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Determinants of Limiting Life-Sustaining Treatment in Critically Ill COVID-19 Patients: A Multicenter Study in Korean Intensive Care Units

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Abstract

Background: Understanding of the life-sustaining treatment (LST) decisions in critically ill coronavirus disease 2019 (COVID-19) patients remains limited. This study aimed to identify factors influencing LST decisions, and compare clinical outcomes between patients with, and without, LST.

Methods: This multicenter, retrospective cohort study analyzed data from 1,081 COVID-19 patients admitted to intensive care units (ICUs) across Korea from January 1, 2020, to August 31, 2021. Patients were divided into LST and non-LST groups. Demographic, clinical, and outcome data were collected and compared.

Results: Of 1,081 patients, 207 (19.2 %) received LST. LST patients were older (median age: 76 years vs. 67 years, p<0.001), and had more comorbidities (85.5% vs. 70.4%, p<0.001), especially cardiovascular and chronic lung disease. They showed higher blood urea nitrogen, lower albumin, and elevated D-dimer levels (all p<0.05). ICU interventions, including mechanical ventilation (82.6% vs. 50.9%, p<0.001) and extracorporeal membrane oxygenation (ECMO) (18.8% vs. 9.8%, p<0.001), were more common.

ICU and hospital mortality rates were significantly higher in LST patients (82.6% and 94.2%, respectively, p<0.001). Logistic regression identified age (odds ratio [OR], 1.054 per year; p<0.001), mechanical ventilation (OR, 2.789; p=0.002), and ECMO use (OR, 3.580; p=0.002) as independent predictors of LST.
Conclusion: Age, comorbidities, and ICU interventions significantly influence LST decisions, highlighting the need for ethical and evidence-based critical care guidelines.

Keywords: COVID-19; Life-Sustaining Treatments; Intensive Care Unit; Mechanical Ventilation; Extracorporeal Membrane Oxygenation; Predictors; Retrospective Cohort; Korea

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has significantly affected healthcare systems worldwide, particularly intensive care units (ICUs). Physicians in ICUs face numerous challenges in treating severely ill patients with COVID-19 who require more aggressive treatment strategies, such as renal replacement therapy (RRT), invasive mechanical ventilation (MV), vasopressor support, and extracorporeal membrane oxygenation (ECMO)[1,2]. Although these treatments are crucial for patient survival, they raise complex ethical and medical explorations regarding limiting life-sustaining treatment (LST), which involves complicated decision-making processes that balance potential benefits, risks, and ethical considerations. Thus, determining LST in critically ill patients depends on various factors that include patient age, comorbid illness, severity of the illness, and overall probabilities of recovery. General guidelines suggest that LST decisions should involve comprehensive evaluation of the patient's prognosis, potential benefits from continuous treatment, and the wishes of the patient or their family[3-6].

Substantial research of the factors influencing LST decisions in the general ICU population is available. However, deeper understanding regarding these decisions is required, especially for patients with COVID-19[7-9], since the global COVID-19 pandemic, along with the significant strain on ICU resources and higher mortality rates among older patients, has increased the complexity of these decisions[10]. The highly contagious airborne transmission of COVID-19, which requires negative-pressure isolation, further complicates LST decisions. From this standpoint, further research on the factors influencing the decision to use LST in patients with COVID-19 is warranted, particularly in ICUs in Korea.

In consequence, this study sought to address this research gap by analyzing data from a nationwide, multicenter, retrospective study of COVID-19 patients admitted to ICUs. The primary aim was to identify the key factors affecting decisions regarding LST in critically ill COVID-19 patients. This study also aimed to compare the clinical outcomes between patients who received LST, and those who did not.

Materials and Methods

1. Study design and population

This study was a secondary analysis of a nationwide, multicenter, retrospective, observational cohort study involving patients with COVID-19 between January 1, 2020, and August 31, 2021. Data were sourced from a registry created by 22 tertiary- or university-affiliated hospitals in Korea, all of which participated in the study. The registry included patients aged ≥19 years who tested positive for COVID-19 via polymerase chain reaction test, and were admitted to the ICU. The patients underwent high-flow nasal cannula (HFNC) oxygen therapy, invasive MV, prone positioning (PP), or ECMO. Our analysis focused on patients admitted to the ICU for acute respiratory failure due to COVID-19.

