Original Article
Yonsei Med J 2022 May;63(5):452-460
https://doi.org/10.3349/ymj.2022.63.5.452

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Trends in Mortality, Treatment, and Costs of Management of Acute Respiratory Distress Syndrome in South Korea: Analysis of Data between 2010 and 2019

Tak Kyu Oh[1,2] and In-Ae Song[1]

[1]Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam;
[2]Department of Anesthesiology and Pain Medicine, College of Medicine, Seoul National University, Seoul, Korea.

Purpose: Despite recent advances in the understanding and management of acute respiratory distress syndrome (ARDS), trends in treatment, mortality, and healthcare costs following these advancements remain to be identified. In the present study, we aimed to investigate these trends using real-world data from a national cohort database in South Korea.
Materials and Methods: Using the National Health Insurance Service database, we collected and analyzed data for critically ill adult patients with ARDS who were admitted to intensive care units in South Korea between 2010 and 2019.
Results: The final analysis included 25431 patients with ARDS. The 30-, 90-, and 365-day mortality rates in 2010 were 43.8%, 56.5%, and 68.2%, respectively. These rates had gradually decreased to 36.6%, 50.2%, and 58.8%, respectively, by 2019. Extracorporeal membrane oxygenation support for patients with ARDS started in 2014 at a rate of 5.1% (118/2309), which gradually increased to 8.3% (213/2568) by 2019. The rate of neuromuscular blockade treatment gradually increased from 22.6% (626/2771) in 2010 to 30.9% (793/2568) in 2019. The renal replacement therapy rate gradually increased from 5.7% (157/2771) in 2010 to 12.0% (307/2568) in 2019. The mean total cost of hospitalization increased from 5986.7 USD in 2010 to 12336.4 USD in 2019.
Conclusion: Real-world data for 2010–2019 indicate that patients with ARDS in South Korea have experienced changes in mortality, treatment, and healthcare costs. Despite the increased financial burden, mortality among patients with ARDS has decreased due to advances in disease management.

Key Words: Critical care, intensive care units, respiratory distress syndrome, mortality, population

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is characterized by respiratory failure due to acute hypoxemia, dyspnea, and increased bilateral pulmonary infiltration.[1] A cohort study based on the Berlin criteria[1] reported an ARDS prevalence of 10.4% among intensive care units (ICUs) in 50 countries,[2] and the mortality rates in patients with ARDS ranged from 11%–87%.[3] The global burden of ARDS is the highest in high-and upper-middle-income countries.[4,5] Moreover, recent evidence has indicated that the global prevalence of ARDS may increase due to the coronavirus disease (COVID-19) pandemic,[6] suggesting that ARDS will become a more important public health issue in the future.

There have been numerous advances in the understanding and management of ARDS, including mechanical ventilation strategies and the use of prone positioning, lung recruitment maneuvers, and extracorporeal membrane oxygenation (ECMO) support.[7] A consensus decision regarding the definition of ARDS according to the Berlin criteria was established in 2012.[1] Afterwards, clinical management of ARDS was influenced by clinical trials that investigated the efficacy of pressure-guided ventilation,[8] neuromuscular blockade (NMBs),[9]

Received: October 7, 2021 **Revised:** January 17, 2022
Accepted: February 9, 2022
Corresponding author: In-Ae Song, MD, PhD, Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro, 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
Tel: 82-31-787-7499, Fax: 82-31-787-4063, E-mail: songoficu@outlook.kr

•The authors have no potential conflicts of interest to disclose.

and ECMO support.[10] These advances would have likely influenced clinical trends in the management of ARDS.[7,11] Although a previous study reported that there were changes among patients with ARDS in the United States between 2001 and 2008,[12] more recent information is lacking, especially for patients in South Korea.

In the present study, we aimed to investigate recent trends in the treatment, mortality, and healthcare costs of ARDS using real-world data from a national cohort database in South Korea. We hypothesized that these trends changed significantly between 2010 and 2019 due to advances in the management of ARDS in South Korea.

