Observational Study

Medicine®

OPEN

National early warning score on admission as risk factor for invasive mechanical ventilation in COVID-19 patients

A STROBE-compliant study

Min Cheol Chang, MD[a], Tae Uk Kim, MD[b], Donghwi Park, MD[c,*]

Abstract

The coronavirus disease (COVID-19) has become a global pandemic. Invasive mechanical ventilation is recommended for the management of patients with COVID-19 who have severe respiratory symptoms. However, various complications can develop after its use. The efficient and appropriate management of patients requires the identification of factors associated with an aggravation of COVID-19 respiratory symptoms to a degree where invasive mechanical ventilation becomes necessary, thereby enabling clinicians to prevent such ventilation. This retrospective study included 138 inpatients with COVID-19 at a tertiary hospital. We evaluated the differences in the demographic and clinical data between 27 patients who required invasive mechanical ventilation and 111 patients who did not. Multivariate logistic regression analysis indicated that the duration of fever, national early warning score (NEWS), and lactate dehydrogenase (LDH) levels on admission were significantly associated with invasive mechanical ventilation in this cohort. The optimal cut-off values were: fever duration ≥1 day (sensitivity 100.0%, specificity 54.95%), NEWS ≥7 (sensitivity 72.73%, specificity 92.52%), and LDH >810 mg/dL (sensitivity 56.0%, specificity 90.29%). These findings can assist in the early identification of patients who will require invasive mechanical ventilation. Further studies in larger patient populations are recommended to validate our findings.

Abbreviations: CKD = chronic kidney disease, IL = interleukin, KCDC = Korea Center for Disease Control and Prevention, LDH = lactate dehydrogenase, NEWS = national early warning score, RT-PCR = real-time polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

Keywords: COVID-19, fever, lactate dehydrogenase, mechanical ventilation, national early warning score, risk factor

Editor: Babak Abdinia.

This study was supported by a National Research Foundation of Korea Grant funded by the Korean government (Grant no. NRF-2021R1A2C1013073).

Financial disclosure: No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Daegu, [b] Department of Physical Medicine and Rehabilitation, College of Medicine, Dankook University, Cheonan, [c] Department of Physical Medicine and Rehabilitation, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea.

[*] Correspondence: Donghwi Park, Department of Physical Medicine and Rehabilitation, Ulsan University Hospital, University of Ulsan College of Medicine, 877 Bangeojinsunghwando-ro, Dong-gu, Ulsan 44033, Republic of Korea (e-mail: bdome@hanmail.net).

How to cite this article: Chang MC, Kim TU, Park D. National early warning score on admission as risk factor for invasive mechanical ventilation in COVID-19 patients: a STROBE-compliant study. Medicine 2021;100:19(e25917).

Received: 6 January 2021 / Received in final form: 16 March 2021 / Accepted: 20 April 2021

http://dx.doi.org/10.1097/MD.0000000000025917

1. Introduction

Following the diagnosis of the first case of coronavirus disease (COVID-19) in December 2019, the infection has rapidly spread worldwide, with the World Health Organization classifying the outbreak as a pandemic on March 11, 2020.[1–3] Although the respiratory symptoms are mild in over 80% of patients with COVID-19, they are severe in 10% to 20%.[4] Approximately 2% to 5% of patients die because of massive alveolar damage and progressive respiratory failure.[5]

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a positive-sense, long (30,000 bp), single-stranded RNA coronavirus that belongs to the family *Coronaviridae* and genus *Betacoronavirus* and very similar to SARS-CoV.[3]

In patients with severe disease, large amounts of fluids and mucus accumulate in the lung, blocking the oxygenation of lung tissues.[6,7] Low oxygen levels in the blood can lead to the death of patients. Therefore, invasive mechanical ventilation is used in these patients. Invasive mechanical ventilation is a life-saving technology that pushes air and oxygen into the lungs of patients using a machine.[8] It helps to stabilize patients with hypoxemic respiratory failure by decreasing the inspiratory work of breathing and enabling gas exchange while the lung infection is treated and proper lung function is restored.[8]

However, its use in COVID-19 patients has led to mucosal ulceration, pneumonia, lung injury, respiratory muscle wasting, swallowing dysfunction, and neuropsychiatric complications.[9] Furthermore, the required intubation or tracheostomy may result

in adverse effects, such as laryngeal or tracheal injury, laryngotracheal stenosis, or tracheomalacia.[10–12] Consequently, it is critical to identify factors associated with an aggravation of COVID-19 respiratory disease to a degree where invasive mechanical ventilation is required so that these patients can be efficiently and appropriately managed, thereby preventing the use of invasive mechanical ventilators.