2. Study population

The study population included 1,081 patients admitted to the ICU with a confirmed diagnosis of COVID-19. The patients were divided into two groups based on the presence or absence of LST, as documented by the physicians in the patients' medical records. The exclusion criteria included patients who were under 18 years of age, those not hospitalized in the ICU, those who did not receive oxygen therapy, or those who received only low-flow oxygen therapy. The study population included only patients admitted to ICUs, including those managed in isolation-capable rooms within the ICU during the early stages of the pandemic due to resource limitations. These isolation rooms were equipped to provide ICU-level care.

3. Data collection

Data on various patient characteristics and clinical parameters were collected, including demographics (age, sex, and body mass index); medical history (smoking status, geographic location (inside or outside Seoul), transfer status from other healthcare facilities, and presence of comorbidities); specific comorbid illness (such as cardiovascular, chronic lung, chronic neurological, chronic kidney, chronic liver, and connective tissue disease, immunocompromised status, hematologic malignancy, and solid tumor malignancy); clinical frailty scale scores (ranging 1 to 9, assessed pre-hospitalization)[11]; severity of critical illness assessed using the sequential organ failure assessment (SOFA) score[12]; ICU interventions (HFNC, MV, ECMO, continuous renal replacement therapy [CRRT], and PP); ICU and hospital stay (duration of ICU and hospital stay, ICU mortality, and hospital mortality); and laboratory results (blood urea nitrogen [BUN], serum creatinine, albumin, total bilirubin, C-reactive protein, D-dimer, lactate dehydrogenase, and lactate levels).

4. ICU interventions and outcomes

We recorded the use of critical ICU interventions to manage patients with COVID-19, including the usage rates of HFNC, incidence of MV, application of ECMO in critically ill patients, use of CRRT, and implementation of PP therapy in both the LST and non-LST groups. The clinical outcomes measured included the duration of ICU and hospital stays, ICU mortality rates, and overall hospital mortality rates.

5. Statistical analysis

Baseline patient characteristics are summarized using descriptive statistics. Continuous variables are expressed as medians with interquartile ranges, and were compared using the Mann–Whitney U test. Categorical variables are presented as frequencies and percentages, and were compared using the chi-squared test or Fisher's exact test, as appropriate. Univariate and multivariate logistic regression analyses were conducted to identify the factors associated with LST. The odds ratio (OR) and 95% confidence interval (CI) for each variable were calculated. Variables that were significant in the univariate analysis ($p<0.05$) were included in the multivariate logistic regression model to adjust for potential confounders, and identify the independent predictors of LST.

6. Ethical considerations

The study adhered to the principles outlined in the Declaration of Helsinki, and received approval from the Institutional Review Boards (IRBs) of all participating centers. Given its retrospective design, the IRBs waived the requirement for informed consent. The IRB approval number from Changwon Gyeongsang National University Hospital for this study is 2022–01016.

Figure 1. Flowchart of patient inclusion and decisions regarding limiting life-sustaining treatment among intensive care unit (ICU)-admitted coronavirus disease 2019 (COVID-19) patients with acute respiratory failure.