MATERIALS AND METHODS

Study design and ethical considerations

This population-based cohort study followed the Reporting of Observational Studies in Epidemiology guidelines.[13] The protocol of this study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (X-2008-630-903), and the National Health Insurance Services (NHIS) approved data sharing following approval of the study protocol (NHIS-2021-1-424). The requirement for informed consent was waived by the IRB because the data analyzed in the study were extracted retrospectively in an anonymized form by an independent medical record technician at the NHIS big data center.

Setting and database

This nationwide cohort study utilized the NHIS database in South Korea. The NHIS is the sole public insurance system in South Korea, and all diseases that are diagnosed are registered in the NHIS database using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes. Most of the prescriptions for procedures and/or drugs must be registered in the database for patients to receive financial coverage for treatment expenses from the government. Since the NHIS database consists of secondary data based on claims information accumulated by the government's health insurance system, information with respect to the prescription of drugs and equipment that were not covered by the NHIS are not available in this database. For example, the inhalation of nitrogen monoxide for ARDS treatment could not be extracted because it is not covered by the NHIS. Data on the dates and main causes of death were extracted from the database of Statistics Korea, the central government organization that generates national statistical data. In South Korea, physicians are instructed to register principal disease diagnoses in the Statistics Korea database using ICD-10 codes for the diseases that are most closely related to the causes of death. Accurate data regarding the dates and causes of death were collected until December 31, 2020.

Study population

The study included critically ill adult (≥18 years old) patients who were diagnosed with ARDS (ICD-10 code: J80) and had been admitted to ICUs between January 1, 2010, and December 31, 2019. Since ARDS is a syndrome that can occur in conjunction with other pathologic conditions,[1] we included both types of cases in which ARDS was the main diagnosis and in which it was the secondary diagnosis (e.g., main diagnosis of pneumonia or sepsis and a secondary diagnosis of ARDS). The main diagnosis listed in the NHIS database, which was defined after the end of hospitalization, was determined based on the disease with the greatest demand for treatment or examination during hospitalization. With regard to the annual trends in ARDS treatment, if a patient was admitted to the ICU twice or more in 1 year during the study period (10 years), only the first episode was included in the analysis.

Study outcomes

The current study aimed to examine trends in ARDS treatment, mortality, and healthcare costs in South Korea between 2010 and 2019. We first calculated 30-, 90-, and 365-day mortality rates. Survival times were calculated from the date of the initiation of ARDS treatment to the date of death or the last follow-up (December 31, 2020). The date of the initiation of ARDS treatment was used because some patients were transferred to another hospital during ARDS treatment due to a lack of medical resources, such as ECMO. For example, if a patient was admitted and started on ARDS treatment on April 1, 2019, transferred to other hospital on April 4, 2019, and then died on April 7, 2019, the survival time was 7 days (from April 1, 2019 to April 7, 2019). When the main cause of death was respiratory disease (J00–J99), the case was included in the calculation of respiratory mortality. We then examined trends in treatment, including the use of ECMO support, NMBs (atracurium, cisatracurium, vecuronium, and rocuronium), and renal replacement therapy (RRT) [i.e., continuous RRT (CRRT) and intermittent hemodialysis] during hospitalization. We excluded cases in which one-time prescriptions of NMBs were provided for specific procedures (e.g., endotracheal intubation). We also evaluated the total costs of hospitalization and cost per day of hospitalization. The cost per day was calculated using the following formula: total cost of hospitalization/length of hospital stay for ARDS treatment. All costs were first extracted in Korean currency (won, ₩) and converted subsequently to USD based on an exchange rate of ₩1080=$1 USD. The cost included drugs and equipment not covered by the NHIS in addition to all the items covered by the NHIS. Finally, we investigated factors associated with 30-day mortality in patients with ARDS.

Covariates

Age and sex were used as covariates. In addition, household income level was utilized as an indicator of socioeconomic status and was divided into quartiles. Other covariates included the department [internal medicine (IM) vs. non-IM] and type of admission (transfer from another hospital, admission through the emergency room, or admission through the outpatient clinic). Since a higher volume of ARDS-related hospitalizations has been shown to be associated with better hospital survival in patients with ARDS,[14] we also included the annual volume of ARDS cases at each hospital over the 10-year study period as a covariate. Patients were divided into quartiles according to the hospital in which they were admitted (Q1 ≤4, Q2: 5–14, Q3: 15–28, and Q4 ≥29). If a patient with ARDS had a main diagnosis of sepsis, the case was classified as sepsis-associated ARDS. We also collected the following information regarding treatment at admission: use of ECMO support, NMBs, RRT, mechanical ventilation, and cardiopulmonary resuscitation (CPR) during hospitalization. Charlson Comorbidity Index (CCI) values were calculated according to the individual underlying diseases based on ICD-10 codes within 1 year before the date of ARDS diagnosis. The comorbidity status among all the patients with ARDS is shown in Supplementary Table 1 (only online).

