Choice of respiratory therapy for COVID-19 patients with acute hypoxemic respiratory failure: a retrospective case series study (#80506)

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Choice of respiratory therapy for COVID-19 patients with acute hypoxemic respiratory failure: a retrospective case series study

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Background: Our aim was to devise a better criterion associated with the cut-off of the ratio of oxygen saturation (ROX) index for high-flow nasal cannula (HFNC) oxygen therapy and mechanical ventilation (MV) initiation. We retrospectively analyzed the ROX index 6 hours after the initiation of HFNC and lung infiltration volume (LIV) calculated from chest computed tomography (CT) images in coronavirus 2019 (COVID-19) patients with acute hypoxemic respiratory failure. **Methods:** We re trospectively analyzed the data for 59 COVID-19 patients with acute hypoxemic respiratory failure in our facility to determine the cut-off value of the ROX index for respiratory therapeutic decisions and the significance of radiological evaluation of pneumonia severity. The physicians chose either HFNC or MV, and the outcomes were retrospectively analyzed using the ROX index after HFNC introduction. The LIV was calculated using chest CT images at admission. **Results:** Among the 59 patients who required high-flow oxygen therapy with HFNC at admission, 24 were later transitioned to MV; the remaining 35 patients recovered. Four of the 24 patients in the MV group died, and the ROX index values of these patients were 9.8, 7.3, 5.4, and 3.0, respectively. These index values indicated that the ROX index of half of the patients who died was higher than the reported cut-off values of the ROX index, which range from 2.7–5.99. The cut-off value of the ROX index 6 hours after the start of HFNC, which was used to classify the management of HFNC or MV as a physician’s clinical decision, was approximately 6.1. The LIV cut-off value on chest CT between HFNC and MV was 35.5%. Using both the ROX index and LIV, the cut-off classifying HFNC or MV was obtained using the equation, LIV = 4.26 × (ROX index) + 7.89, and the area under the curve improved to 0.94 with a sensitivity of 0.79 and specificity of 0.91 using both the ROX index and LIV. **Conclusion:** The accuracy of clinical decisions could be improved by adding the LIV calculated from chest CT images rather than by evaluating the ROX index alone.

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Abstract

Instead of mentioning methods in b/g, you can give some b/g info on the use of cut-off; for physicians not from ICU, the abstract may not provide enough info; it can be explained better

Background: Our aim was to devise a better criterion associated with the cut-off of the ratio of oxygen saturation (ROX) index for high-flow nasal cannula (HFNC) oxygen therapy and mechanical ventilation (MV) initiation. We retrospectively analyzed the ROX index 6 hours after the initiation of HFNC and lung infiltration volume (LIV) calculated from chest computed tomography (CT) images in coronavirus 2019 (COVID-19) patients with acute hypoxemic respiratory failure.

Methods: We retrospectively analyzed the data for 59 COVID-19 patients with acute hypoxemic respiratory failure in our facility to determine the cut-off value of the ROX index for respiratory therapeutic decisions and the significance of radiological evaluation of pneumonia severity. The physicians chose either HFNC or MV, and the outcomes were retrospectively analyzed using the ROX index after HFNC introduction. The LIV was calculated using chest CT images at admission.

Results: Among the 59 patients who required high-flow oxygen therapy with HFNC at admission, 24 were later transitioned to MV; the remaining 35 patients recovered. Four of the 24 patients in the MV group died, and the ROX index values of these patients were 9.8, 7.3, 5.4, and 3.0, respectively. These index values indicated that the ROX index of half of the patients who died was higher than the reported cut-off values of the ROX index, which range from 2.7–5.99. The cut-off value of the ROX index 6 hours after the start of HFNC, which was used to classify the management of HFNC or MV as a physician's clinical decision, was approximately 6.1. The LIV cut-off value on chest CT between HFNC and MV was 35.5%. Using both the ROX index and LIV, the cut-off classifying HFNC or MV was obtained using the equation, LIV = 4.26 × (ROX index) + 7.89, and the area under the curve improved to 0.94 with a sensitivity of 0.79 and specificity of 0.91 using both the ROX index and LIV.

Conclusion: The accuracy of clinical decisions could be improved by adding the LIV calculated from chest CT images rather than by evaluating the ROX index alone.

Introduction

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease currently causing a global pandemic. COVID-19 patients often present with mild symptoms; however, these may develop into more serious medical conditions, such as acute hypoxemic respiratory failure (AHRF) and septic shock, especially in older adults and patients with underlying illnesses. AHRF is a significant symptom in COVID-19 patients and requires the administration of high oxygen levels (Attaway et al. 2021; Berlin et al. 2020).

For mild AHRF associated with COVID-19, oxygen administration therapy using a nasal cannula or oxygen mask is the basic treatment strategy. However, for moderate or higher-severity AHRF, depending on the severity, high-flow nasal cannula (HFNC) oxygen therapy, mechanical ventilation (MV), or extracorporeal membrane oxygenation have been considered. Oxygen therapy with HFNC, which can provide a maximum oxygen flow of 60 L/min, has been used for COVID-19 patients who do not require MV (Frat et al. 2015; Mellado-Artigas et al. 2021a; Roca et al. 2016a). HFNC is more tolerable for patients than non-invasive ventilation (NIV) and MV (Panadero et al. 2020), and almost half of those who receive HFNC can be successfully weaned without the need for MV (Calligaro et al. 2020). However the use of HFNC in COVID-19 patients may delay the initiation of MV if respiratory failure worsens (Kang et al. 2015). The failure of HFNC has been associated with increased mortality compared with the failure of NIV and MV alone (Miller et al. 2022). Therefore, when treating COVID-19 patients with AHRF, it is critical to appropriately evaluate whether to continue treatment with HFNC or to initiate MV.

Since the beginning of the COVID-19 pandemic, which began in Japan in April 2020, clinicians have considered the risk factors that influence the course of the disease when choosing respiratory therapy. Among the physiological parameters, the ratio of oxygen saturation (ROX) index ($SpO_2 \times$ respiratory rate$^{-1} \times F_iO_2^{-1}$, which is the combination of percutaneous blood oxygen saturation, respiratory rate, and inspired oxygen concentration, respectively) is a useful indicator to evaluate the severity of AHRF in COVID-19 patients (Roca et al. 2019; Roca et al. 2016b). The cut-off value of the ROX index is a proposed criterion for discontinuing HFNC and initiating NIV or tracheal intubation for MV (Ferrer et al. 2021; Hu et al. 2020; Vega et al. 2022). However, although the ROX index could be a potential marker to identify patients with a higher risk of HFNC failure, the prediction efficiency is moderate, and the optimal cut-off value and the acquisition time of the ROX index continue to be discussed (Junhai et al. 2022). In fact, in our facility, as shown in this article, some patients died even if the ROX index was higher than the cut-off values reported by others. Conversely, other patients were saved using HFNC even if the ROX index was much lower than the cut-off values.