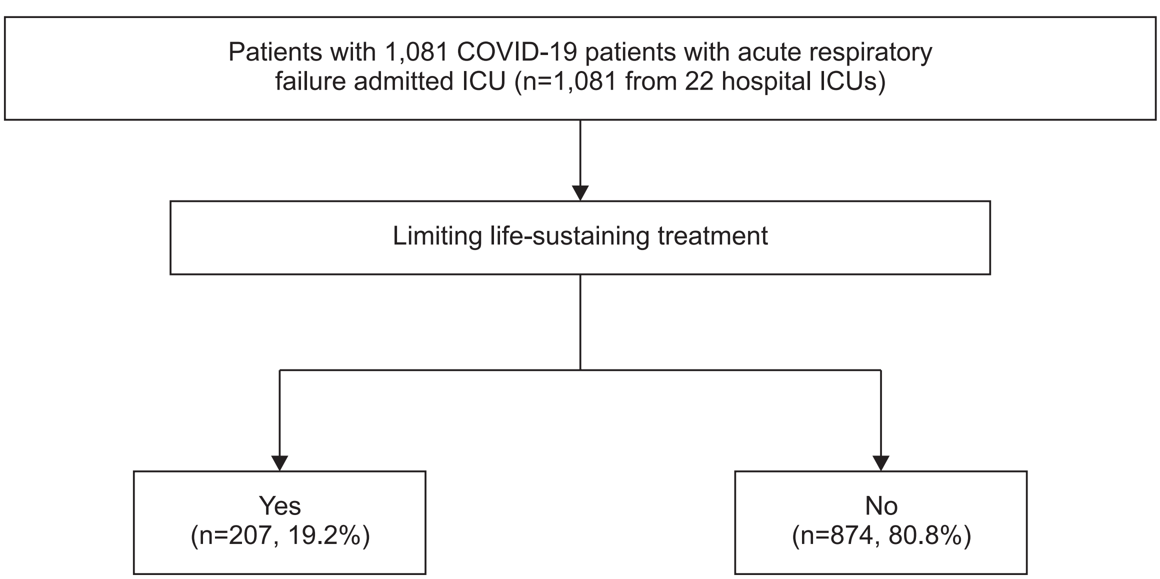


Table 1. Baseline characteristics of enrolled patients

Variable	Total (n=1,081)	LST		p-value
		Yes (n=207)	No (n=874)	
Age, yr	69 (21–99)	76 (22–99)	67 (21–94)	0.001
Male sex	656 (60.7)	127 (61.4)	529 (60.5)	0.827
BMI, kg/m^2	25.6 (23.3–28.7)	24.2 (14.7–36.8)	24.6 (8.3–44.9)	0.470
Smoking, current	67 (5.7)	5 (2.4)	62 (7.1)	0.041
Location of area, outside Seoul	327 (30.2)	73 (35.3)	254 (29.1)	0.196
Transfer from nursing care facility or other hospital	118 (10.9)	42 (20.3)	76 (8.7)	0.000
Presence of comorbidities	792 (73.3)	177 (85.5)	615 (70.4)	0.000
Hypertension	576 (53.3)	115 (55.6)	461 (52.7)	0.466
Diabetes	358 (34.6)	71 (34.3)	287 (32.8)	0.668
Cardiovascular disease	128 (10.2)	37 (17.9)	91 (10.4)	0.003
Chronic lung disease	89 (3.9)	28 (13.5)	61 (7.0)	0.002
Chronic neurological disease	152 (7.9)	45 (21.7)	107 (12.2)	0.000
Chronic kidney disease	76 (8.7)	17 (8.2)	59 (6.8)	0.459
Chronic liver disease	29 (3.9)	7 (3.4)	22 (2.5)	0.489
Immunocompromised	26 (1.6)	9 (4.3)	17 (1.9)	0.042
Connective tissue disease	18 (1.7)	3 (1.4)	15 (1.7)	0.787
Hematologic malignancy	15 (1.4)	6 (2.9)	9 (1.0)	0.039
Solid tumor, malignancy	74 (5.5)	30 (14.5)	44 (5.0)	0.000
Clinical frailty scale	3 (1–9)	3 (1–9)	3 (1–8)	0.684
SOFA score before HFNC	3 (0–14)	4 (1–13)	3 (0–12)	0.000
SOFA score before MV	7 (0–16)	7 (2–16)	7 (0–14)	0.003
Corticosteroid use	1,028 (97.6)	199 (96.1)	829 (94.9)	0.442
Remdesivir use	810 (61.4)	145 (70.0)	665 (76.1)	0.071
Tocilizumab use	94 (9.4)	22 (10.6)	72 (8.2)	0.489
Laboratory results				
White blood cells, ×10^9/L	10.8 (6.3–14.9)	8.69 (0.4–36.0)	7.58 (0.7–139)	0.879
Hemoglobin, g/dL	12.9 (11.7–14.5)	12.3 (6.4–17.2)	12.3 (4.2–29.2)	0.965
Platelets, ×10^6/L	175 (133–232)	164 (16–487)	192 (16–487)	0.656
Blood urea nitrogen, mg/dL	20.6 (14.0–31.5)	25 (4.7–113.2)	18 (4.0–137)	0.025
Serum creatinine, mg/dL	0.83 (0.62–1.20)	0.93 (0.3–9.8)	0.77 (0.2–17.2)	0.810
Albumin, g/dL	3.3 (1.5–7.1)	3.1 (1.6–4.3)	3.3 (1.8–7.1)	0.000
Total bilirubin, mg/dL	0.55 (0.40–0.80)	0.6 (0.2–3.4)	0.51 (0.0–5.4)	0.347
C-reactive protein, mg/L	12.0 (6.3–18.4)	11.1 (0.1–263)	9.9 (0–270)	0.579
D-dimer, μg/mL	1.03 (0–76)	1.56 (0–70)	0.98 (0–60)	0.000
Lactate dehydrogenase, IU/L	549 (349–751)	511 (95–18,655)	492 (49–5,371)	0.478
Lactate, mmol/L	1.8 (1.3–2.7)	1.8 (0–40)	1.5 (0–12)	0.040

Values are presented as median (interquartile range) or number (%).
LST: limiting life-sustaining treatment; BMI: body mass index; SOFA: sequential organ failure assessment; HFNC: high-flow nasal cannula; MV: mechanical ventilation.