Statistical analysis

The clinicopathological characteristics of all patients with ARDS are presented as mean values with SD for continuous variables and numbers with percentages for categorical variables. Annual trends in the use of ECMO support, NMBs, and RRT are presented as numbers with percentages. The Cochran-Armitage test for trend was conducted to examine the statistical significance of annual trends in categorical variables, and the results are presented as Z values.

Annual trends in the total cost of hospitalization and cost per day of hospitalization are presented as mean values. Linear regression analysis was performed to examine the statistical significance of annual trends in continuous variables, and the results are presented as standard beta coefficients. Multivariable Cox regression models were constructed to examine factors associated with 30-day mortality. All covariates were included in the adjusted multivariate model, including the age, sex, household income level, admitting department, type of hospital admission, annual case volume, main diagnosis of ARDS, sepsis-associated ARDS, CCI, 17 individual underlying comorbidities at hospital admission for ARDS, treatment information (duration of ECMO support, RRT use, duration of mechanical ventilation, and experience of CPR), and year of hospital admission. The CCI and 17 individual underlying comorbidities at hospital admission for ARDS were included in a separate multivariable model to avoid multi-collinearity among the variables. In addition, we performed a subgroup analysis of patients who underwent mechanical ventilatory support for ARDS because the P/F ratio of patients who did not undergo mechanical ventilatory support could not be measured accurately. A log-log plot was used to confirm that the central assumption of the Cox proportional hazards model was satisfied. A variance inflation factor <2.0 was used to confirm that there was no issue of multi-collinearity between the variables. All statistical analyses were performed using R software (version 4.0.3, R packages, R Project for Statistical Computing, Vienna, Austria). The statistical significance was set at $p<0.05$.

RESULTS

Study population

From January 1, 2010 to December 31, 2019, there were 27889 cases of ICU admission among patients with ARDS. Among them, there were 1979 patients with two or more admissions within 1 year and 479 pediatric cases (age <18 years), who were excluded from the analysis. Thus, the data of 25431 patients with ARDS were included in the final analysis.

Clinicopathological characteristics

The clinicopathological characteristics of the included patients are presented in Table 1. The mean age was 70.7 years (SD: 15.6 years), and 61.3% (15600) of the patients were male. The mean total length of hospitalization was 17.2 days (SD: 14.5 days). The mean total costs of hospitalization and the cost per day of hospitalization were 8844.9 USD (SD: 12373.8 USD) and 597.2 USD (SD: 747.3 USD), respectively. A total of 1024 (4.0%), 6881 (27.1%), and 2489 (9.8%) patients received ECMO support, NMB therapy, and RRT therapy, respectively. Mechanical ventilation was utilized in 23072 patients (90.7%) for a mean duration of 6.2 days (SD: 9.4 days). A total of 2215 patients (12.3%) underwent CPR during hospitalization for ARDS.

Annual trends in ARDS treatment

Fig. 1 shows the annual trends in 30-, 90-, and 365-day mortality after a diagnosis of ARDS. The 30-, 90-, and 365-day mortality rates in 2010 were 43.8%, 56.5%, and 68.2%, respectively, and these decreased gradually to 36.6%, 50.2%, and 58.8%, respectively, in 2019. The Z values of the trends for 30-, 90-, and 365-day mortality were -1.90 ($p<0.001$), -1.86 ($p<0.001$), and -1.89 ($p<0.001$), respectively. The specific values indicated in Fig. 1 are presented in Supplementary Table 2 (only online). Fig. 2 shows the annual trends for ECMO support (Fig. 2A), NMB use (Fig. 2B), and RRT use (Fig. 2C) between 2010 and 2019. The prevalence of ECMO support after the diagnosis of ARDS was 0 between 2010 and 2013 and 5.1% (118/2309) in 2014, with a gradual increase to 8.3% (213/2568) in 2019. NMB use in patients with ARDS also increased gradually from 22.6% (626/2771) in 2010 to 30.9% (793/2568) in 2019. RRT use in patients with ARDS increased gradually from 5.7% (157/2771) in 2010 to 12.0% (307/2568) in 2019. The specific values indicated in Fig. 2 are presented in Supplementary Table 3 (only online). The Z values for the trends of ECMO support, NMB use, and