Since the start of the COVID-19 pandemic, the role of chest computed tomography (CT) in the management of COVID-19 patients has evolved in terms of the indications in the acute phase and the prediction of pathological conditions in the subacute phase (Komurcuoglu et al. 2022; Lyu et al. 2020; Machnicki et al. 2021; Sayeed et al. 2021). COVID-19 pneumonia is characterized by extensive infiltration shadows in the lungs on chest CT images. Thus, chest CT in COVID-19 patients has provided radiological information of the severity of pneumonia. Additionally, clinicians can make judgments about treatment options by assessing not only the oxygenation-associated physiological parameters but also other parameters associated with medical image analysis, such as the evaluation of pneumonia severity. In this study, in COVID-19 patients with AHRF, we retrospectively analyzed the ROX index 6 hours after the initiation of HFNC and other parameters, including lung infiltration volume (LIV) calculated from chest CT images. We devised a better criterion associated with the cut-off of the ratio of oxygen saturation (ROX) index for high-flow nasal cannula (HFNC) oxygen therapy and mechanical ventilation (MV) initiation.

Materials & Methods

The objectives or outcomes can be mentioned separately

Target patients and the choices of respiratory therapies

This study was a retrospective observational study accompanying the Kyoto Prefectural University of Medicine (KPUM) COVID-19 Registry Study (ERB-C-1810, approved by the Institutional Review Board of KPUM on 3 September 3, 2020). Informed consent was obtained from all subjects and/or their legal guardian(s), and all methods were performed in accordance with the relevant guidelines and regulations. The Kyoto Prefectural University of Medicine Hospital is a nationally accredited first-class infectious disease-designated hospital in Kyoto Prefecture, Japan. This hospital has been performing inpatient treatment for COVID-19 patients with severe respiratory failure, mainly via referral requests from other medical institutions in Kyoto Prefecture to control centers in Kyoto Prefecture. From April 2020 to September 2021, 188 patients diagnosed as COVID-19-positive were hospitalized (**Fig. 1**). Of these, 112 were mildly ill patients who did not require advanced oxygen therapy. Of the 76 patients who required high-flow oxygen therapy, after excluding 14 patients who had already been hospitalized and were receiving MV and 3 patients who did not receive MV because of palliative care, 59 patients who started HFNC therapy immediately after admission were the subjects of this study. HFNC therapy was started using Optiflow (Fisher & Paylek Healthcare, Auckland, New Zealand) to maintain a respiratory rate of less than 30 breaths per minute by adjusting oxygen flow and oxygen concentration. The indication for MV was empirically determined by the attending physicians in charge of the patient with reference to the patient's age, comorbidities, oxygenation assessment, and chest CT images. The major criteria were: hypoxemic respiratory failure with $SpO_2 < 90\%$ or a ratio of the partial pressure of arterial oxygen to FiO_2 of < 200 despite receiving the maximal FiO_2 possible with HFNC; hypercapnic respiratory failure accompanied by blood pH < 7.3; respiratory rate > 30 breaths per minute; and hypotension (systolic blood pressure < 90 mmHg) despite catecholamine and/or fluid administration. The following data were also collected at admission: age, gender, weight, height, body mass index (BMI), comorbidities (hypertension, diabetes, lung disease, heart disease, cerebrovascular disease), blood clinical laboratory data, pneumonia severity index (Fine et al. 1997), and Charlson comorbidity index (Charlson et al. 1987).

ROX index

The oxygen flow rate was adjusted according to the patient's body condition, and the concentration was adjusted so that SpO_2 was maintained at $\geq 95\%$ at rest. The ROX index was then calculated approximately 6 hours after admission.

Chest CT analysis

All patients underwent CT before transfer to our hospital or immediately after admission. 3D Slicer software (ver.4.11, https://www.slicer.org/) was used to calculate the ratio of lung infiltration volume (LIV) by chest CT image analysis (Balbi et al. 2021; Cattabriga et al. 2020; Digumarthy et al. 2019). According to each Hounsfield units value, the segmented lung images were color-coded using 1-mm-volume reconstructions. The LIVs were calculated and expressed as percentages. Chest CT images of the HFNC and MV groups were analyzed using 3D Slicer to determine the volume of the normal lung range and the ratio of the LIV (Lanza et al. 2020).

Logistic model and statistical analysis

SPSS (ver. 27; IBM Corp., Armonk, NY, USA) and the χ-squared test was used for statistical analysis. Using R programming language (R Foundation, Indianapolis, IN, USA), multiple binomial logistic regression analysis (MLRA) was performed. Open-source Python (ver. 3.8; https://www.python.org) with the Seaborn (https://seaborn.pydata.org) library was used for graphing.

Results

Patients' therapeutic backgrounds

The first wave of the COVID-19 pandemic started in April 2020 in Kyoto, and five pandemic waves occurred by September 2021. From December 2020, more active use of HFNC was promoted at our facility, and as a result, the number of patients who underwent HFNC or MV management increased gradually until September 2021, which was the end of the study period (**Fig. S1**). During the 18-month study period, among the hospitalized patients, three who were under HFNC therapy but who were not candidates for MV therapy were excluded from this study in accordance with the hospital's code of ethics. Fourteen patients had been mechanically ventilated under tracheal intubation by the time they were transferred to our hospital. The remaining 59 patients were the target of further analysis in this study. Of these patients, within 2.8 ± 3.6 days, 24 were considered indicated for MV and were changed to MV management under tracheal intubation. Comparing the primary data of the 35 patients who were successfully treated with HFNC (HFNC group) and the 24 patients who required MV (MV group), no statistically significant difference was detected for gender, age, body weight, height, and BMI (**Table 1**). Regarding the presence or absence of underlying disease, no statistically significant difference was detected (**Table S1**). The primary treatment was antiviral drugs, such as favipiravir or remdesivir, anti-immunotherapy, mainly with dexamethasone, and anticoagulant therapy with heparin. There was no significant difference in drug therapy between the two groups (**Table S2**). A multidisciplinary conference was held by the attending physician and infectious disease specialist, infectious disease control team, and intensive care specialist, and baricitinib, tocilizumab, and steroid pulse therapy were given as additional anti-immunotherapies when needed. No patients were treated with monoclonal antibodies and none were vaccinated.

The patients' blood laboratory test data showed significantly higher lactate dehydrogenase concentrations at admission in the MV group than those in the HFNC group (**Table 1**). The mean ROX index value in the HFNC group was significantly higher than that in the MV group (**Table 1**). Regarding the analysis of chest CT images by 3D Slicer, the LIVs and their proportions were significantly higher in the MV group compared with the HFNC group (**Table 1**). **Figure 2** and **Supplementary Video Clips A–F** show the analysis of the chest CT images of six cases with different pneumonia severity according to 3D Slicer. The period from onset to admission to our hospital and the period from onset to intervention with HFNC were significantly longer in the HFNC group than those in the MV group.

As a clinical outcome in both groups, the length of hospital stay was significantly longer in the MV group than that in the HFNC group. Patients in the HFNC group were intubated and transferred to the MV group if their respiratory status deteriorated. Therefore, no deaths occurred in the HFNC group; however, four patients died in the MV group (**Table S3**). In the HFNC group, HFNC was performed for an average of 7.1 ± 10.3 (range: 1–62) days. In the MV group, the average period from HFNC to MV was 2.8 ± 3.6 (range: 0–16) days, and this was followed by 15.2 ± 23.6 (range 2–97) days of MV.