Results

1. Demographic and baseline clinical characteristics

Figure 1 shows a flowchart of the selection of 1,081 patients with COVID-19 with acute respiratory failure admitted to the ICUs across 22 hospitals. Of these, 207 (19.2%) made decisions regarding LST, whereas 874 (80.8%) did not (Figure 1). The median age of the LST group was higher (76 years) than that of the non-LST group (67 years) (p=0.001). More patients in the LST group had comorbidities (85.5% vs. 70.4%, p<0.001) such as cardiovascular disease (17.9% vs. 10.4%, p=0.003) and chronic lung disease (13.5% vs. 7.0%, p=0.002), than did those in the non-LST group. Laboratory results showed higher BUN levels (25 mg/dL vs. 18 mg/dL, p=0.025), lower albumin levels (3.1 g/dL vs. 3.3 g/dL, p<0.001), and higher D-dimer levels (1.56 μg/mL vs. 0.98 μg/mL, p<0.001) in the LST group, than that in the non-LST group (Table 1).

2. ICU intervention and clinical outcomes

The data on ICU interventions and clinical outcomes revealed significant differences between the LST and non-LST groups. The use of HFNC was lower in the LST group than that in the non-LST group at 74.4% vs. 83.9%, respectively (p=0.001). Conversely, MV use was higher in the LST group than that in the non-LST group at 82.6% vs. 50.9%, respectively (p<0.001). Similarly, the use of ECMO at 18.8% vs. 9.8%, respectively (p<0.001), and use of CRRT at 26.6% vs. 7.8%, respectively (p<0.001), were more common in the LST group, compared to those in the non-LST group. These interventions indicated the higher level of critical care required by patients in the LST group. The median ICU stay was longer in the LST group than that in the non-LST group at 19.5 days vs. 15 days, respectively (p=0.001). Mortality rates were significantly different between the groups, with ICU mortality being greater in the LST group than in the non-LST group at 82.6% vs. 8.9%, respectively (p<0.001); and hospital mortality was greater for the LST group than for the non-LST group at 94.2% vs. 9.3%, respectively (p<0.001) (Table 2). Kaplan-Meier survival curves showed significant differences in survival probabilities between patients with and without LST (log-rank p<0.001) (Figure 2).

3. Factors influencing LST decision

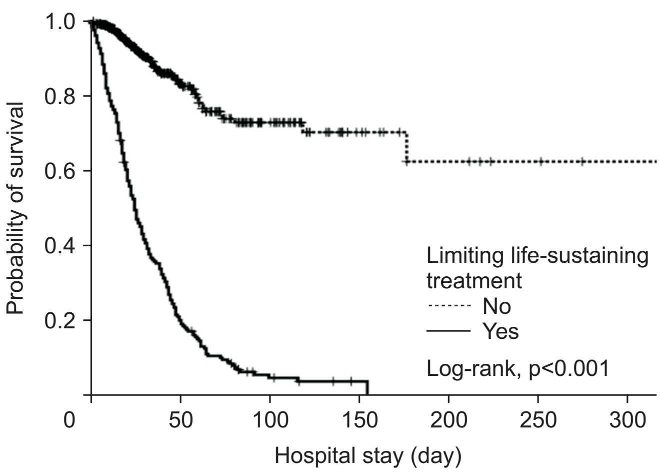
The results of both univariate and multivariate logistic regression analyses identified significant factors associated with LST. In the multivariate model, the predictors included age (OR, 1.054; 95% CI, 1.026 to 1.083; p<0.001), with each additional year increasing the odds of LST by 5.4%. The use of MV (OR, 2.789; 95% CI, 1.446 to 5.378; p=0.002) and ECMO (OR, 3.580; 95% CI, 1.604 to 7.990; p=0.002) were also significant predictors, indicating a higher likelihood of LST in patients requiring these interventions (Table 3).