https://doi.org/10.3349/ymj.2022.63.5.452

Table 1. The Total Clinicopathological Characteristics of All ARDS Patients

Variable	Value
Age, yr	70.7±15.6
Sex, male	15600 (61.3)
National income level at ARDS treatment	
Q1 (lowest)	7623 (30.0)
Q2	3598 (14.1)
Q3	4770 (18.8)
Q4 (highest)	8923 (35.1)
Unknown	516 (2.0)
Treatment result	
Discharge, and follow up in same hospital	8861 (34.8)
Transfer to other long-term facility center	1591 (6.3)
Discharge, and outpatient clinic follow up	6405 (25.2)
Death within hospitalization	8573 (33.7)
Admitting department	
IM	19897 (78.2)
Non-IM	5533 (21.8)
Length of hospitalization, day	17.2±14.5
Total cost for hospitalization, USD	8844.9±12373.8
Cost per day, USD	597.2±747.3
Hospital admission	
Transfer from other hospital	1415 (5.6)
Admission through Emergency Room	13417 (52.8)
Admission through outpatient clinic	10598 (41.7)
Annual case volume of ARDS admission	
Q1 ≤4	6393 (25.1)
Q2: 5–14	6190 (24.3)
Q3: 15–28	6292 (24.7)
Q4 ≥29	6555 (25.8)
Main diagnosis of ARDS	12800 (50.3)
Sepsis associated ARDS	3828 (15.1)
CCI at hospital admission for ARDS*	4.1 (3.0)
Myocardial infarction	2086 (8.2)
Congestive heart failure	7842 (30.8)
Peripheral vascular disease	4107 (16.2)
Cerebrovascular disease	4565 (18.0)
Dementia	4758 (18.7)
Chronic pulmonary disease	12864 (50.6)
Rheumatic disease	2041 (8.0)
Peptic ulcer disease	7720 (30.4)
Mild liver disease	9123 (35.9)
Diabetes without chronic complication	14145 (55.6)
Diabetes with chronic complication	4522 (17.8)
Hemiplegia or paraplegia	2368 (9.3)
Renal disease	2718 (10.7)
Any malignancy	4881 (19.2)
Moderate or severe liver disease	871 (3.4)
Metastatic solid tumor	1135 (4.5)
AIDS/HIV	58 (0.2)

Table 1. The Total Clinicopathological Characteristics of All ARDS Patients (continued)

Variable	Value
ECMO support	1024 (4.0)
Duration of ECMO support, day	3.2±6.1
NMB use	6881 (27.1)
RRT use	2489 (9.8)
CRRT use	1877 (7.4)
Intermittent HD during hospitalization	954 (3.8)
Both CRRT and intermittent HD use during hospitalization	342 (1.3)
Mechanical ventilator use	23072 (90.7)
Duration of mechanical ventilator use, day	6.2±9.4
Experience of CPR during hospitalization	2215 (12.3)
30-day mortality	10369 (40.8)
30-day respiratory mortality	4870 (19.2)
90-day mortality	13832 (54.4)
90-day respiratory mortality	6293 (24.7)
365-day mortality	16524 (65.0)
365-day respiratory mortality	7148 (28.1)
Year of admission for ARDS	
2010	2771 (10.9)
2011	2511 (9.9)
2012	2307 (9.1)
2013	2126 (8.4)
2014	2309 (9.1)
2015	2360 (9.3)
2016	2887 (11.4)
2017	2776 (10.9)
2018	2815 (11.1)
2019	2568 (10.1)

ARDS, acute respiratory distress syndrome; IM, internal medicine; CCI, Charlson Comorbidity Index; ECMO, extracorporeal membrane oxygenation; NMB, neuromuscular blockade; CRRT, continuous renal replacement therapy; CPR, cardiopulmonary resuscitation; RRT, renal replacement therapy; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; HD, hemodialysis.
Data are presented as mean±standard deviation or n (%).
CCI at hospital admission for ARDS* was included in the another separate model to avoid multi-collinearity.