The various cut-off levels of the ROX index and the clinical outcomes

As stated, no patients died among the 35 patients who received HFNC until their recovery (because patients who were initially receiving HFNC but who were later intubated owing to worsening respiratory status were subsequently assigned to the MV group). In contrast, 4 of the 24 patients in the MV group died. The ROX index values of these patients were 9.8, 7.3, 5.4, and 3.0, respectively, suggesting that the ROX index of half of the patients who died was higher than the reported cut-off values of the ROX index, which range from 2.7–5.99 (Prakash et al. 2021).

The MV group comprised seven patients with ROX index values ≥ 6, of whom five had LIV values ≥ 35.5%, indicating severe lung injury. Conversely, 2 of the 34 survivors in the HFNC group had a ROX index of ≤ 5. Therefore, the attending physicians selected respiratory therapy (HFNC or MV) without being bound only by the ROX index. When the cut-off value of the ROX index varied from 4 to 7 in increments of 0.1, we calculated the percentages of HFNC patients whose ROX index was ≤ the cut-off value and the rates of MV patients whose ROX index was > the cut-off value. The rates of HFNC patients with ROX index values ≤ the cut-off value and the rates of MV patients with ROX index values > the cut-off value crossed over at 25%, where the cut-off value of the ROX index was approximately 6.2 (**Fig. 3A**).

Next, we calculated the percentage of HFNC patients with LIV values ≤ 35.5 (we explained this LIV cut-off value in the next section) and ROX index ≤ the cut-off value and the rate of MV patients with LIV values > 35.5 and ROX index values > the cut-off value. The percentage lines of both HFNC and MV patients crossed over at 17%, where the cut-off value of the ROX index was approximately 6.1 (**Fig. 3B**). These results mean that the judging criteria for the cut-off value of the ROX index by the attending physician was approximately 6.1–6.2, which is slightly higher than the reported cut-off value of the ROX index (2.7–5.99) (Prakash et al. 2021). This finding suggests that adding LIV evaluation to the treatment policy decision may better contribute to reducing false positives and false negatives compared with setting a more stringent ROX index cut-off value. The authors can elaborate how this finding suggests this conclusion

MLRA of the indications for HFNC and MV

MLRA was performed using the five factors involved in the decision to initiate MV management: the period from onset to admission to our hospital, the period from onset to the initiation of HFNC, laboratory examination data (lactate dehydrogenase concentration), a lung injury parameter (LIV) from chest CT imaging, and the ROX index (**Table 2**). Note that we did not include characteristics related to history and underlying diseases for the MLRA because these diagnostic criteria are ambiguous (**Table S1**). Covariates with *p*-values ≥ 0.05 were excluded from the regression analysis (**Table 2**). As a result, the results for the ROX index (odds ratio, 0.32; 95% confidence interval (CI), 0.13–0.77; p=0.012) and LIV on chest CT images (odds ratio, 1.25; 95% CI, 1.06–1.46; p=0.008) were significant. Note that the pairs plot shows significantly different distributions for the ROX index and LIV when the patients were divided into two groups (MV group and HFNC group) (**Fig**. **S1**). Next, MLRA was repeated using only the ROX index and LIV. Optimal cut-off values for the ROX index and LIV were then determined for the two management groups (38 patients who underwent MV and 35 patients who were treated with HFNC alone). As a result, the boundary score (SCORE) for classifying patients selected for MV was calculated as SCORE = −1.50–0.81 × [ROX index] + 0.19 × [LIV]. The ROX index and LIV cut-off values were 6.1 and 35.5%, respectively.

We plotted all 59 patients by ROX index and LIV values with color codes demonstrating HFNC or MV (cases of transition from HFNC to MV), and drew the distribution density as a kernel density estimation (KDE) plot (**Fig. 4A)**. The KDE plot indicated that higher patient density was associated with more concentrated patient distribution. Next, the KDE plot was drawn separately for the HFNC and MV groups, namely 35 patients who were treated with HFNC alone and 24 patients who underwent MV (**Fig. 4B**).

what inference done drawn from KDE?

Cut-off by ROX index and/or LIV for the classification of HFNC or MV

With 6.1 as the cut-off for the ROX index, 18 (75.0%) of the 24 patients managed with MV were classified as the severe group, and 32 (80.0%) of the 35 patients managed with HFNC were classified as the mild group (**Table S4**). In contrast, when the LIV cut-off was 35.5%, 18 (75.0%) of the 24 patients managed with MV were classified as the severe group, and 31 (88.6%) of the 35 patients managed with HFNC were classified as the mild group (**Table S4**). As shown in **Fig. 3**, compared with the vertical cut-off line with a ROX index of 6.1 alone, the cut-off line by MLRA SCORE LIV = 4.26 × (ROX index) + 7.89 was tilted in the positive direction of the ROX index and the LIV axes. When using the SCORE cut-off, 19 (79.2%) of the 24 the patients managed with MV were classified as the severe group, and 32 (91.4%) of the 35 patients managed with HFNC were classified as the mild group (**Table S4**). These findings indicate that the left side (severe side) of the cut-off line of the ROX index is considered a good indication for MV and the right side (mild side) as a good indication for HFNC (**Table 3**). Patients located above the SCORE are more likely to require MV, even if the ROX index is ≥ 6.1.

When using the cut-off value of 6.1 for the ROX index to draw the receiver operating characteristic (ROC) curve using the prediction formula, the summary area under the curve (AUC) was 0.83 (95% CI, 0.73–0.94) with a sensitivity of 0.75, specificity of 0.80, accuracy of 0.78, positive likelihood ratio (PLR) of 3.75, negative likelihood ratio (NLR) of 0.31, and diagnostic odds ratio (DOR) of 12 for predicting MV therapy (**Fig. 5** and **Table 3**). From the ROC curve using the cut-off value of 35.5% for the LIV, the AUC was 0.89 (95% CI, 0.80–0.98), with a sensitivity of 0.75, specificity of 0.89, accuracy of 0.83, PLR of 6.56, NLR of 0.28, and DOR of 23. From the ROC curve created using with prediction formula using both the ROX index and LIV, the AUC was 0.94 (95% CI, 0.88–0.99), sensitivity was 0.79, specificity was 0.91, accuracy was 0.86, PLR was 9.24, NLR was 0.23, and DOR was 41 (**Fig. 5** and **Table 3**). These findings suggest, in terms of the accuracy rate, that classification by the MLRA SCORE cut-off line was better than that by the cut-off of the ROX index alone or LIV alone.
This MLRA analysis excluded gender, age, and BMI from the main factors influencing the need for MV, as stated. However, there are many reports in which these factors are involved in the aggravation of COVID-19. Therefore, we confirmed whether these factors affected the need for MV and whether they affected the grouping according to the three cut-offs. As a result, gender, age ≥ 65 years, and BMI > 25 were uniformly distributed in both the HFNC and MV groups (**Fig. S2** and **Table S5**). These commonly reported aggravating factors did not significantly affect the application of HFNC and MV in our patient cohort.