In the current study, we retrospectively reviewed the files of COVID-19 patients who had been admitted to our university hospital and compared various demographic and clinical factors between patients who required invasive mechanical ventilation and those who did not.

2. Methods

2.1. Study design and participants

This retrospective study reviewed the medical records of adult inpatients (aged ≥19 years) at the Yeungnam University Hospital in Daegu, Republic of Korea. All patients diagnosed with COVID-19 according to the World Health Organization interim guidance were eligible for participation. The study period was from February 11, 2020 (i.e., when the first patients were admitted) and June 15, 2020.

Based on these criteria, the data of a total of 138 adult patients with COVID-19 were extracted and analyzed in this study.

The protocol of this study was approved by the Institutional Review Board of Yeungnam University Hospital. The requirement for informed consent was waived by the Ethics Commission because of the nature of this study as a retrospective file review. All methods were performed in accordance with relevant guidelines and regulations for retrospective file reviews.

2.2. Data collection

Using a standardized data collection form, demographic, epidemiological, and clinical data were extracted from the electronic medical records of the patients by 2 physicians.

2.3. Laboratory tests

After fasting for at least 8 hours, blood samples were drawn from the ante-cubital vein into vacuum tubes and analyzed at the Yeungnam University Hospital's certified laboratories.[13] We recorded the following variables:

2.3.1. Real-time polymerase chain reaction test. COVID-19 tests were performed for all patients within 48 hours of admission. After January 31, 2020, each of the local government's Public Health and Environmental Research Institutes in the Republic of Korea began diagnosing COVID-19 using the real-time polymerase chain reaction (RT-PCR) kit approved by the Korea Center for Disease Control and Prevention (KCDC) and Korean Ministry of Food and Drug Safety.[14] For SARS-CoV-2 detection using RT-PCR, the following steps are required: sample collection, sample preparation, nucleic acid extraction, reverse transcription, and PCR using real-time fluorescence signal detection. The RT-PCR test for COVID-19 requires 2 separate assays over a 24-hour period using nasopharyngeal and oropharyngeal swabs.[14] Therefore, in this study, upper respiratory specimens (including both nasopharyngeal and oropharyngeal swabs) were used. All COVID-19 diagnoses using the RT-PCR kits in this study were made by the Department of Diagnostic Examination Medicine at Yeungnam University Hospital.

2.3.2. Risk factors and symptoms recorded. Based on previous research on the risk factors for COVID-19 and the classification system announced by the KCDC, the presence of chronic underlying diseases, such as diabetes, chronic kidney disease (CKD), carcinoma, cardiovascular disease, chronic lung disease, dyslipidemia, and hypertension, was recorded.[15] Chronic lung disease was defined as asthma, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, interstitial lung disease, or bronchiectasis.[16,17] Additionally, any neurological disorders, such as Alzheimer disease, were also recorded.[15]

We further noted the details of patients' symptoms, such as fever (>37.7°C), duration of fever, chills, dyspnea, non-productive cough, productive cough, sore throat, myalgia, rhinorrhea, diarrhea, and headache at any point during the disease.

2.3.3. Radiological factors. We investigated initial lung involvement using chest radiography. We recorded whether the patient's lungs were unilaterally or bilaterally affected.[18] A radiologist checked and confirmed the radiological findings.

2.3.4. National early warning score. We recorded the national early warning score (NEWS) of patients on admission.[19–21] The NEWS was originally designed to identify deteriorating patients in hospital wards, specifically those at an increased risk of intensive care unit (ICU) admission, cardiac arrest, or death within 24 hours.[19–21] Recently, the NEWS has been increasingly used to predict the prognosis of patients with COVID-19. The NEWS consists of 6 parameters and is designed to improve the early detection of and response to clinical deterioration.[19–21] The score ranges for each parameter from 0 to 3, and the individual scores for each parameter are combined to produce an overall score. An additional 2 points are added if the patient is receiving oxygen therapy. The overall score ranges from 0 to 20: the higher the score, the greater the clinical risk.[19–21]

2.4. Statistical analysis

Continuous data were presented as the mean ± standard deviation and range. Categorical data were presented as the number and percentage.