RRT use were -2.15 (p<0.001), -2.03 (p<0.001), and -2.89 (p<0.001), respectively. Fig. 3 shows the annual trends in the total costs of hospitalization (Fig. 3A) and the cost per day of hospitalization (Fig. 3B) in patients with ARDS. The mean total cost of hospitalization increased from 5986.7 USD in 2010 to 12336.4 USD in 2019. The mean cost per day of hospitalization also increased from 382.9 USD in 2010 to 879.1 USD in 2019. The specific values indicated in Fig. 3 are presented in Supplementary Table 4 (only online). The standard beta coefficients for the total costs of hospitalization and cost per day of hospitalization were 0.152 (p<0.001) and 0.187 (p<0.001), respectively.

Survival analysis

Table 2 shows the results of the multivariable Cox regression model for 30-day mortality among patients with ARDS. Older

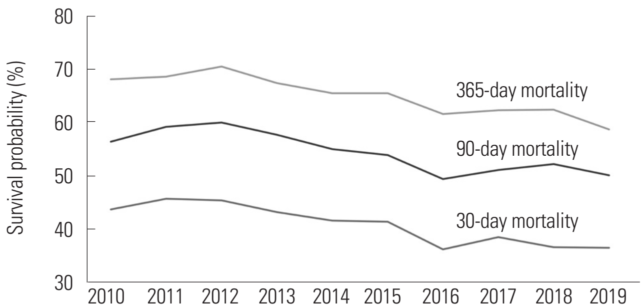

Fig. 1. Annual trends in 30-, 90-, and 365-day mortality rates after diagnosis of ARDS between 2010 and 2019. ARDS, acute respiratory distress syndrome.

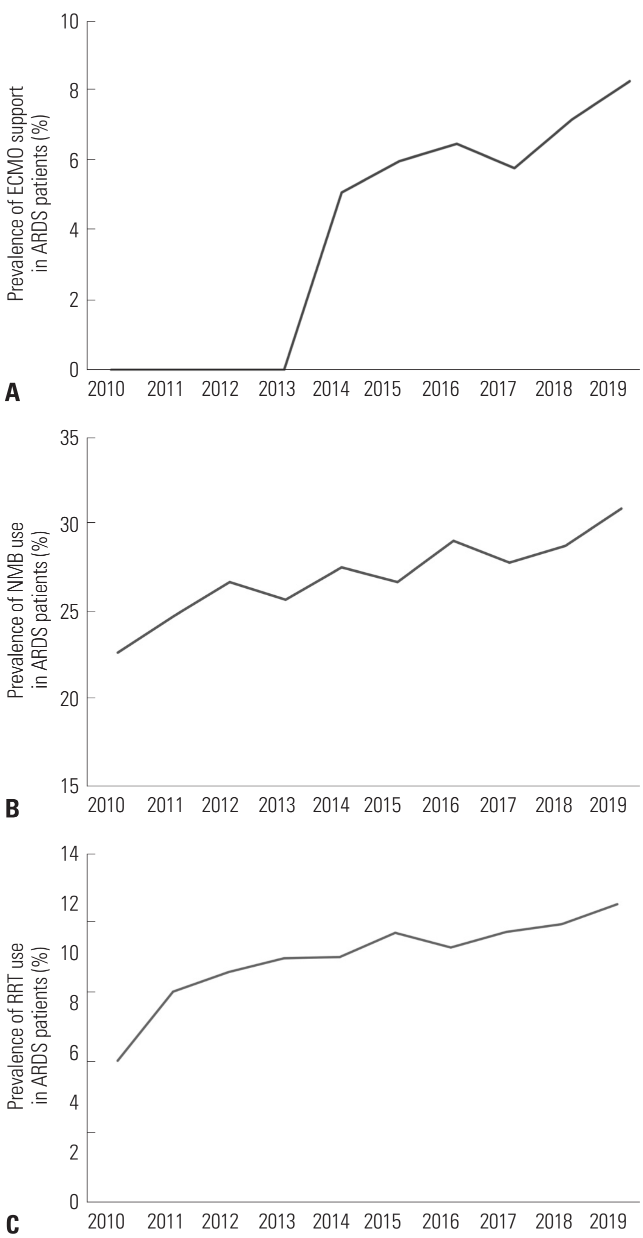

Fig. 2. Annual trends in the use of ECMO support (A), NMBs (B), and RRT (C) between 2010 and 2019. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; NMB, neuromuscular blockade; CRRT, continuous renal replacement therapy.