Discussion

Discuss/compare c/ diff CT severity score systems

In the choice of HFNC or MV management in the treatment of COVID-19, the ROX index was proposed as a clinical indicator (Roca et al. 2019; Roca et al. 2016b). However, the reported cut-off value of the ROX index ranges widely from 2.7 to 5.9 (Junhai et al. 2022). In an early study, the cut-off value 6–12 hours after receiving HFNC was reported as 4.88, with a 95% CI of 4.2–5.4 (Roca et al. 2019; Roca et al. 2016b). A meta-analysis of COVID-19 patients with AHRF suggested that the ROX index is an excellent indicator for the prediction of HFNC failure although the cut-off value of the index varied from 2.7 to 5.99 (Prakash et al. 2021). Other recent meta-analyses demonstrated that a high chance of successful therapy is expected if a patient's ROX index is > 5.4, and that patients are at a high risk of HFNC failure and should be considered to require escalation of respiratory support if the ROX index is < 4.2 (Zhou et al. 2022). Additionally, a cut-off value of the ROX index of > 5 indicates expected successful weaning from HFNC (Junhai et al. 2022).

In the ex-post analysis of the ROX index cut-off value in our case, a slightly higher value of 6.1 was detected, probably because the clinicians in charge made the decision to transition patients from HFNC to MV when the severity of the lung injury on CT images was high despite the fact that the ROX index exceeded 5. In fact, seven patients (20% of 35 HFNC patients) whose ROX index values were ≤ 6.0 successfully recovered with HFNC alone, and seven patients (29.1% of 24 MV patients) whose ROX index values were > 6.0 were treated with MV. Unfortunately, two of the patients with ROX values > 6.0 of died. These patients had significantly high lung injury severity. Therefore, choosing to initiate MV solely on the basis of the ROX index may create a high healthcare burden given the presence of COVID-19 patients with a variety of pathologies, and more complex criteria may be required to achieve higher sensitivity and specificity.

As an additional clinical parameter to support the ROX index in clinical judgment, lung injury severity assessment from chest CT images, as proposed in this case series, is one idea. However, we believe that there is room for further examination of the composite judgment criteria proposed by other researchers. For example, the prediction of the ROX index may be improved by combining the index with different parameters, such as the Sequential Organ Failure Assessment score (Mellado-Artigas et al. 2021b) and heart rate (Goh et al. 2020). HACOR, which is a prediction index for non-invasive MV failure (Duan et al. 2017), is an acronym for heart rate, acidosis, state of consciousness, oxygenation, and respiratory rate, and this index was reported to work successfully as a prediction index for MV in HFNC patients (Valencia et al. 2021).

In the present study, based on MLRA, the severity of lung injury calculated from chest CT images was added to the patient evaluation, with the ROX index. Patients with AHRF from COVID-19 pneumonia present with highly-variable pathophysiological characteristics, such as respiratory mechanics and responses to the prone position and recruitment maneuvers, despite a similar degree of hypoxemia (Rossi et al. 2022). Therefore, we suspected that some critically ill COVID-19 patients might require MV management even if their ROX index was higher than the reported cut-off value.

Notably, it is difficult to compare our data with other big data because our data were derived from a small number of patients at a single institution. Therefore, we do not propose a definitive cut-off value for the ROX index. Based on our experience in this case series, we suggest that it may be possible to construct a complex diagnostic criterion that will lead to better clinical judgment for respiratory therapy selection.

Conclusions

Our study demonstrates that, by evaluating the pathophysiology of COVID-19 respiratory distress by adding the extent of the anatomical severity of pneumonia via chest CT to the ROX index, more appropriate guidance for the choice of respiratory management, either HFNC or MV, can be achieved for severely ill COVID-19 patients. This study was a single-center retrospective study, and a prospective multicenter study of statistically-processed predictive probabilities is needed.

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ADDITIONAL INFORMATION AND DECLARATIONS

Funding

No funding was received.

Competing Interest

The authors declare that they have no competing interests.

Author Contributions

- Kazuki Sudo developed the initial idea for this study, analyzed the data and drafted the article, and approved the final draft.
- Kohsuke Kushimoto, Ryogo Yoshii, Kento Yuasa, Keita Inoue, and Masaki Yamasaki participated in the patient management, and approved the final draft.
- Kunihiko Kooguchi reviewed the article, provided suggestions for its improvement, and approved the final draft.
- Teiji Sawa took responsibility for designing the study, analyzed the data and drafted the article, and approved the final draft.

Human Ethics

This study was conducted in accordance with the guidelines of the Declaration of Helsinki. This study was a retrospective observational study accompanying the Kyoto Prefectural University of Medicine (KPUM) COVID-19 Registry Study (ERB-C-1810, approved by the Institutional Review Board of KPUM on 3 September 3, 2020). Informed consent was obtained from all subjects and/or their legal guardian(s), and all methods were performed in accordance with the relevant guidelines and regulations.

Data Availability

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Supplementary Information

The online version of this article contains supplementary material available at https://doi.org/XXXXXXXXX.

Additional file 1.

Table S1. Complications in the high-flow nasal cannula oxygen therapy and mechanical ventilation groups. **Table S2.** Therapeutic interventions in the high-flow nasal cannula oxygen therapy and mechanical ventilation groups. **Table S3.** Clinical outcomes in the high-flow nasal cannula oxygen therapy and mechanical ventilation groups after admission. **Table S4.** Classification by ratio of oxygen saturation index and/or lung infiltration volume, and high-flow nasal cannula oxygen therapy/mechanical ventilation ratios and mortality. **Table S5.** Classification by oxygen saturation index and/or lung infiltration volume, and the positive ratios of high-flow nasal cannula oxygen therapy or mechanical ventilation.

Additional file 2.

Fig. S1. Statistics of coronavirus 2019 (COVID-19) cases in Kyoto Prefecture, Japan and monthly COVID-19 patients in this study. **Fig. S2**. Pairs plot showing the difference in the distribution of each analysis factor when patients were divided into a mechanical ventilation group and a high-flow nasal cannulation oxygen therapy group, using ggpairs() in the GGally package in R. **Fig. S3**. Kernel density estimation of patient distribution.

Additional files 3.

Supplementary Video Clips (SupplementaryVideoClip1_A_LIV, SupplementaryVideoClip2_B_LIV, SupplementaryVideoClip3_C_LIV, SupplementaryVideoClip4_D_LIV, SupplementaryVideoClip5_E_LIV, SupplementaryVideoClip6_F_LIV).

Chest CT images are read with a 3D Slicer (https://www.slicer.org/) and classified into normal infiltration, blood vessels, and emphysema according to the volume of 1 mm^3 unit of CT concentration to calculate the ratio of lung infiltration volume (LIV). **A**. A patient who did not need oxygen administration. Most are normal findings. **B**. A patient who was successfully treated with low-flow oxygen. A slight infiltration shadow is seen on the dorsal side. **C**. A patient who was successfully treated with HFNC. Infiltration shadows are seen extensively on the dorsal side. This patient was effectively treated with prone position therapy. **D**. A patient who was treated with HFNC for several days but failed and was switched to MV. The patient was found to have diffused ventral shadows. Poor prone position therapy was not effective in this patient who failed to be treated with HFNC. **E**. A patient who was treated with HFNC but switched to MV on the same day. Extensive infiltration shadows were noted. **F**. A patient who was treated with HFNC for several days and moved to MV. Infiltration shadows are observed in most of the lung fields. This patient was unable to maintain oxygenation after initiation of MV and required extracorporeal membrane oxygenation. HFNC, high-flow nasal cannula; LIV, lung infiltration volume; MV, mechanical ventilation.

Additional file 4.

Supplementary data file (Excel file).