Table 2. ICU intervention and clinical outcomes

Variables	Total (n=1,081)	LST		p-value
		Yes (n=207)	No (n=874)	
HFNC	887 (80.9)	154 (74.4)	733 (83.9)	0.001
MV	616 (56.9)	171 (82.6)	445 (50.9)	0.000
ECMO	125 (11.6)	39 (18.8)	86 (9.8)	0.000
CRRT	123 (11.4)	55 (26.6)	68 (7.8)	0.000
Prone positioning	223 (20.6)	66 (31.9)	157 (18)	0.000
Inhaled nitric oxide administration	43 (4.0)	27 (13.0)	16 (17.9)	0.000
Tracheostomy	206 (19.1)	70 (33.8)	136 (15.6)	0.000
ICU stay, day	15 (0–351)	19.5 (0–124)	15 (0–351)	0.001
Hospital stay, day	21 (0–374)	25 (0–155)	21 (1–374)	0.696
ICU mortality	249 (23)	171 (82.6)	78 (8.9)	0.000
Hospital mortality	276 (25.5)	195 (94.2)	81 (9.3)	0.000

Values are presented as number (%) or median (interquartile range).
ICU: intensive care unit; LST: limiting life-sustaining treatment; HFNC: high-flow nasal cannula; MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy.

Figure 2. Kaplan-Meier survival curves comparing the probability of survival between patients with and without limiting life-sustaining treatment.



Discussion

The COVID-19 pandemic has led to a significant increase in the number of critically ill patients requiring ICU admission. Despite aggressive treatment, several patients deteriorate, necessitating decisions regarding LST because of poor prognosis and impending death. This study aimed to identify the factors influencing these decisions, and compare the outcomes between patients who received LST, and those who did not. Our findings revealed that age, comorbidities, and severity of illness significantly influenced LST decisions. Older patients and those with multiple comorbidities were more likely to undergo LST. Clinical indicators, such as the need for invasive MV, ECMO, and vasopressor support, were also significant in determining LST. These treatments indicate the presence of severe illness, and often result in poor prognosis, making them crucial to these decision-making processes.

In the present study, the proportion of patients with

Table 3. Univariate and multivariate logistic regression for LST

Variable	Univariate model		Multivariable model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.061 (1.046–1.076)	0.000	1.054 (1.026–1.083)	0.000
Male sex	1.035 (0.759–1.413)	0.827		
BMI	0.949 (0.913–0.986)	0.007		
Transfer from nursing care facility or other hospital	2.267 (1.769–4.037)	0.000		
Presence of comorbidities	2.485 (1.644–3.756)	0.000		
Clinical frailty scale	1.298 (1.198–1.407)	0.000		
SOFA score at HFNC	1.307 (1.205–1.418)	0.000		
SOFA score at MV	1.091 (1.033–1.153)	0.002		
Blood urea nitrogen, mg/dL	1.024 (1.015–1.032)	0.000		
Serum albumin	0.464 (0.345–0.624)	0.000		
D-dimer, μg/mL	1.038 (1.017–1.058)	0.000		
Lactate	1.264 (1.126–1.419)	0.000		
HFNC	0.559 (0.390–0.801)	0.002		
MV	4.579 (3.122–6.717)	0.000	2.789 (1.446–5.378)	0.002
ECMO	2.140 (1.415–3.236)	0.000	3.58 (1.604–7.990)	0.002
CRRT	4.317 (2.907–6.413)	0.000		
Prone positioning	2.138 (1.522–3.002)	0.000		
Inhaled nitric oxide administration	8.089 (4.269–15.325)	0.000		
Tracheostomy	2.831 (2.011–3.985)	0.000		

LST: limiting life-sustaining treatment; OR: odds ratio; CI: confidence interval; BMI: body mass index; SOFA: sequential organ failure assessment; HFNC: high-flow nasal cannula; MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy.