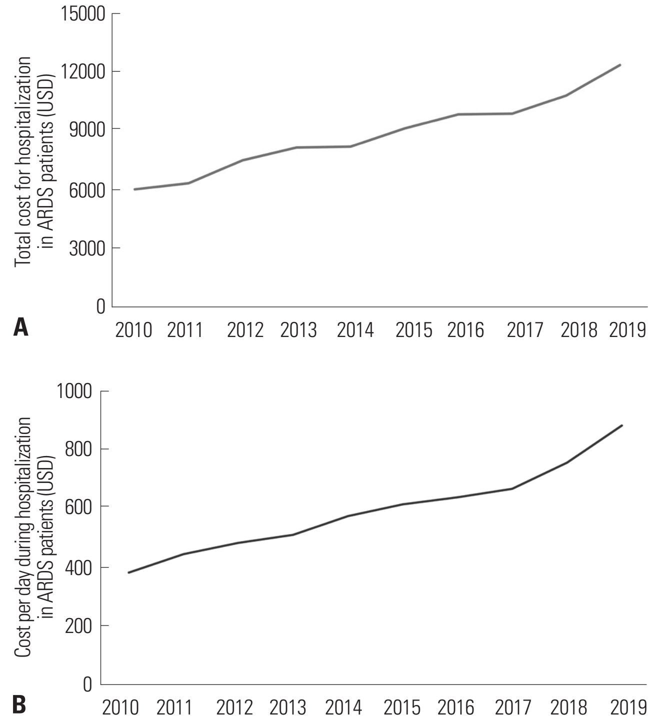

Fig. 3. Annual trends in the total cost of hospitalization (A) and cost per day of hospitalization (B) in patients with ARDS between 2010 and 2019. ARDS, acute respiratory distress syndrome.

age [hazard ratio (HR): 1.02, 95% confidence interval (CI): 1.02–1.02; $p<0.001$] and admission to an IM department (vs. non-IM: HR: 1.16, 95% CI: 1.09–1.24; $p<0.001$) were associated with a higher risk of 30-day mortality. When compared with Q1 with respect to the annual case volume, Q3 (HR: 0.84, 95% CI: 0.78–0.90; $p<0.001$) and Q4 (HR: 0.91, 95% CI: 0.84–0.97; $p=0.008$) exhibited a lower risk of 30-day mortality. In addition, an increased CCI value (HR: 1.09, 95% CI: 1.09–1.10; $p<0.001$), NMB use (HR: 1.20, 95% CI: 1.15–1.26; $p<0.001$), and experience of CPR (HR: 2.87, 95% CI: 2.72–3.04; $p<0.001$) were associated with a higher risk of 30-day mortality in patients with ARDS. Table 3 shows the results of the multivariable Cox regression model for 30-day mortality among patients with ARDS who received mechanical ventilator support (n=23072).

DISCUSSION

This population-based cohort study investigated trends in ARDS treatment, mortality, and healthcare costs between 2010 and 2019 in South Korea using real-world data. Our analysis revealed that mortality rates decreased gradually over this 10-year period, while increases in treatment with ECMO, NMBs, and RRT were associated with an increase in health care costs. These findings suggest that although more treatment options are available for patients with ARDS, the financial burden of such treatments has also increased.

https://doi.org/10.3349/ymj.2022.63.5.452

Table 2. Multivariable Cox Regression Model for 30-Day Mortality after Diagnosis of ARDS

