



Weekend effect in extracorporeal membrane oxygenation therapy initiation: a nationwide cohort study in South Korea

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Background: Extracorporeal membrane oxygenation (ECMO) therapy requires close monitoring and optimal management after initiation. However, it remains unclear whether the day of the week of ECMO initiation affects patient outcomes. We aimed to investigate whether the initiation of ECMO therapy during a weekend was associated with increased mortality risk.

Methods: We performed a population-level cohort study, based on health records obtained from the National Health Insurance Service database in South Korea. All critically ill adult patients who received ECMO therapy in the intensive care unit during 2005–2018 were enrolled. The primary endpoint was the 60-day mortality rate following ECMO therapy. Multivariable Cox regression was used for the analysis.

Results: Data from a total of 21,129 ECMO patients were included in the analysis, of whom 12,825 (60.7%) died within 60 days. There were 4,647 (22.0%) patients who received ECMO therapy during a weekend (weekend group). Multivariable Cox regression revealed that the weekend group was at increased risk of 60-day mortality compared to the weekday group (hazard ratio: 1.05, 95% confidence interval: 1.01 to 1.09; P=0.025). In the sensitivity analysis, ECMO patients whose therapy started on a Saturday were at higher risk of 60-day mortality (hazard ratio relative to those whose therapy started on a Wednesday: 1.11, 95% confidence interval: 1.04–1.19; P=0.003). However, starting ECMO therapy on other weekdays (Thursday, Friday, Sunday, Monday, or Tuesday) did not affect mortality outcomes (P>0.05).

Conclusions: ECMO therapy initiated during a weekend was associated with a slightly increased risk of 60-day mortality compared to that associated with ECMO therapy initiated on a weekday. This association was more evident in patients who received ECMO therapy that started on a Saturday. Further studies are needed to confirm these findings.

Keywords: Extracorporeal membrane oxygenation (ECMO); critical care; intensive care units; mortality; cohort studies

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Introduction

Extracorporeal membrane oxygenation (ECMO) is an artificial extracorporeal support system that is used to treat refractory cardiac and/or respiratory failure (1,2). The clinical indications for ECMO use include heart failure, pulmonary hypertension, myocarditis, post-cardiac surgery management, intractable arrhythmia, trauma, shock, respiratory failure, and acute respiratory distress syndrome (ARDS) (3-7). Recently, ECMO has been used as rescue therapy in patients with coronavirus disease (8,9), and the number of potential indications for its use in intensive care units (ICUs) continues to expand (10).

The “weekend effect” is a phenomenon wherein increased mortality rates are observed among patients admitted to a hospital on Saturdays and/or Sundays (off-hours) (11). This effect has been attributed to the reduced size of hospital staff during weekends (12), and greater illness severity in patients that require an off-hours admission (13). Previous studies of critically ill patients have shown an association between ICU admission during a weekend and increased risk of in-hospital mortality (14,15). In South Korea, only 17.3% and 29.4% of ICUs had intensive care specialists with a 5-day work week in 2009 and 2014, respectively, and most ICUs did not have intensivist staffing on weekends (16). Therefore, the “weekend effect” might exist in the ICUs of South Korea.

The initiation of ECMO therapy may cause immediate, complex, and systemic inflammatory reactions that are similar to those seen in systemic inflammatory response syndrome (17). These inflammatory reactions, if severe, can cause endothelial injury; disruption of microcirculation; and major organ injuries, such as severe kidney injury, pneumonia, and liver dysfunction (18). Moreover, ECMO patients usually require fluid resuscitation or blood transfusion due to hypotension or bleeding after the initiation of ECMO therapy (19). Thus, the fluid balance, electrolyte loss, and nutritional status of ECMO patients require close monitoring and proper management in the first 1–2 days after the initiation of ECMO therapy (19). Accordingly, starting ECMO therapy on a weekend may affect patient outcomes. Although the weekend effect has been reported in patients that underwent extracorporeal cardiopulmonary resuscitation (20), no previous study has examined whether patient outcomes associated with the initiation of ECMO therapy are also subject to this effect. In South Korea, the National Health Insurance Service

(NHIS) maintains electronic health records with regard to ECMO therapy.

Using the NHIS database, we aimed to investigate whether the initiation of ECMO therapy during a weekend was associated with increased mortality risk among ECMO patients. We hypothesized that starting ECMO therapy on weekends was associated with mortality risk higher than that associated with starting ECMO on weekdays. We present the following article in accordance with the STROBE reporting checklist (21) (available at <http://dx.doi.org/10.21037/atm-21-180>).