The raw data of all 59 patients is available in the supplementary files 4 (raw_data_f16.xlsx).

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Figure Legends

Fig. 1. Patient flowchart.

One hundred eighty-eight patients were referred to the University Hospital of Kyoto Prefectural University of Medicine from April 2020 to September 2021; 122 patients were mildly ill individuals who did not require high levels of oxygen therapy. Of the 76 severe COVID-19 patients who required high-flow oxygen therapy, 59 patients received HFNC therapy after admission after excluding 3 patients who did not receive MV because of palliative care and 14 patients who had already been hospitalized under MV. Thirty-five patients completed treatment with HFNC and 24 were intubated for management with MV. HFNC, high-flow nasal cannulation; MV, mechanical ventilation; HFNC→MV, cases transitioned from HFNC to MV.

Fig. 2. Chest CT images. Chest CT settings were as follows: voltage, 120 kV; tube current, 266 mA; slice thickness, 5.00 mm; window width, 1500 Hounsfield units (HU); window level, −600 HU. According to the different HU intervals, lung volumes were segmented and extracted as follows: emphysema (density between −1050 HU and −950 HU), normal lung ventilation (density between −949 HU and −750 HU), infiltration shadow (density between −749 HU and −400 HU), collapsed lung (density between −399 HU and 0 HU), and blood vessels and soft tissue (density between 1 HU and 1000 HU). Chest CT images were read with 3D Slicer

software and classified into normal infiltration, blood vessels, and emphysema according to the volume of 1 mm^3 unit of CT concentration. **A.** Findings in a patient who did not require oxygen administration. Most findings are normal findings. **B.** Findings in a patient who was successfully treated with low-flow oxygen therapy. A slight infiltration shadow is seen dorsally. **C.** Findings in a patient who was successfully treated with HFNC. Infiltration shadows are seen extensively dorsally. This patient was effectively treated in the prone position. **D.** A patient who was treated with HFNC for several days but failed this therapy and was transitioned to MV. The patient had diffuse ventral shadows on imaging. Therapy in the prone position was not effective in this patient. **E.** Findings in a patient who was treated with HFNC but who was transitioned to MV on the same day. Extensive infiltration shadows are noted. **F.** Findings in a patient who was treated with HFNC for several days and subsequently transitioned to MV. Infiltration shadows are observed in most of the lung fields. This patient was unable to maintain oxygenation after initiation of MV and required extracorporeal membrane oxygenation. CT, computed tomography; HFNC, high-flow nasal cannulation; MV, mechanical ventilation.

Fig. 3. The relationships between the cut-off values of the ROX index and the respiratory therapeutic choice (HFNC or MV). **A.** The percentages of HFNC cases with a ROX index ≤ ROX-cut-off and MV cases with a ROX index > ROX-cut-off. **B.** The percentage of HFNC cases with an LIV value ≤ 35.5 and ROX index ≤ ROX- cut-off, and the percentage of MV cases with an LIV > 35.5 and ROX index > ROX- cut-off. HFNC, high-flow nasal cannula oxygen therapy; LIV, lung infiltration volume; MV, mechanical ventilation; ROX index, ratio of oxygen saturation index.

Fig. 4. Kernel density estimation of patient distribution, HFNC, and ventilator management. The cut-off to classify patients with HFNC and ventilatory management was (LIV) = 4.51 × (ROX index) + 1.75. The ROX index and LIV values were significant in the multiple logistic regression analysis. **A.** Kernel density plot using all 59 patients' data. **B.** Kernel density plots for the MV and HFNC groups. HFNC, high-flow nasal cannula; MV, mechanical ventilation; HFNC→MV, cases transitioned from HFNC to MV; ROX index, ratio of oxygen saturation index.

Fig. 5. ROC curves. ROC curve results for the ROX index and LIV (AUC: 0.94, 95% CI: 0.89–0.99, sensitivity: 0.88, specificity: 0.832) compared with the ROX index alone (AUC: 0.83, 95% CI: 0.75–0.92, sensitivity: 0.79, specificity: 0.77) and LIV alone (AUC: 0.89, 95% CI: 0.82–0.96, sensitivity: 0.79, specificity: 0.77). AUC, area under the curve; CI, confidence interval; LIV, lung infiltration volume; MV, mechanical ventilation; ROC, receiver operating characteristic; ROX index, ratio of oxygen saturation index.

Figure 1

Patient flowchart.

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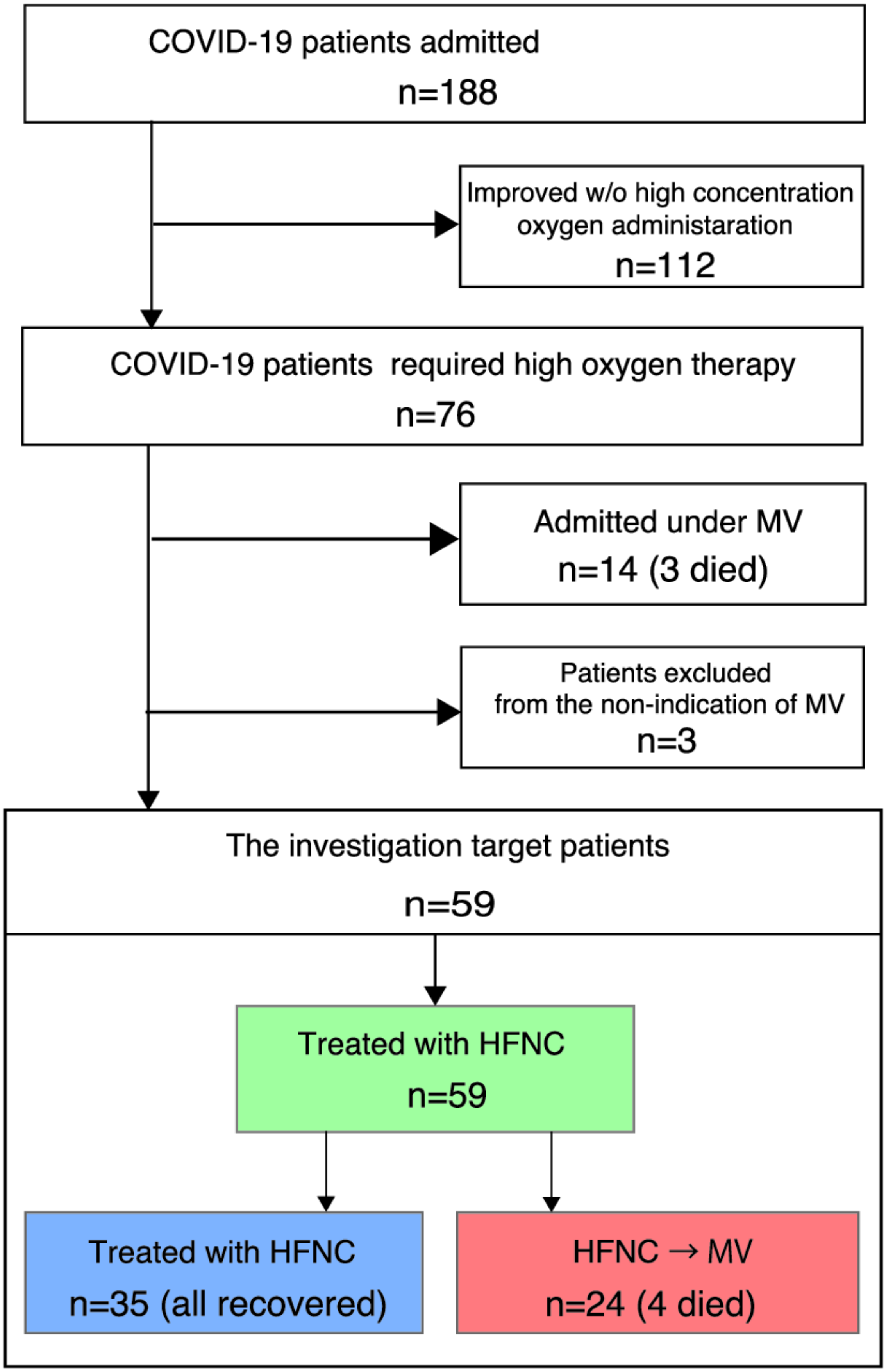
COVID-19 patients admitted
n=188
Improved w/o high concentration oxygen administaration
n=112
COVID-19 patients required high oxygen therapy
n=76
Admitted under MV
n=14 (3 died)
Patients excluded from the non-indication of MV
n=3
The investigation target patients
n=59
Treated with HFNC
n=59
Treated with HFNC
n=35 (all recovered)
HFNC → MV
n=24 (4 died)