Variable	HR (95% CI)	*p* value
Age	1.02 (1.02, 1.02)	<0.001
Sex, male	1.03 (0.99, 1.07)	0.178
Household income level at ARDS treatment		
Q1 (lowest)	1	
Q2	1.04 (0.97, 1.11)	0.250
Q3	1.02 (0.96, 1.08)	0.479
Q4 (highest)	0.95 (0.90, 0.99)	0.033
Unknown	0.84 (0.73, 0.98)	0.021
Admitting department: IM (vs. non-IM)	1.27 (1.20, 1.34)	<0.001
Hospital admission		
Transfer from other hospital	1	
Admission through Emergency Room	1.08 (0.99, 1.18)	0.068
Admission through outpatient clinic	0.80 (0.73, 0.88)	<0.001
Annual case volume of ARDS admission		
Q1 ≤4	1	
Q2: 5–14	0.94 (0.89, 1.00)	0.050
Q3: 15–28	0.85 (0.80, 0.90)	<0.001
Q4 ≥29	0.93 (0.87, 0.99)	0.015
Main diagnosis of ARDS (vs. secondary diagnosis of ARDS)	1.03 (0.99, 1.07)	0.198
Sepsis-associated ARDS	1.24 (1.18, 1.31)	<0.001
CCI at hospital admission for ARDS*	1.09 (1.09, 1.10)	<0.001
Myocardial infarction	1.08 (1.02, 1.15)	0.270
Congestive heart failure	1.17 (1.12, 1.22)	<0.001
Peripheral vascular disease	1.13 (1.07, 1.19)	0.002
Cerebrovascular disease	0.78 (0.74, 0.84)	<0.001
Dementia	1.44 (1.37, 1.51)	<0.001
Chronic pulmonary disease	1.92 (1.84, 2.00)	<0.001
Rheumatic disease	1.06 (0.99, 1.13)	0.015
Peptic ulcer disease	1.24 (1.19, 1.30)	<0.001
Mild liver disease	1.34 (1.28, 1.39)	<0.001
Diabetes without chronic complication	0.90 (0.86, 0.94)	<0.001
Diabetes with chronic complication	0.94 (0.89, 1.00)	0.023
Hemiplegia or paraplegia	0.83 (0.77, 0.90)	<0.001
Renal disease	0.90 (0.84, 1.08)	<0.001
Any malignancy	1.26 (1.20, 1.32)	<0.001
Moderate or severe liver disease	1.24 (1.13, 1.36)	<0.001
Metastatic solid tumor	1.29 (1.19, 1.40)	0.002
AIDS/HIV	0.81 (0.53, 1.24)	0.511
NMB use	1.20 (1.15, 1.26)	<0.001
Duration of ECMO support	1.00 (0.98, 1.01)	0.616
RRT use during hospitalization	1.51 (1.42, 1.61)	<0.001
Duration of mechanical ventilator use	0.97 (0.96, 0.97)	<0.001
Experience of CPR during hospitalization	2.87 (2.72, 3.04)	<0.001
Year of admission for ARDS		
2010	1	
2011	1.13 (1.03, 1.24)	0.011
2012	1.09 (0.99, 1.20)	0.077
2013	1.08 (0.97, 1.19)	0.154
2014	1.04 (0.95, 1.15)	0.391
2015	1.13 (1.03, 1.25)	0.012
2016	1.11 (1.01, 1.22)	0.034
2017	1.12 (1.02, 1.24)	0.019
2018	0.99 (0.89, 1.09)	0.777
2019	0.91 (0.82, 1.00)	0.057

HR, hazard ratio; CI, confidence interval; ARDS, acute respiratory distress syndrome; IM, internal medicine; CCI, Charlson Comorbidity Index; ECMO, extracorporeal membrane oxygenation; NMB, neuromuscular blockade; CPR, cardiopulmonary resuscitation; RRT, renal replacement therapy; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
CCI at hospital admission for ARDS* was included in another separate model to avoid multi-collinearity.