The independent *t* test and chi-square test were used to identify potential risk factors for invasive mechanical ventilation by comparing the patients who required it with those who did not. Any factors showing a significant association were then further investigated using multivariate logistic regression analysis. We performed a receiver operating characteristic (ROC) analysis to evaluate the accuracy of predictive factors for invasive mechanical ventilation. We used the maximum Youden index to determine the cut-off values for parameters shown to be significant.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). A P-value $<.05$ was considered to be statistically significant.

3. Results

3.1. Patient demographics

The mean patient age was 60.03 ± 17.09 (21–95) years. The male-to-female ratio was 60 to 78. Forty-eight patients (48/138;

34.78%) had an underlying disease. Hypertension was the most common comorbidity, affecting 34.06% (47/138) of the patients, followed by diabetes (27/138; 19.57%) and cardiovascular disease (7/138; 5.07%).

Twenty-seven patients (27/138; 19.56%) received invasive mechanical ventilation during hospitalization. Of the 138 patients, 22 patients (15.2%) died during hospitalization. Among these, 14 had received invasive mechanical ventilation, whereas 8 had not. Fifteen (10.9%) patients were admitted to the ICU, 7 (4.90%) were treated with extracorporeal membrane oxygenation, 54 (39.1%) were treated with oxygen therapy, and 25 (18.1%) were treated with a high-flow nasal cannula.

The clinical characteristics of all patients and differentiated between those who required ventilation, and those who did not, is shown in Table 1.

3.2. Drug therapy

All patients were treated with either hydroxychloroquine sulfate 400 mg (Oxiklorine, Myungmoon Pharm. Co., Ltd., Seoul, South

Table 1

Clinical characteristics of hospitalized patients (n = 138) with COVID-19.

Variable	All patients (n = 138)	MV (+) (n = 27)	MV (–) (n = 111)	*P*-value
Age, mean ± SD, y	. . .	72.44 ± 11.15	56.7 ± 17.12	<.001
Male, n (%)	60 (43.5)	15 (10.9)	45 (32.6)	.158
Female, n (%)	78 (56.5)	12 (8.7)	66 (47.8)	
Laboratory parameters on admission (mean ± SD)				
Fasting blood sugar, mg/dL		178.2 ± 102.1	127.8 ± 46.8	.001
White blood count ($\times 10^9$/L)		8494.1 ± 3950.2	6366.5 ± 2751.6	.012
Neutrophils (%)		64.5 ± 12.8	82.4 ± 10.2	<.001
Platelets ($\times 10^9$/L)		166.6 ± 68.9	250.3 ± 101.6	<.001
C-reactive protein, mg/L		16.0 ± 8.5	4.5 ± 7.3	<.001
Plasma creatinine, μmol/L		1.4 ± 1.2	0.8 ± 0.3	.001
Lactate dehydrogenase, IU/L		1143.0 ± 978.9	567.6 ± 241.6	<.001
D-dimer, mg/L		10.7 ± 24.0	2.1 ± 3.1	.131
Aspartate transaminase (. . .)		91.3 ± 98.8	41.8 ± 43.2	<.001
Alanine aminotransferase (. . .)		51.2 ± 80.0	33.7 ± 34.3	.842
Blood urea nitrogen (. . .)		26.6 ± 19.4	15.0 ± 8.0	<.001
Hematocrit (%)		36.7 ± 5.4	38.1 ± 4.2	.229
Total bilirubin, mg/dL		1.1 ± 0.5	1.2 ± 4.2	.008
Procalcitonin (. . .)		1.2 ± 2.5	0.2 ± 1.1	<.001
aPTT, s		34.8 ± 10.4	32.9 ± 6.2	.668
PTT, s		15.6 ± 13.0	13.3 ± 4.9	.175
Ferritin, ng/mL		1434.47		
NEWS		8.0 ± 3.2	2.8 ± 2.6	<.001
Comorbidities, n (%)				
Hypertension	47 (34.3)	14 (51.9)	33 (30.0)	.032
Diabetes mellitus	27 (19.7)	11 (40.7)	16 (14.5)	.002
Chronic kidney disease	4 (2.9)	3 (11.1)	1 (0.9)	.005
Dyslipidemia	6 (4.3)	1 (3.7)	5 (4.5)	.855
Chronic lung disease	5 (3.6)	2 (7.4)	3 (2.7)	.245
Malignancy	6 (4.3)	0 (0.0)	6 (5.4)	.217
Cardiovascular disease	7 (5.1)	1 (3.7)	6 (5.5)	.711
Dementia	6 (4.3)	3 (11.1)	3 (2.7)	.056
Smoking	5 (3.6)	2 (7.4)	3 (2.7)	.245
Symptoms, n (%)*				
Presence of any symptom	130 (94.2)	27 (100.0)	103 (92.8)	.151
Fever	90 (65.2)	24 (88.9)	66 (59.5)	.004
Duration of fever, mean ± SD, d		6.4 ± 5.6	2.0 ± 3.4	<.001
Chilling (%)	26 (18.8)	3 (11.1)	23 (20.7)	.252
Cough (%)	85 (61.6)	16 (59.3)	69 (62.2)	.781
Dyspnea (%)	62 (44.9)	22 (81.5)	40 (36.0)	<.001
Sore throat (%)	24 (17.4)	3 (11.1)	21 (18.9)	.337
Sputum (%)	68 (49.3)	13 (48.1)	55 (49.5)	.896
Rhinorrhea (%)	16 (11.6)	2 (7.4)	14 (12.6)	.449
Myalgia (%)	51 (37.0)	7 (25.9)	44 (39.6)	.185
Headache (%)	48 (34.8)	4 (14.8)	44 (39.6)	.015
Diarrhea (%)	25 (18.1)	5 (18.5)	20 (18.0)	.952
Radiologic findings, n				
Abnormal findings in chest radiograph (%)	114 (85.1)	27 (100.0)	87 (81.3)	.015
Unilateral involvement	32	2	30	.009
Bilateral involvement	86	25	61	