Figure 2

Chest CT images

Chest CT settings were as follows: voltage, 120 kV; tube current, 266 mA; slice thickness, 5.00 mm; window width, 1500 Hounsfield units (HU); window level, −600 HU. According to the different HU intervals, lung volumes were segmented and extracted as follows: emphysema (density between −1050 HU and −950 HU), normal lung ventilation (density between −949 HU and −750 HU), infiltration shadow (density between −749 HU and −400 HU), collapsed lung (density between −399 HU and 0 HU), and blood vessels and soft tissue (density between 1 HU and 1000 HU). Chest CT images were read with 3D Slicer software and classified into normal infiltration, blood vessels, and emphysema according to the volume of 1 mm^3 unit of CT concentration. **A.** Findings in a patient who did not require oxygen administration. Most findings are normal findings. **B.** Findings in a patient who was successfully treated with low-flow oxygen therapy. A slight infiltration shadow is seen dorsally. **C.** Findings in a patient who was successfully treated with HFNC. Infiltration shadows are seen extensively dorsally. This patient was effectively treated in the prone position. **D.** A patient who was treated with HFNC for several days but failed this therapy and was transitioned to MV. The patient had diffuse ventral shadows on imaging. Therapy in the prone position was not effective in this patient. **E.** Findings in a patient who was treated with HFNC but who was transitioned to MV on the same day. Extensive infiltration shadows are noted. **F.** Findings in a patient who was treated with HFNC for several days and subsequently transitioned to MV. Infiltration shadows are observed in most of the lung fields. This patient was unable to maintain oxygenation after initiation of MV and required extracorporeal membrane oxygenation. CT, computed tomography; HFNC, high-flow nasal cannulation; MV, mechanical ventilation.

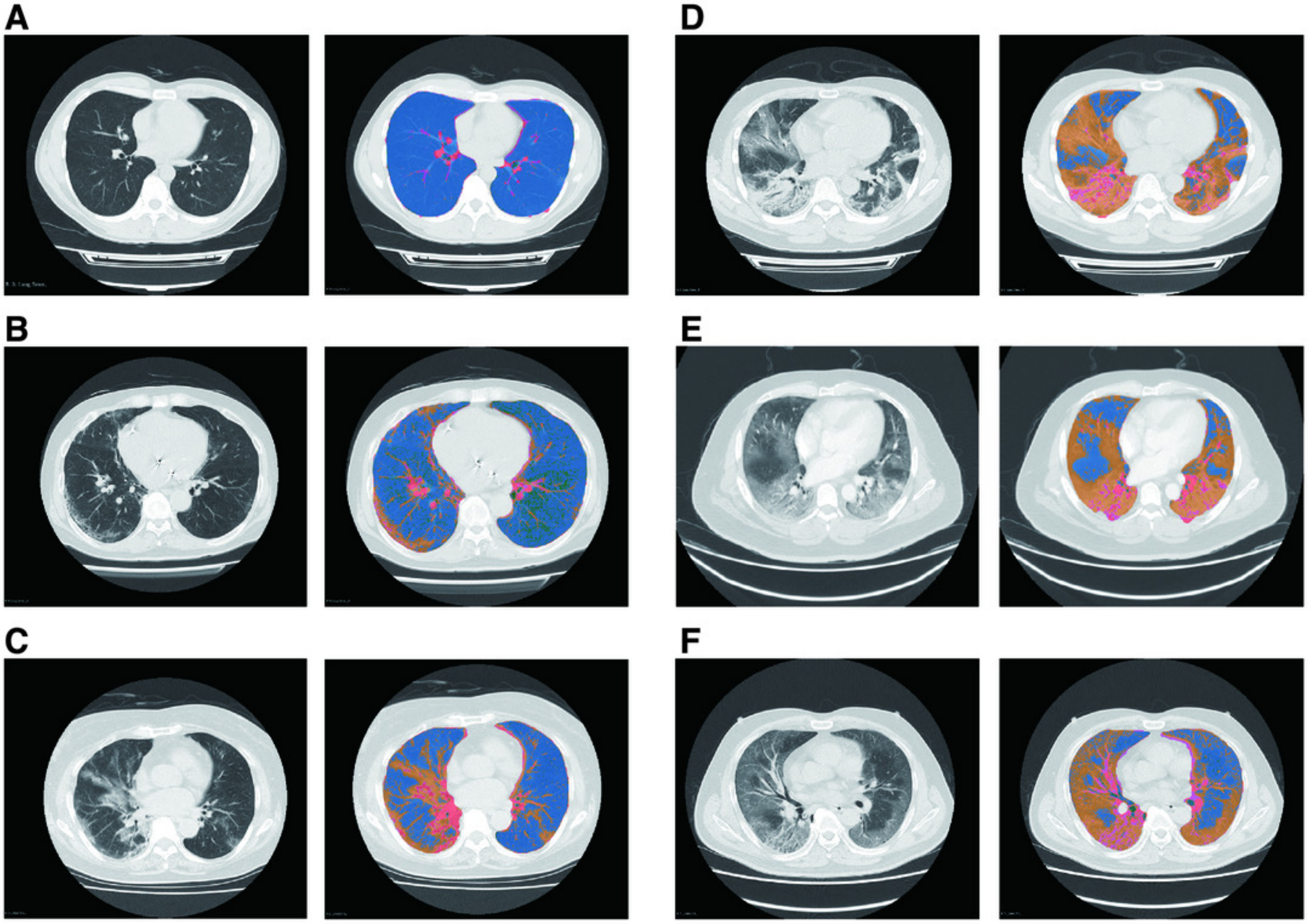
A
B
C
D
E
F

Figure 3

The relationships between the cut-off values of the ROX index and the respiratory therapeutic choice (HFNC or MV).

