0.05 were considered significant. BMI: body mass index; IQR: interquartile range

Table 2 The comparisons of each laboratory parameter between the two groups.

| Laboratory parameters          | Total (n = 148) | Severe Case |
|--------------------------------|----------------|-------------|
| Median CRP level, mg/dl (IQR)  | 3.5 [0.9–8.1]  | 7.9 [3.6–11.6] | 0.003 |
| Median LDH level, IU/L (IQR)   | 257 [204–351]  | 333 [235–460] | 0.002 |
| Median D-dimer level, µg/ml (IQR) | 0.5 [0.2–0.9] | 1.0 [0.5–1.3] | 0.001 |
| Median Lymphocyte count, /mm³ (IQR) | 864 [652–1166] | 688 [567–935] | 0.044 |
| Median WBC count, ×10³/mm³ (IQR) | 4.8 [3.6–5.7] | 5.7 [4.7–7.5] | 0.007 |
| Mean Lymphocyte/WBC ratio (±SD) | 0.20 ± 0.09   | 0.14 ± 0.06  | <0.001 |

Normal and non-normal distributed continuous variables were expressed as mean and standard deviation or median and interquartile range, respectively. P < 0.05 were considered significant. IQR: interquartile range; SD: standard deviation; CRP: C-reactive protein; LDH: lactate dehydrogenase; WBC: white blood cell

Table 3 Diagnostic characteristics of each marker to predict respiratory failure with mechanical ventilation.

| Variable                      | AUC (CI)     | Cutoff | Sensitivity (%) | Specificity (%) |
|-------------------------------|--------------|--------|-----------------|-----------------|
| CRP level (mg/dl)             | 0.69 [0.58–0.80] | 3.60   | 76.0 [54.9–90.6] | 57.7 [48.5–66.6] |
| LDH level (IU/L)              | 0.70 [0.58–0.81] | 290    | 68.0 [46.5–85.1] | 65.9 [56.8–74.2] |
| D-dimer level (µg/ml)         | 0.70 [0.59–0.82] | 1.20   | 48.0 [27.8–68.7] | 86.2 [78.8–91.7] |
| Lymphocyte count (/mm³)       | 0.63 [0.50–0.75] | 704    | 60.0 [38.7–78.9] | 73.2 [64.4–80.8] |
| WBC count (×10³/mm³)          | 0.67 [0.54–0.80] | 5.10   | 72.0 [50.6–87.9] | 61.8 [52.6–70.4] |
| Lymphocyte/WBC ratio          | 0.74 [0.63–0.84] | 0.15   | 64.0 [42.5–82.0] | 76.4 [67.9–83.6] |

CRP: C-reactive protein; LDH: lactate dehydrogenase; WBC: white blood cell; AUC: area under the curve; CI: 95% confidence interval
lymphocyte count and LWR were significantly lower in LDH, D-dimer, and WBC were significantly higher, and were measured upon hospital admission, levels of CRP, were decreased lymphocyte counts [11]. Other previous studies suggested that severe COVID-19 cases tended to have decreased lymphocyte counts [11]. Other previous studies with severe and fatal diseases had increased WBC and our results.

Discussion

In this retrospective study in which laboratory markers were measured upon hospital admission, levels of CRP, LDH, D-dimer, and WBC were significantly higher, and lymphocyte count and LWR were significantly lower in the SVG than in the nSVG. This result indicates that these laboratory parameters were associated with the severity of COVID-19 infection. Furthermore, our data, in which the AUC of LDH, D-dimer, and LWR in predicting progression to a severe condition was ≥0.7, suggested that these parameters may predict respiratory failure with mechanical ventilation therapy. Additionally, the OR of D-dimer and LWR showed high values, indicating consistency with the AUC results.

The inflammatory response plays an important role in severe and critical COVID-19 cases, which show rapid deterioration of lung lesions and result in respiratory illnesses, such as acute respiratory distress syndrome (ARDS). Viral infection induces a series of immune responses that lead to a cytokine storm. Based on the cytokine response, previous studies demonstrated that CRP and LDH could be used as independent factors to predict disease severity [9, 10]. An inflammatory cytokine storm, for which interleukin-6 (IL-6) acts as the primary trigger, can cause respiratory distress in COVID-19. Following IL-6, CRP is a non-specific acute-phase protein produced in the liver, leading to a hyperinflammatory state [10]. LDH, a biochemical marker, is expressed in the cytoplasm of all human tissues, with the highest levels in the heart, liver, lungs, muscles, and kidneys, and is considered a general indicator of acute or chronic tissue damage. Thus, this enzyme is also regarded as an inflammatory marker induced by acute and severe lung damage. These pathophysiological reactions indicate that CRP and LDH can be used to identify patients at high risk of acute respiratory failure, which is consistent with our results.