aPTT = activated partial thromboplastin time; MV (–) = did not receive mechanical ventilation; MV (+) = received mechanical ventilation; NEWS = national early warning score; PTT = partial thromboplastin time.
* Except where indicated otherwise.

Korea) per day alone or a combination of hydroxychloroquine sulfate 400 mg (Oxiklorine, Myungmoon Pharm. Co., Ltd., Seoul, South Korea) and lopinavir/ritonavir 200 mg/50 mg (Kaletra, AbbVie Inc., North Chicago, IL) per day.

3.3. Risk factors for COVID-19 patients treated with invasive mechanical ventilation

In patients receiving invasive mechanical ventilation, the prevalence of fever, dyspnea, headache, abnormal findings on chest radiographs, bilateral involvement of the lungs, diabetes, hypertension, neurologic disease, and CKD was statistically significantly higher than that in patients who were not ventilated ($P < .05$; Table 1). In addition, the systolic blood pressure, white blood cell and platelet count, percentage of neutrophils, percentage of lymphocytes, total bilirubin, aspartate transaminase, glucose, blood urea nitrogen, creatinine, procalcitonin, C-reactive protein, lactate dehydrogenase (LDH), duration of fever, oxygen saturation, and NEWS on admission were significantly different between COVID-19 patients with and without invasive mechanical ventilation ($P < .05$; Table 1).

The multivariate logistic regression analysis indicated that only the duration of fever, NEWS, and LDH level on admission were significantly associated with invasive mechanical ventilation. In these patients, the area under the ROC (AUROC) for the duration of fever in predicting invasive mechanical ventilation was 0.825 (95% confidence interval [CI], 0.751–0.884; $P < .0001$). The optimal cut-off value was ≥1 day (sensitivity 100.0%, specificity 54.95%). The AUROC for the NEWS in predicting invasive mechanical ventilation was 0.889 (95% CI, 0.821–0.937; $P < .0001$), and the optimal cut-off score was ≥7 (sensitivity 72.73%, specificity 92.52%). The AUROC for the LDH level in predicting invasive mechanical ventilation was 0.799 (95% CI, 0.720–0.865; $P < .0001$), and the optimal cut-off value was >810 mg/dL (sensitivity: 56.0%, specificity: 90.29%) (Table 2 and Fig. 1).