Methods

The study was a population-level cohort study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by Institutional Review Board of Seoul National University Bundang Hospital (X-2001-586-902). The informed consent requirement was waived, as the data were anonymized and analyzed retrospectively, using a dataset extracted from the South Korean NHIS database. The data were extracted by an independent medical records technician (SY Park) at the NHIS center who had no conflicts of interest associated with this study. In South Korea, all the disease diagnosis- and prescription-related information corresponding to medications and/or procedures, including surgeries, should be registered in the NHIS database by physicians in order for the patients to receive proper financial coverage of any treatment charges.

ECMO patients

All critically ill adult patients (age ≥ 18 years old) who had received ECMO therapy in the ICU (outside the operating room), following hospitalization during 2005–2018 were included in this study. The codes related to ECMO use in the NHIS database were O1901-1904. Cases involving Novalung therapy (O1905) were not considered as ECMO therapy cases in this study.

Exposure: weekend initiation of ECMO therapy

ECMO patients whose therapy started on a weekend (Saturday or Sunday) were defined as the “weekend” group. ECMO patients whose therapy started on a weekday (Monday-Friday) were defined as the “weekday” group.

Primary endpoints: 60-day mortality

The primary endpoint was the 60-day mortality rate, which was defined as any death within 60 days after the date of ECMO therapy initiation. The 60-day mortality rate was set as the primary endpoint based on a previous study (2) because some ECMO patients, including those who were waiting for heart or lung transplantation, received ECMO therapy for long periods. Data on the exact dates of death of all patients who had received ECMO therapy until December 31, 2019 were extracted.

Covariates

The following information was extracted as covariates of interest: demographic information (age and sex) and socioeconomic characteristics (area of residence and annual income level); and Charlson Comorbidity Index (CCI) scores, which were calculated using the International Classification of Diseases, 10th revision, codes assigned during a period of 1 year prior to the start date of ECMO therapy, as shown in [Table S1](#). In addition, treatment-related information was extracted, including the duration of hospitalization and ECMO therapy (days), and the main indication for initiating ECMO therapy. The main diagnoses at the initiation of ECMO therapy were extracted and classified into nine groups: cardiovascular disease, ARDS or respiratory failure, post-cardiac arrest, cancer, gastrointestinal tract disease, sepsis, shock, trauma, burn and injury, and others.

The volume of cases involving ECMO therapy during the 14-year study period was used to determine the treatment capacity of the ECMO centers in South Korea; previous studies have suggested this capacity to be a factor affecting ECMO therapy outcomes (22). The volume of cases involving ECMO therapy was defined as the sum of the total number of cases involving ECMO therapy administered to adults during the 14-year period at each hospital. This was divided into four groups, using quartile ratios (Q1, <190; Q2, 190–393; Q3, 394–883; and Q4, >883).

Statistical analysis

First, we assessed the normality of continuous variables (age, CCI, duration of hospitalization, and duration of ECMO therapy) using the Kolmogorov-Smirnov test. As a result, the continuous variables did not follow the normal

distribution. Accordingly, the clinico-epidemiological characteristics of the patients who underwent ECMO therapy were presented as median values with interquartile range (IQR) for continuous variables, and counts with percentages for categorical variables. To compare the clinico-epidemiological characteristics between the weekend and control groups, the Mann-Whitney U test and chi-square test were used for continuous and categorical variables, respectively. Next, we performed univariable and multivariable Cox regression analyses to investigate whether the initiation of ECMO therapy on weekends was associated with an increased risk of 60-day mortality. In this time-to-event analysis, the survival time was set as the duration, and death within 60 days was considered the event of interest. All the covariates were included in the multivariable Cox regression model. The absence of multicollinearity in all the multivariable models was confirmed by a variance inflation factor of <2.0.

As a sensitivity analysis, another multivariable Cox regression model was fitted to investigate the association between the initiation of ECMO therapy on a specific day of the week and 60-day mortality risk. Specifically, the risk of 60-day mortality among patients who received ECMO therapy on any day other than Wednesday was compared with that of patients who received ECMO therapy on a Wednesday. The results of the Cox regression were presented as hazard ratios (HRs) with 95% confidence intervals (CIs), and C-statistics were used to identify the C-index of the multivariable Cox regression model. In addition, a log-minus-log plot was used to confirm that the Cox proportional hazards assumption was satisfied. All statistical analyses were performed using R software (version 4.0.3 with R packages, the R Project for Statistical Computing, Vienna, Austria). P values of <0.05 were considered indicative of a statistically significant finding.