A. The percentages of HFNC cases with a ROX index ≤ ROX-cut-off and MV cases with a ROX index > ROX-cut-off. **B.** The percentage of HFNC cases with an LIV value ≤ 35.5 and ROX index ≤ ROX- cut-off, and the percentage of MV cases with an LIV > 35.5 and ROX index > ROX- cut-off. HFNC, high-flow nasal cannula oxygen therapy; LIV, lung infiltration volume; MV, mechanical ventilation; ROX index, ratio of oxygen saturation index.

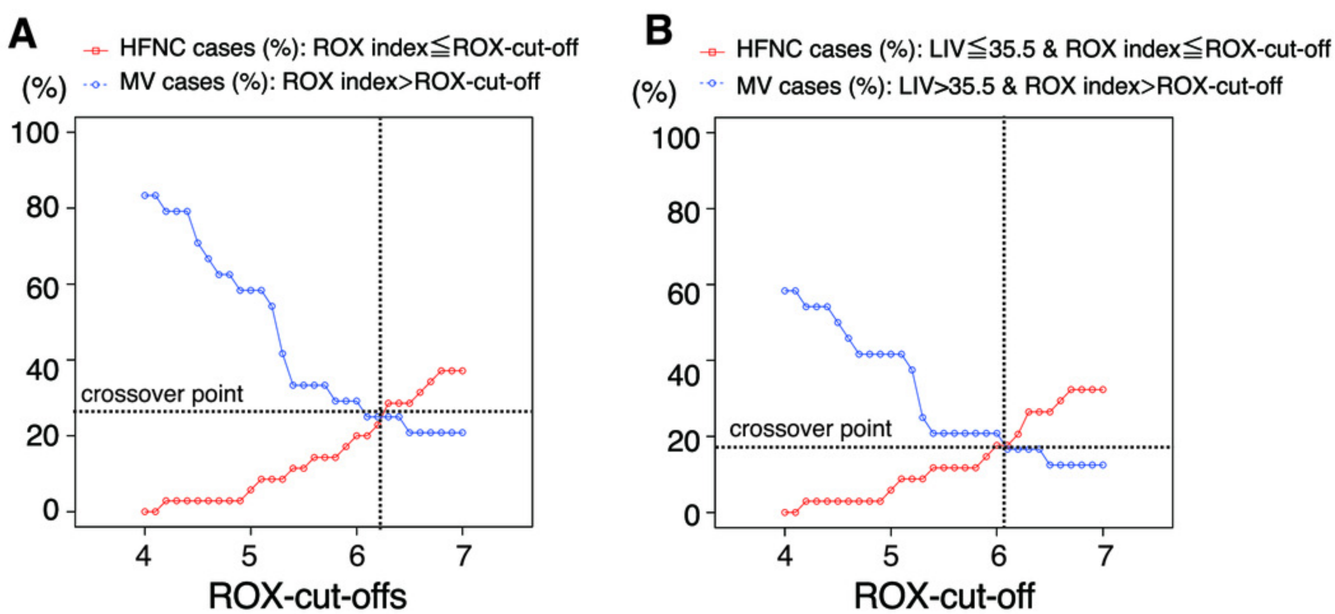

Figure 4

Kernel density estimation of patient distribution, HFNC, and ventilator management.

The cut-off to classify patients with HFNC and ventilatory management was (LIV) = 4.51 × (ROX index) + 1.75. The ROX index and LIV values were significant in the multiple logistic regression analysis. **A.** Kernel density plot using all 59 patients' data. **B.** Kernel density plots for the MV and HFNC groups. HFNC, high-flow nasal cannula; MV, mechanical ventilation; HFNC→MV, cases transitioned from HFNC to MV; ROX index, ratio of oxygen saturation index.

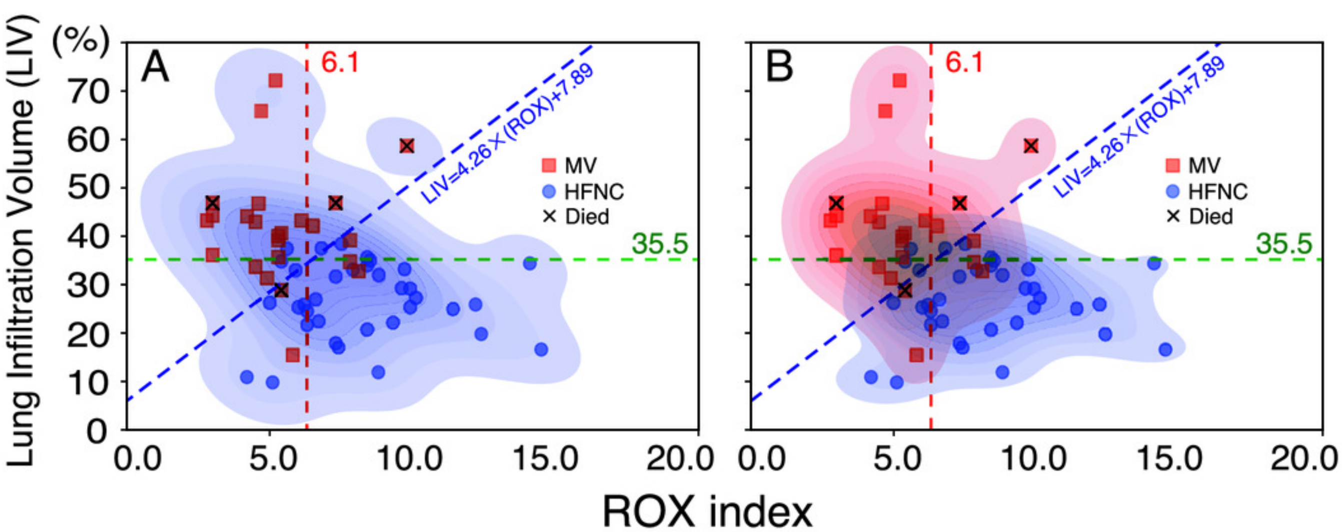

Figure 5

ROC curves.

ROC curve results for the ROX index and LIV (AUC: 0.94, 95% CI: 0.89–0.99, sensitivity: 0.88, specificity: 0.832) compared with the ROX index alone (AUC: 0.83, 95% CI: 0.75–0.92, sensitivity: 0.79, specificity: 0.77) and LIV alone (AUC: 0.89, 95% CI: 0.82–0.96, sensitivity: 0.79, specificity: 0.77). AUC, area under the curve; CI, confidence interval; LIV, lung infiltration volume; MV, mechanical ventilation; ROC, receiver operating characteristic; ROX index, ratio of oxygen saturation index.