4. Discussion

In this retrospective study, we investigated the risk factors for requiring invasive mechanical ventilation in patients with COVID-19 who were admitted to our university hospital. We found that fever for >1 day, a NEWS ≥7, and an LDH level >810 mg/dL on admission were risk factors that aggravated the respiratory symptoms in these patients to the degree that invasive mechanical ventilation was necessary. The accuracy of these risk factors in indicating the later need for invasive mechanical ventilation was good (AUROC: fever = 0.825, NEWS = 0.889, LDH level = 0.799).

Fever is a response to pyrogenic cytokines such as tumor necrosis factor, interleukin (IL)-1, IL-6, and interferons being released into the bloodstream.[22] These cytokines activate alveolar macrophages and recruit neutrophils to the lungs, which in turn activate leukotrienes, oxidants, platelet-activating factors, and proteases.[23] These substances damage the capillary and alveolar epithelium, thereby disrupting the barrier between the capillaries and the air spaces.[24] This can cause edema with fluid and cellular debris filling the air spaces and lung interstitium, resulting in airspace collapse, ventilation-perfusion mismatch, and disruption of the surfactant microarchitecture.[24] Fever for >1 day can lead to a larger release of pyogenic cytokines, which can damage lung tissue to the degree that patients require invasive mechanical ventilation.

NEWS is a tool developed by the Royal College of Physicians to improve the early detection of clinical deterioration in adult patients with acute illnesses.[21] It determines the degree of acute illness in a patient and prompts critical care intervention. It is widely used in clinical practice, but thus far, only a few studies have evaluated its usefulness during the COVID-19 pandemic.[25,26] In our study, a NEWS ≥7 on admission indicated a high risk of invasive mechanical ventilation. Our results are similar to those of a previous study in 66 COVID-19 patients (13 patients died during hospitalization, and 53 were discharged alive) who were hospitalized in a general public hospital in Oslo, Norway.[27] The authors defined severe disease as a composite measure of death and ICU treatment during hospitalization. They reported that a NEWS2 ≥6 on admission predicted progression to the severe disease with a sensitivity of 80% and a specificity of 84%.

Our study also showed that patients with an elevated LDH level >810 mg/dL on admission were more likely to require invasive mechanical ventilation. Increased serum LDH levels are an indicator of tissue damage and inflammation.[28] Thus, they may indicate severe damage or inflammation of the lung in patients with COVID-19. This finding concurs with the results of previous studies. Zheng et al[29] performed a meta-analysis of 13 studies on the risk factors of critical or mortal COVID-19 cases. Furthermore, Guan et al,[30] in their analysis of >1000 patients in China reported that an elevation of LDH is one of the predictive factors of critical or mortal COVID-19.

To date, several studies have evaluated risk factors of severe COVID-19 and mortality.[30–36] These indicate that male sex, age >65 years, active smoking, comorbidities (hypertension, diabetes, and cardiovascular disease), dyspnea, and elevated HLD, white blood count, aspartate transaminase, creatinine, and D-dimer levels are risk factors for the development of a critical condition. However, thus far, risk factors for the use of invasive mechanical ventilation in COVID-19 have not been evaluated.

Our results need to be interpreted within the limitations of this study. Our study is characterized by its relatively small number of patients, resulting in a selection bias.

Table 2

Risk factors associated with the need for invasive mechanical ventilation in hospitalized adult patients (n = 138) with COVID-19.

	Beta coefficient	Standard error	Multivariable OR (95% CI)	*P*-value
Duration of fever	0.341	0.111	1.406 (1.131–1.748)	.002*
Initial NEWS	0.555	0.170	1.742 (1.249–2.429)	.001*
Initial LDH level	0.005	0.002	1.005 (1.001–1.008)	.006*

All *P*-values resulting from multivariate logistic analysis.

LDH = Lactate dehydrogenase; NEWS = national early warning score; OR = odds ratio.

* Significant difference ($P < .05$).