Results

From January 1, 2005, to December 31, 2018, a total of 22,793 critically ill patients received ECMO therapy at 128 ECMO centers in South Korea. After excluding 1,664 patients aged <18 years, data from a total of 21,129 patients were included in the analysis, of whom 12,825 (60.7%) died within 60 days of initiating therapy ([Figure 1](#)). The clinico-epidemiological characteristics of the cohort are presented in [Table 1](#). The patients received ECMO therapy for 8.2±13.7 days, and were hospitalized for 17.4±15.8 days. The number of ECMO patients in the

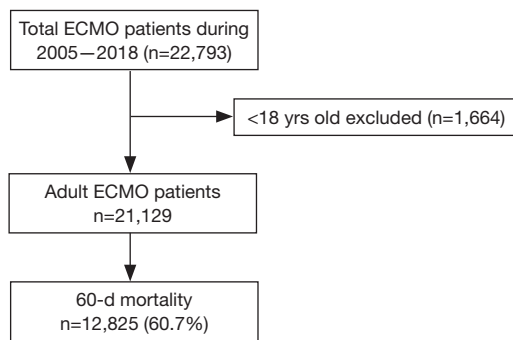


Figure 1 Flow chart depicting ECMO patient selection. ECMO, extracorporeal membrane oxygenation

Table 1 The clinico-epidemiological characteristics of the overall patients

Variable	Number (%)
Age, year, median [IQR]	61.0 [50, 70]
Sex, male	13,986 (66.2)
Residence at ECMO treatment	
Capital city (Seoul)	4,993 (23.6)
Other metropolitan city	4,844 (22.9)
Other area	11,292 (53.4)
Year of ECMO treatment	
2005–2008	1,400 (6.6)
2009–2012	4,660 (22.1)
2013–2015	6,640 (31.4)
2016–2018	8,429 (39.9)
Annual income level at ECMO treatment	
Q1 (Lowest) or unknown	5,222 (24.7)
Q2	3,809 (18.0)
Q3	4,849 (22.9)
Q4 (Highest)	7,249 (34.3)
Case volume of ECMO treatment for 14 yrs	
Q1 <190	5,154 (24.4)
Q2: 190–393	5,518 (26.1)
Q3: 394–883	5,740 (27.2)
Q4 >883	4,717 (22.3)
Charlson comorbidity index, median [IQR]	4 [2, 6]
Length of hospital stay, day, median [IQR]	13 [5, 28]

Table 1 (continued)

Table 1 (continued)

Variable	Number (%)
Duration of ECMO therapy, day, median [IQR]	4 [1, 9]
Starting ECMO therapy on weekend	4,647 (22.0%)
Monday	3,870 (18.3)
Tuesday	3,297 (15.6)
Wednesday	3,243 (15.3)
Thursday	3,138 (14.9)
Friday	2,934 (13.9)
Saturday	2,199 (10.4)
Sunday	2,448 (11.6)
Main diagnosis at ECMO treatment	
Cardiovascular disease	11,130 (52.7)
ARDS or respiratory failure	2,616 (12.4)
Post-cardiac arrest	1,781 (8.4)
Cancer	2,011 (9.5)
Gastrointestinal disease	1,248 (5.9)
Sepsis	566 (2.7)
Shock	388 (1.8)
Trauma, burn, and injury	422 (2.0)
Others	967 (4.6)

IQR, interquartile range; ECMO, extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation.

weekend group was 4,647 (22.0%). Comparisons of clinico-epidemiological characteristics between the weekend and weekday groups are presented in *Table 2*. The weekend group was younger than the weekday group [median: 60 years (IQR, 49–70 years) and 61 years (IQR, 50–71 years), respectively, $P=0.018$], and the proportion of male patients was higher on the weekend (68.1%) than on weekdays (65.7%) group ($P=0.002$). The CCI in the weekday group was higher than that in the weekend group [median: 4 (IQR, 2–6) and 3 (IQR, 2–6), respectively, $P=0.036$]. No other clinico-epidemiological characteristics differed significantly between the groups.