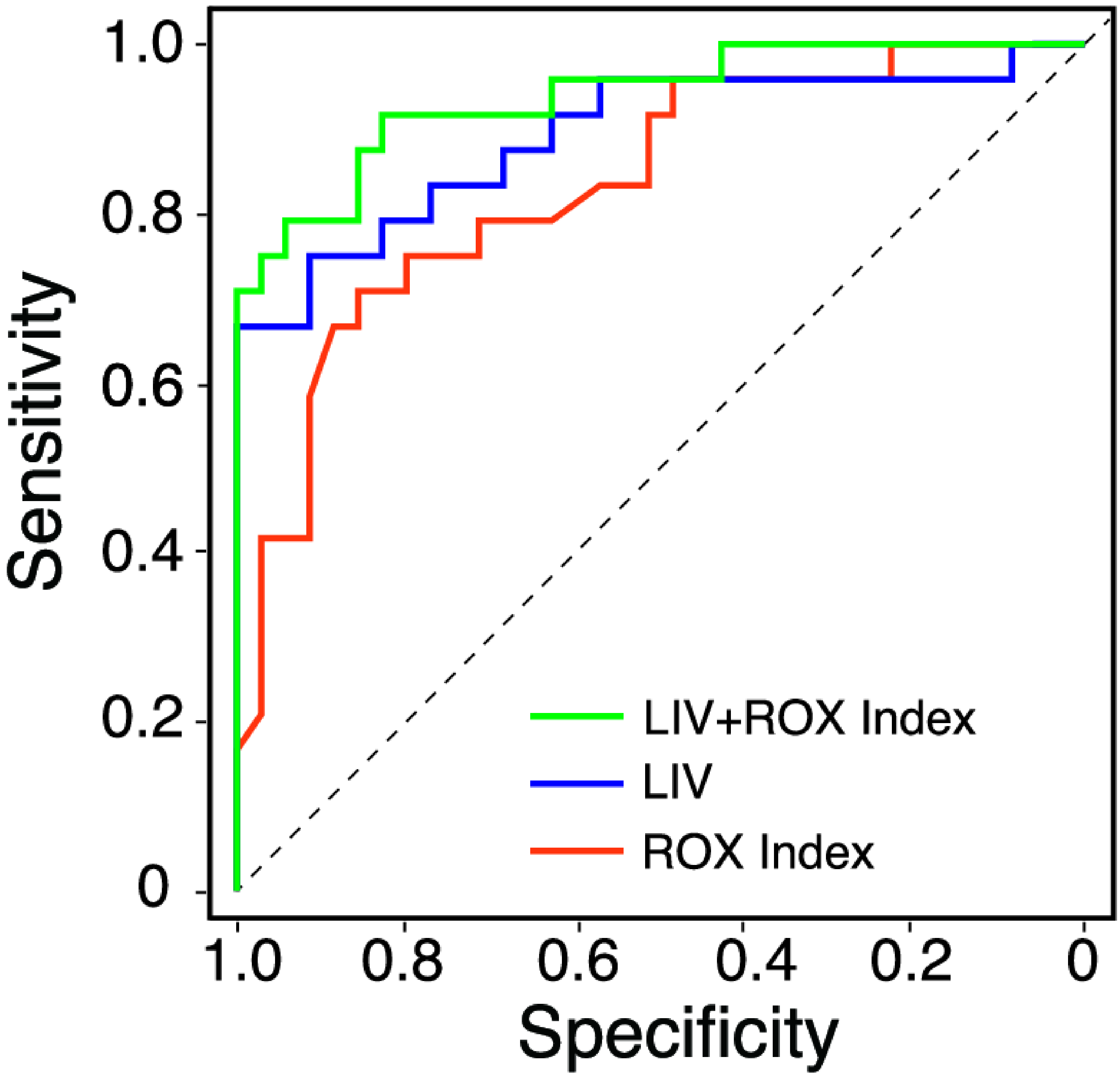
1.0
0.8
0.6
0.4
0.2
0
Sensitivity
1.0
0.8
0.6
0.4
0.2
0
Specificity
LIV+ROX Index
LIV
ROX Index

Table 1(on next page)

Major characteristics of HFNC and MV groups

Table 1 Major characteristics of HFNC and MV groups

Characteristics	HFNC	MV	*p*-value
n	35	24	
Female/male, n/n	9/26	6/18	0.951
Age (years old), mean±SD	61.1±12.3 (43–84)	58.0±14.5 (36–81)	0.403
Body weight (kg), mean±SD	69.4±16.3 (41.7–106.5)	73.4±17.5 (44.6–127)	0.378
Height (cm), mean±SD	166.4±8.7 (149–184)	166.4±10.7 (137–185)	0.988
Body mass index (kg/m^2)	24.8±4.4 (18.5–34.8)	26.6±6.5 (17.6–48.1)	0.253
Period from onset to admission to our hospital (days)	9.7±2.7 (4–17)	7.5±3.1 (2–16)	0.008*
Period from onset to the introduction of HFNC (days)	9.8±2.7 (6–17)	7.5±2.5 (3–13)	0.001*
Laboratory data (admission)			
White blood cells (/μL)	8257±5377 (1800–25600)	7775±4259 (1500–16900)	0.703
Creatinine (mg/dL)	1.3±2.0 (0.44–10.63)	1.7±2.2 (0.37–10.55)	0.233
C-reactive protein (mg/L)	9.3±7.3 (0.55–32.16)	10.6±7.7 (1.2–31.2)	0.508
Lactate dehydrogenase (U/L)	397.0±72.1 (226–598)	557.5±237.8 (122–1086)	0.004*
D-dimer (mg/L)	2.9±7.2 (0.3–36.0)	3.3±5.7 (0.5–21.7)	0.820
Indices for organ damage			
Pneumonia severity index	86.8±27.8 (43–139)	102.8±51.8 (29–245)	0.175
Charlson comorbidity index	1.7±2.0 (0–10)	2.0±2.0 (0–8)	0.612
Lung analysis			
Lung infiltration volume (mL)	972.2±321.7 (518–1845)	1340±482 (438–2319)	0.002*
Lung infiltration volume (%)	26.7±7.8 (9.8–38.4)	41.9±11.7 (15.5–72.2)	<0.001*
ROX index	7.7±2.4 (4.4–17.1)	5.4±1.8 (2.8–9.8)	<0.001*

*$p<0.05$, statistically significant difference between HFNC and MV. HFNC, high-flow nasal cannula; MV, mechanical ventilation; ROX index, ratio of oxygen saturation index.

Table 2 (on next page)

Covariate results used for multiple logistic analysis

Table 2 Covariate results used for multiple logistic analysis

Covariates	Odds ratio	95% CI	*p*-value
Laboratory data (admission)			
Lactate dehydrogenase	1.01	1.00–1.02	0.09
Period from onset to admission to our hospital (days)	0.67	0.42–1.08	0.10
Period from onset to the introduction of HFNC (days)	0.89	0.54–1.46	0.64
Lung analysis			
Lung infiltration volume (%)	1.25	1.06–1.46	0.008*
ROX index	0.32	0.13–0.77	0.012*

CI, confidence interval; HFNC, high-flow nasal cannula; ROX index, ratio of oxygen saturation index.

Table 3(on next page)

Indices for organ damage in HFNC and MV groups

Table 3 Indices for organ damage in HFNC and MV groups

Cut-off parameters	Sensitivity	Specificity	Accuracy	PLR	NLR	DOR	AUC
ROX index	0.75	0.80	0.78	3.75	0.31	12	0.83 (0.73–0.94)
LIV	0.75	0.89	0.83	6.56	0.28	23	0.89 (0.80–0.98)
ROX index and LIV	0.79	0.91	0.86	9.24	0.23	41	0.94 (0.88–0.99)

AUC, area under the curve; DOR, diagnostic odds ratio; HFNC, high-flow nasal cannula; LIV, lung infiltration volume; MV, mechanical ventilation; NRL, negative likelihood ratio; PRL, positive likelihood ratio; ROX index, ratio of oxygen saturation index.