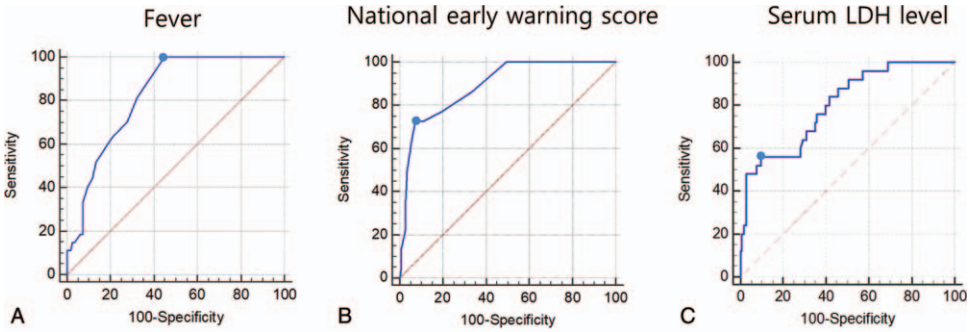

Figure 1. The cut-off values of the risk factors for invasive mechanical ventilation identified in this cohort of patients (n = 138) with COVID-19. (A) The area under the receiver operating characteristic curve (AUROC) of the duration of fever for predicting invasive mechanical ventilation was 0.825 (95% confidence interval [CI], 0.751–0.884; $P < .0001$). The optimal cut-off value assessed using the maximum Youden index (J) was ≥1 day (sensitivity 100.0%, specificity 54.95%). (B) The AUROC of the national early warning score on admission for predicting invasive mechanical ventilation was 0.889 (95% CI, 0.821–0.937; $P < .0001$), and the optimal cut-off value was ≥7 points (sensitivity 72.73%, specificity 92.52%). (C) The AUROC of the LDH levels on admission for predicting invasive mechanical ventilation was 0.799 (95% CI, 0.720–0.865; $P < .0001$), and the optimal cut-off value was >810 mg/dL (sensitivity 56.0%, specificity 90.29%). LDH = lactate dehydrogenase.

In conclusion, we found that fever for >1 day, a NEWS ≥7, and an LDH level >810 mg/dL on admission were risk factors of invasive mechanical ventilation in patients with COVID-19. Therefore, special attention must be paid to COVID-19 patients with these risk factors. We recommend timely and personalized treatment in these patients to enhance efficacy and reduce the risk of aggravation of their respiratory symptoms. We believe our study can help to identify patients at risk of requiring invasive mechanical ventilation early. Further studies with larger cohorts are recommended.

Author contributions

Conceptualization: Min Cheol Chang, Tae Uk Kim, Donghwi Park.
Writing – original draft: Min Cheol Chang, Donghwi Park.
Writing – review & editing: Min Cheol Chang, Donghwi Park.