Sixty-day mortality risk and weekend admission

Table S2 and *Table 3* present the results of univariable and multivariable Cox regression analyses of 60-day mortality

Table 2 Comparisons of clinico-epidemiological characteristics between the weekend and weekday groups

Variable	Weekend group, n=4,647	Weekday group, n=16,482	P value
Age, year	60 [49, 70]	61 [50, 71]	0.018
Sex, male	3,165 (68.1)	10,821 (65.7)	0.002
Residence at ECMO treatment			0.669
Capital city (Seoul)	1,121 (24.1)	3,872 (23.5)	
Other metropolitan city	1,057 (22.7)	3,787 (23.0)	
Other area	2,469 (53.1)	8,823 (53.5)	
Annual income level at ECMO treatment			0.792
Q1 (Lowest) or unknown	1,140 (24.5)	4,082 (24.8)	
Q2	861 (18.5)	2,948 (17.9)	
Q3	1,057 (22.7)	3,792 (23.0)	
Q4 (Highest)	1,589 (34.2)	5,660 (34.3)	
Year of ECMO treatment			0.201
2005–2008	292 (6.3)	1,108 (6.7)	
2009–2012	1,054 (22.7)	3,606 (21.9)	
2013–2015	1,415 (30.4)	5,225 (31.7)	
2016–2018	1,886 (40.6)	6,543 (39.7)	
Case volume of ECMO treatment for 14 yrs			0.092
Q1 <190	1,135 (24.4)	4,019 (24.4)	
Q2: 190–393	1,207 (26.0)	4,311 (26.2)	
Q3: 394–883	1,212 (26.1)	4,528 (27.5)	
Q4 > 883	1,093 (23.5)	3,624 (22.0)	
Charlson comorbidity index	3 [2, 6]	4 [2, 6]	0.036
Length of hospital stay, day	13 [4, 28]	13 [5, 28]	0.241
Duration of ECMO therapy, day	4 [1, 9]	4 [1, 9]	0.956
60-day mortality	2,860 (61.5)	9,965 (60.5)	0.181
Main diagnosis at ECMO treatment			0.112
Cardiovascular disease	2,403 (51.7)	8,727 (52.9)	
ARDS or respiratory failure	577 (12.4)	2,039 (12.4)	
Post-cardiac arrest	431 (9.3)	1,350 (8.2)	
Cancer	436 (9.4)	1,575 (9.6)	
Gastrointestinal disease	261 (5.6)	987 (6.0)	
Sepsis	145 (3.1)	421 (2.6)	
Shock	95 (2.0)	293 (1.8)	
Trauma, burn, and injury	90 (1.9)	332 (2.0)	
Others	209 (4.5)	758 (4.6)	

Presented as number with percentage or median value with interquartile range. ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome.

Table 3 Multivariate Cox regression analyses of 60-day mortality risk among ECMO patients

Variable	Cox regression model, HR (95% CI)	P value
Weekend group (vs. weekday group; model 1)	1.05 (1.01, 1.09)	0.025
Sensitivity analysis (model 2)		
Wednesday	1	
Thursday	1.02 (0.95, 1.08)	0.652
Friday	1.06 (0.99, 1.13)	0.086
Saturday	1.11 (1.04, 1.19)	0.003
Sunday	1.01 (0.95, 1.08)	0.709
Monday	1.00 (0.94, 1.06)	0.873
Tuesday	0.99 (0.93, 1.05)	0.750
Age, year	1.01 (1.01, 1.02)	<0.001
Sex, male	0.97 (0.99, 1.01)	0.111
Residence at ECMO treatment		
Capital city (Seoul)	1	
Other metropolitan city	1.07 (1.02, 1.11)	0.004
Other area	1.00 (0.95, 1.04)	0.849
Year of ECMO treatment		
2005–2008	1	
2009–2012	1.29 (1.20, 1.40)	<0.001
2013–2015	1.24 (1.14, 1.33)	<0.001
2016–2018	1.01 (0.93, 1.09)	0.882
Annual income level at ECMO treatment		
Q1 (lowest) or unknown	1	
Q2	1.01 (0.97, 1.06)	0.576
Q3	1.01 (0.96, 1.07)	0.671
Q4 (highest)	0.98 (0.93, 1.02)	0.295
Case volume of ECMO treatment for 14 yrs		
Q1 <190	1	
Q2: 190–393	0.94 (0.90, 0.99)	0.015
Q3: 394–883	0.78 (0.74, 0.82)	<0.001
Q4 >883	0.66 (0.63, 0.70)	<0.001
Charlson comorbidity index	1.10 (1.10, 1.11)	<0.001