PONTI ET AL. demonstrated that patients with COVID-19 with severe and fatal diseases had increased WBC and decreased lymphocyte counts [11]. Other previous studies suggested that severe COVID-19 cases tended to have lower lymphocyte count and lymphocyte percentage and higher leukocyte counts than mild cases, resulting from dysregulation of the immune response [12, 13]. Similar to recent studies, in our study, severe patients with COVID-19 showed significantly higher WBC and lower lymphocyte counts and LWR than non-severe cases. In particular, LWR, a combined parameter of lymphocytes and WBCs, showed a high AUC value of 0.74 [0.63–0.84] and a high age-adjusted OR value of 5.6 [2.2–14.3]. SARS-CoV-2 mainly infects lymphocytes, especially T lymphocytes [12]. Lymphocytes express the angiotensin-converting enzyme 2 receptor, which is speculated to be used for direct cell invasion by the virus that possibly targets lymphocytes. Viral infection may cause persistent consumption of lymphocytes, leading to a decrease in peripheral lymphocyte count.

Under extreme inflammatory conditions in patient with COVID-19, patients exhibit abnormal coagulation. A sustained inflammatory response could activate the coagulation cascade, leading to D-dimer production, which is induced when plasmin cleaves fibrin to break down clots [6]. Wu et al. showed that high D-dimer levels are associated with ARDS risk and the progression from ARDS to death [14]. Moreover, a previous study on patients with COVID-19 reported that D-dimer concentrations above 1 μg/mL are related to an 18 times increased OR for fatal outcomes, which means that a hypercoagulable state could contribute to the severity of the disease and increase death [15]. Importantly, autopsy data from seven patients who died from COVID-19 indicated that the lungs from patients with COVID-19 had widespread vascular thrombosis with microangiopathy [16]. McGonagle et al. suggested that diffuse intravascular coagulopathy associated with COVID-19 could be typical in the lungs in the early stage of COVID-19 and could be different from disseminated intravascular coagulation (DIC) [17]. Cases that develop overt systemic DIC are likely to be restricted to the late-stage COVID-19 clinical course, representing multiorgan dysfunction. This can be explained by the fact that platelet counts and fibrinogen concentrations are not substantially reduced in patients with COVID-19, despite remarkably increased D-dimer levels. Our study indicated that D-dimer showed a high specificity value of 86.2% [78.8–91.7] with a corresponding optimal cut-off value of 1.2 and showed an age-adjusted

| Variable          | Crude OR (CI)   | P value  | Age-adjusted OR (CI) | P value |
|-------------------|-----------------|----------|----------------------|---------|
| CRP               | 4.3 [1.6–11.6]  | 0.004    | 4.2 [1.5–11.3]        | 0.005   |
| LDH               | 4.1 [1.6–10.3]  | <0.001   | 4.2 [1.6–10.7]        | 0.003   |
| D-dimer           | 5.8 [2.3–14.7]  | <0.001   | 5.5 [1.9–15.9]        | 0.002   |
| Lymphocyte        | 4.1 [1.7–10.0]  | <0.001   | 4.1 [1.7–10.2]        | 0.002   |
| WBC               | 4.2 [1.6–10.7]  | 0.003    | 4.0 [1.5–10.3]        | 0.005   |
| Lymphocyte/WBC ratio | 5.5 [2.2–13.8]  | <0.001   | 5.6 [2.2–14.3]        | <0.001  |

CRP: C-reactive protein; LDH: lactate dehydrogenase; WBC: white blood cell; OR: odds ratio; CI: 95% confidence interval
OR value of 5.5 [1.9–15.9]. This result may reveal that the higher D-dimer levels upon admission in the early stage of the clinical course reflect pulmonary vascular thrombosis, which develops into respiratory failure.

This study had some limitations. First, this was a single-center retrospective observational study. Thus, the number of patients included in this study was small, and more than 50% of the eligible patients were excluded due to a lack of laboratory values. In this study, each physician determined which blood markers of each patient should be examined according to patient’s condition at the time of admission to the hospital, which could induce a selection bias. Second, although only six parameters related to inflammatory conditions were measured, there may be more predictive markers for severe respiratory illness. Finally, while the P/F ratio as a respiratory function parameter may be more accurate for determining the initiation of supplemental oxygen and mechanical ventilation therapy than SpO₂, this respiratory parameter was not evaluated in all patients admitted to our hospital.

5. Conclusion

D-dimer level and LWR upon hospital admission predict mechanical ventilation therapy for acute respiratory failure in patients with COVID-19. However, further studies are needed to confirm the validity of these parameters in association with COVID-19 respiratory failure.

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Institutional Review Board Statement The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the local ethics committee of Otsu City Hospital (No. 70).

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Conflict of Interest The authors declare no conflicts of interest.

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