LST was approximately 20%. However, the proportion of ICU patients with LST varies widely globally, with some studies reporting rates ranging 4.8% to 27.2%[3,13,14]. This variability is because of the complexity of decisions regarding LST in critically ill patients, which vary significantly across countries and communities, reflecting diverse ethical, social, and medical perspectives. For example, northern European countries make LST decisions more frequently than do southern European countries. In North America, parents are often the primary decision-makers regarding LST, whereas in Europe and South America, doctors play a more dominant role in determining LST in critically ill pediatric patients[14,15]. Moreover, physicians in the United States are more likely to accommodate requests to continue LST[16], while LST is more common in high-income countries, and less frequent in religious or lower-income regions[17]. Significant differences in LST practices are also observed in East Asia. A study comparing LST in ICUs across China, Korea, and Japan found that Chinese physicians were the least likely to apply do-not-resuscitate (DNR) orders. In contrast, Japanese physicians were most likely to practice DNR in terminally ill patients during cardiac arrest, even without prior orders. Korean physicians' attitudes regarding the withdrawal of treatments, such as total parenteral nutrition, antibiotics, dialysis, and suctioning, were intermediate[18]. Thus, decisions regarding LST are often influenced by the specific ICU and medical specialty services involved, including oncology and heart failure units[19]. In addition, there is a trend towards increasing LST over time, reflecting changing attitudes towards aggressive end-of-life care decisions[3].

The 'Act on hospice and palliative care and decisions on life-sustaining treatment for patients at the end of life,' enacted in Korea in February 2018[20], has shaped LST decision-making processes in hospitals, including ICUs. The law provides clear guidelines to ensure ethical and transparent LST decisions, while respecting the wishes of patients or their families. Recent studies in South Korea indicate an increasing trend in LST decisions, influenced by older age, frequent ICU readmissions, and specific diseases like cancer. Most LST decisions were made by family members, highlighting the need for improved communication and support for families[21].

To enhance ICU management and decision-making in future pandemics, several strategies are recommended. Developing flexible systems to fairly distribute ICU beds, ventilators, and staff, along with implementing centralized tools to monitor and allocate resources in real-time, can help address regional disparities and ensure equitable care[22]. Establishing clear and culturally sensitive guidelines for LST decision-making that aligns with ethical standards is critical, as is providing regular training for ICU teams on ethical considerations and transparent decision-making processes during crises[22]. Improving communication with families is equally important. Families should receive clear and consistent information about patients' conditions, treatment options, and prognoses. Dedicated support, such as social workers or palliative care teams, can help provide emotional and psychological support during these challenging times[23]. Promoting multicenter research collaborations to evaluate LST practices and patient outcomes is vital to improve policies and clinical guidelines. Establishing data-sharing platforms will enable real-time insights into ICU capacity and treatment outcomes, allowing healthcare systems to respond more effectively during crises[24].

This study had several strengths. First, the nationwide sample from diverse ICUs across Korea enhances the generalizability of the findings. Second, the extended study period allowed the pandemic's evolving nature and its impact on ICU practices to be captured. Third, the extensive dataset thoroughly examined factors influencing LST decisions. However, the study's retrospective design may have introduced biases in data collection, and limited its applicability outside Korea. Incomplete data and missing information may also have affected the results. Additionally, variability in end-of-life care policies across hospitals and reliance on medical records may have led to the underreporting or misclassifying of some variables.

In conclusion, this study highlighted the complexity of LST decisions for critically ill patients with COVID-19. Our results emphasize that identifying the key factors and ethical considerations provides a foundation to improve clinical guidelines and decision-making processes during future pandemics and similar healthcare crises.

Authors' Contributions

Conceptualization: Kim HC. Methodology: Heo IR, Kim HC. Formal analysis: Heo IR, Kim HC. Data curation: Jung WJ, Seong GM, Kwon SJ, Moon JY, Lee SI, Moon DS, Kim TO, Park C, Choi EY, Yoo JW, Park S, Baek AR, Lim SY, Kim JS, Lee J, Chung CR, Lee SM, Lee SH, Baek MS, Huh JW, Cho WH, Kim HC. Software: Kim HC. Validation: Heo IR, Jung WJ, Seong GM, Kwon SJ, Moon JY, Lee SI, Moon DS, Kim TO, Park C, Choi EY, Yoo JW, Park S, Baek AR, Lim SY, Kim JS, Lee J, Chung CR, Lee SM, Lee SH, Baek MS, Huh JW, Cho WH, Kim HC. Investi-

gation: Heo IR, Jung WJ, Seong GM, Kwon SJ, Moon JY, Lee SI, Moon DS, Kim TO, Park C, Choi EY, Yoo JW, Park S, Baek AR, Lim SY, Kim JS, Lee J, Chung CR, Lee SM, Lee SH, Baek MS, Huh JW, Cho WH, Kim HC. Writing - original draft preparation: Heo IR, Kim HC. Writing - review and editing: Kim HC. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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