Table 3 (continued)**Table 3** (continued)

Variable	Cox regression model, HR (95% CI)	P value
Duration of ECMO therapy, day	0.99 (0.99, 0.99)	<0.001
Main diagnosis at ECMO treatment		
Cardiovascular disease	1	
ARDS or respiratory failure	0.95 (0.89, 1.00)	0.058
Post-cardiac arrest	1.99 (1.88, 2.11)	<0.001
Cancer	0.60 (0.56, 0.65)	<0.001
Gastrointestinal disease	0.46 (0.41, 0.51)	<0.001
Sepsis	1.26 (1.14, 1.40)	<0.001
Shock	1.56 (1.38, 1.75)	<0.001
Trauma, burn, and injury	1.14 (1.01, 1.29)	0.037
Others	1.13 (1.04, 1.23)	0.005

ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; CI, confidence interval; ARDS, acute respiratory distress syndrome; CPR, cardiopulmonary resuscitation.

risk among ECMO patients. In the multivariable Cox regression model, the weekend group had a higher risk of 60-day mortality than the weekday group (HR: 1.05, 95% CI: 1.01–1.09; P=0.025). In sensitivity analysis, ECMO patients who had ECMO therapy initiated on a Saturday had an 11% higher risk of 60-day mortality than those who had ECMO therapy initiated on a Wednesday (HR: 1.11, 95% CI: 1.04–1.19; P=0.003); however, starting ECMO therapy on other days (Thursday, Friday, Sunday, Monday, or Tuesday) was not associated with an increased 60-day mortality risk (*Figure 2*). The C-index of the multivariable model was 0.87 (95% CI: 0.86–0.88), indicating that the model was highly predictive of 60-day mortality.

Discussion

This population-based cohort study showed that starting ECMO therapy on a weekend day was associated with a 60-day mortality risk that was slightly higher than that associated with starting ECMO therapy on a weekday. In the sensitivity analysis, this association was particularly evident in patients who received ECMO therapy starting on Saturday. This is the first nationwide cohort study of the weekend effect in the initiation of ECMO therapy in

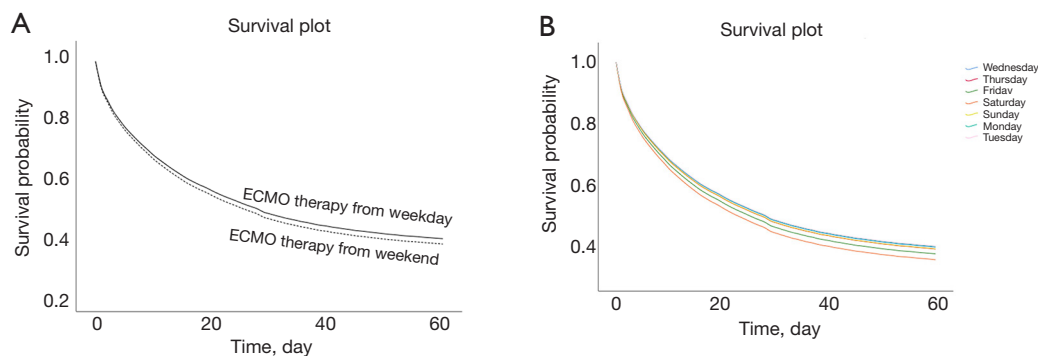


Figure 2 Sixty-day survival estimates, derived from multivariable Cox regression models: (A) Initiation of ECMO therapy during the weekend *vs.* weekday and (B) Initiation of ECMO therapy on a Thursday, Friday, Saturday, Sunday, Monday, and Tuesday *vs.* Wednesday. ECMO, extracorporeal membrane oxygenation.

South Korea. This study has shown that the differences in mortality risk between the weekend and weekday groups were independent of patient characteristics, which were similar between the groups (*Table 2*). As the number of clinical indications for ECMO therapy and its adoption are increasing (10), the present study findings may be relevant to improving survival outcomes in this patient group.