References

[1] Chang MC, Baek JH, Park D. Lessons from South Korea regarding the early stage of the COVID-19 outbreak. Healthcare (Basel) 2020;8:229.
[2] Chang MC, Hur J, Park D. Strategies for the prevention of the intra-hospital transmission of COVID-19: a Retrospective Cohort Study. Healthcare (Basel) 2020;8:195.
[3] Alexpandi R, De Mesquita JF, Pandian SK, Ravi AV. Quinolines-based SARS-CoV-2 3CLpro and RdRp inhibitors and Spike-RBD-ACE2 inhibitor for drug-repurposing against COVID-19: an in silico analysis. Front Microbiol 2020;11:1796.
[4] Chang MC, Park YK, Kim BO, Park D. Risk factors for disease progression in COVID-19 patients. BMC Infect Dis 2020;20:445.
[5] Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). StatPearls: Treasure Island (FL); 2020.
[6] Fahy JV, Dickey BF. Airway mucus function and dysfunction. N Engl J Med 2010;363:2233–47.
[7] Gonzales JN, Lucas R, Verin AD. The acute respiratory distress syndrome: mechanisms and perspective therapeutic approaches. Austin J Vasc Med 2015;2:1009.
[8] Mora Carpio AL, Mora JI. Ventilator Management. 2020;StatPearls [Internet],
[9] Brochard L. Mechanical ventilation: invasive versus noninvasive. Eur Respir J Suppl 2003;47:31s–7s.
[10] Quinones-Ossa GA, Durango-Espinosa YA, Padilla-Zambrano H, et al. Current status of indications, timing, management, complications, and outcomes of tracheostomy in traumatic brain injury patients. J Neurosci Rural Pract 2020;11:222–9.
[11] Park D. Application of different ventilator modes in patients with amyotrophic lateral sclerosis according to certain clinical situations: a Case Report. Medicine (Baltimore) 2017;96:e7899.
[12] Park D, Lee GJ, Kim HY, Ryu JS. Different characteristics of ventilator application between tracheostomy- and noninvasive positive pressure ventilation patients with amyotrophic lateral sclerosis. Medicine (Baltimore) 2017;96:e6251.
[13] Chang MC, Hwang JM, Jeon JH, et al. Fasting plasma glucose level independently predicts the mortality of patients with coronavirus disease 2019 infection: a multicenter, retrospective cohort study. Endocrinol Metab (Seoul) 2020;35:595–601.
[14] Chang MC, Hur J, Park D. Interpreting the COVID-19 test results: a guide for physiatrists. Am J Phys Med Rehabil 2020;99:583–5.
[15] Hwang JM, Kim JH, Park JS, Chang MC, Park D. Neurological diseases as mortality predictive factors for patients with COVID-19: a retrospective cohort study. Neurol Sci 2020;41:2317–24.
[16] Sockrider M, Tal-Singer R. Managing your chronic lung disease during the COVID-19 pandemic. Am J Respir Crit Care Med 2020;202:P5–6.
[17] Assari S, Chalian H, Bazargan M. Race, ethnicity, socioeconomic status, and chronic lung disease in the U.S. Res Health Sci 2020;5:48–63.
[18] Chang MC, Lee W, Hur J, Park D. Chest computed tomography findings in asymptomatic patients with COVID-19. Respiration 2020;99:748–54.
[19] Smith ME, Chiovaro JC, O'Neil M, et al. Early warning system scores for clinical deterioration in hospitalized patients: a systematic review. Ann Am Thorac Soc 2014;11:1454–65.
[20] Klepstad PK, Nordseth T, Sikora N, Klepstad P. Use of National Early Warning Score for observation for increased risk for clinical deterioration during post-ICU care at a surgical ward. Ther Clin Risk Manag 2019;15:315–22.
[21] Brangan E, Banks J, Brant H, et al. Using the National Early Warning Score (NEWS) outside acute hospital settings: a qualitative study of staff experiences in the West of England. BMJ Open 2018;8:e022528.
[22] Netea MG, Kullberg BJ, Van der Meer JW. Circulating cytokines as mediators of fever. Clin Infect Dis 2000;31(suppl):S178–84.
[23] Swank DW, Moore SB. Roles of the neutrophil and other mediators in adult respiratory distress syndrome. Mayo Clin Proc 1989;64:1118–32.
[24] Mach WJ, Thimmesch AR, Pierce JT, Pierce JD. Consequences of hyperoxia and the toxicity of oxygen in the lung. Nurs Res Pract 2011;2011:260482.
[25] Jang JG, Hur J, Hong KS, Lee W, Ahn JH. Prognostic accuracy of the SIRS, qSOFA, and NEWS for early detection of clinical deterioration in SARS-CoV-2 infected patients. J Korean Med Sci 2020;35:e234.
[26] Tirkkonen J, Karlsson S, Skrifvars MB. National early warning score (NEWS) and the new alternative SpO2 scale during rapid response team reviews: a prospective observational study. Scand J Trauma Resusc Emerg Med 2019;27:111.

[27] Myrstad M, Ihle-Hansen H, Tveita AA, et al. National Early Warning Score 2 (NEWS2) on admission predicts severe disease and in-hospital mortality from Covid-19 - a prospective cohort study. Scand J Trauma Resusc Emerg Med 2020;28:66.
[28] Klein R, Nagy O, Tothova C, Chovanova F. Clinical and diagnostic significance of lactate dehydrogenase and its isoenzymes in animals. Vet Med Int 2020;2020:5346483.
[29] Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect 2020;81: e16–25.
[30] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
[31] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395: 497–506.
[32] Hou W, Zhang W, Jin R, Liang L, Xu B, Hu Z. Risk factors for disease progression in hospitalized patients with COVID-19: a retrospective cohort study. Infect Dis (Lond) 2020;52:498–505.
[33] Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis 2020 Mar 16; ciaa270. doi: 10.1093/cid/ciaa270. Online ahead of print.
[34] Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Crit Care 2020;24:108.
[35] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844–7.
[36] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.