ECMO therapy is associated with complications that may result in subsequent adverse outcomes (18). A recent review article reported complications following ECMO therapy, including renal failure requiring continuous venovenous (VV) hemofiltration (52%), bleeding (33%), pneumonia (33%), sepsis (26%), oxygenator dysfunction requiring replacement (29%), hemolysis (18%), liver dysfunction (16%), venous thrombosis (10%), leg ischemia (10%), central nervous system complications (8%), gastrointestinal bleeding (7%), disseminated intravascular coagulation (5%), and aspiration pneumonia (5%) (23). These complications occur primarily in patients who received veno-arterial (VA) ECMO therapy. However, it has been reported that 40.2% of patients who received VV-ECMO experience complications such as bleeding (29.3%), intracranial hemorrhage (5.4%), deep vein thrombosis/pulmonary embolism (6.4%), pneumothorax (5.7%), cannula infection (9.9%), oxygenator failure (12.8%), and cannula failure (4.5%) (24).

These complications have been reported to have a close relationship with acute inflammatory reactions that occur in the early period after initiation of ECMO therapy (18). When ECMO therapy is initiated, the blood is exposed to extracorporeal circulation, which results in the activation of the humoral and cellular immunity response (25). This is a rapid process that involves coagulation factors such as

Factor XIIa, which reaches maximal levels in the ECMO circuit within 10 minutes of initiation (26). In addition to promoting coagulation factor activation, kallikrein production during ECMO therapy directly activates neutrophils, while bradykinin stimulates the release of nitric oxide, tumor necrosis factor- α , and interleukin 10 (26,27). Thus, the initiation of ECMO therapy might cause a systemic inflammatory response syndrome-like reaction, which might lead to endothelial cell activation (25). Some critical complications such as renal failure, sepsis, and pneumonia might be caused by this systemic reaction after the initiation of ECMO therapy (25); therefore, close monitoring and proper treatment are essential for patients undergoing ECMO therapy. In our study, the initiation of ECMO therapy on weekends, in particular, on Saturdays, was associated with mortality risk higher than that associated with ECMO therapy initiation on weekdays, suggesting that close monitoring or proper management during the weekend might be insufficient.

ICU staffing patterns in South Korea may partly account for these findings. In 2014, a survey of 220 ICUs at nine hospitals in South Korea, revealed that 38 (17.3%) ICUs employed intensive care specialists on a 5-weekday work week basis, and only 17 (7.7%) employed full-time adult critical care subspecialists (28), suggesting that most ICUs in South Korea might not have sufficient staff of experienced intensivists available for weekend shifts. In addition, a separate analysis reported that there was relatively poor ICU staffing in areas outside the capital city (Seoul) (16,28). A recent study reported that a dedicated 24/7 ECMO service using a multidisciplinary team and defined protocols was able to reduce the rate of complications due to VA-ECMO therapy in patients with

refractory cardiogenic shock (29). Overall, the weekend-weekday discrepancies in ICU staffing in South Korea may affect the quality of ECMO management and monitoring, and the associated outcomes. However, the assessment of intensivist staffing patterns in South Korea and their impact on patient outcomes was outside the scope of this study, precluding any meaningful discussions on the impact of ICU staff on patient outcomes following ECMO therapy.

The present study has several limitations. First, patient characteristics such as body mass index, and smoking and drinking status were not considered, as the NHIS database does not record this type of information. Second, the disease severity of patients undergoing ECMO was neither evaluated nor confirmed through objective methods such as the Acute Physiology and Chronic Health Disease Classification System II or Simplified Acute Physiology Score II. Third, although we collected and adjusted for some confounders in this study, there may still be residual and unmeasured confounders that might affect the results. Lastly, we did not distinguish between VA-ECMO and VV-ECMO in this study due to the limitations of the ECMO prescription codes used in South Korea. As a result, the specific relevance of the present findings to patients undergoing each type of ECMO therapy cannot be ascertained.

Conclusions

This population-based cohort study in South Korea showed that weekend initiation of ECMO therapy was associated with a slightly increased 60-day mortality risk compared to that associated with weekday initiation of this therapy. This effect was particularly evident in patients who received ECMO therapy starting on a Saturday. This is the first study to report the evidence of the weekend effect in ECMO therapy initiation. Future studies are needed to confirm these findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-21-180>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-21-180>). The authors have no conflict of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Seoul National University Bundang Hospital (X-2001-586-902). The informed consent requirement was waived, as the data were anonymized and analyzed retrospectively, using a dataset extracted from the South Korean National Health Insurance Service (NHIS) database.

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