Recent research has indicated that ECMO support can lower mortality risk in patients with severe ARDS.[15] Although our study revealed that ECMO support for ARDS has increased in South Korea, the findings regarding ECMO support should be interpreted with caution, as information related to ECMO prescription for ARDS was not available for the 2010–2013 period in the NHIS database. In the United States, the use of ECMO support for ARDS showed an increase from 2008 to 2012,[16] and the influenza pandemic also led to further increases in the use of ECMO support among patients with ARDS.[17] In a recent report, the authors highlighted an increase in the use of ECMO support in patients with ARDS or respiratory failure from 2005 to 2018 in South Korea.[18] Moreover, a previous study reported that 439 patients with a primary diagnosis of ARDS or respiratory failure (J96) received ECMO support between 2009 and 2012. However, the patients who underwent ECMO support had been diagnosed with respiratory failure (J96), not ARDS.[18] In our analysis of data between 2010 and 2013, we observed that a primary diagnosis of respiratory failure was registered commonly for patients who underwent ECMO support, which may have affected our results. The diagnosis of ARDS in patients who used ECMO support may have become more common in South Korea following the consensus decision regarding the use of the Berlin definition in 2012.[1] Therefore, it is possible that patients with ARDS who used ECMO support were registered with a diagnosis of respiratory failure rather than ARDS prior to this period, which may explain the lack of cases in the NHIS database.

Our findings indicated that the use of NMBs in patients with ARDS increased in South Korea from 2010 to 2019. The clinical usefulness of NMB administration remains an important but controversial issue. While the use of NMBs can decrease dyssynchrony and breathing effort in patients with ARDS,[19] the prolonged use of NMBs may cause side effects, such as neuromuscular weakness.[20] In addition, there is a need for deep sedation during NMB administration.[21] Furthermore, randomized

Table 3. Multivariable Cox Regression Model for 30-Day Mortality after Diagnosis of ARDS among Patients Who Received Mechanical Ventilator Support (n=23072)

Variable	HR (95% CI)	*p* value
Age	1.02 (1.02, 1.02)	<0.001
Sex, male	0.99 (0.94, 1.04)	0.622
National income level at ARDS treatment		
Q1 (lowest)	1	
Q2	1.03 (0.96, 1.10)	0.481
Q3	1.00 (0.94, 1.07)	0.906
Q4 (highest)	0.95 (0.90, 1.01)	0.098
Unknown	0.88 (0.74, 1.04)	0.124
Admitting department: IM (vs. non-IM)	1.16 (1.09, 1.24)	<0.001
Hospital admission		
Transfer from other hospital	1	
Admission through Emergency Room	1.01 (0.92, 1.10)	0.915
Admission through outpatient clinic	0.84 (0.76, 0.92)	<0.001
Annual case volume of ARDS admission		
Q1 ≤4	1	
Q2: 5–14	0.98 (0.92, 1.06)	0.638
Q3: 15–28	0.84 (0.78, 0.90)	<0.001
Q4 ≥29	0.91 (0.84, 0.97)	0.008
Main diagnosis of ARDS (vs. secondary diagnosis of ARDS)	1.03 (0.99, 1.08)	0.168
Sepsis-associated ARDS	1.20 (1.13, 1.27)	<0.001
CCI at hospital admission for ARDS*	1.09 (1.09, 1.10)	<0.001
Myocardial infarction	1.04 (0.97, 1.12)	0.270
Congestive heart failure	1.15 (1.10, 1.21)	<0.001
Peripheral vascular disease	1.09 (1.03, 1.16)	0.002
Cerebrovascular disease	0.78 (0.74, 0.84)	<0.001
Dementia	1.30 (1.22, 1.37)	<0.001
Chronic pulmonary disease	1.81 (1.72, 1.90)	<0.001
Rheumatic disease	1.10 (1.02, 1.18)	0.015
Peptic ulcer disease	1.18 (1.13, 1.24)	<0.001
Mild liver disease	1.32 (1.26, 1.38)	<0.001
Diabetes without chronic complication	0.87 (0.83, 0.91)	<0.001
Diabetes with chronic complication	0.93 (0.88, 0.99)	0.023
Hemiplegia or paraplegia	0.82 (0.75, 0.90)	<0.001
Renal disease	0.88 (0.82, 0.94)	<0.001
Any malignancy	1.19 (1.12, 1.25)	<0.001
Moderate or severe liver disease	1.25 (1.13, 1.38)	<0.001
Metastatic solid tumor	1.17 (1.06, 1.29)	0.002
AIDS/HIV	0.86 (0.54, 1.36)	0.511
NMB use	1.20 (1.15, 1.26)	<0.001
Duration of ECMO support	1.00 (0.98, 1.01)	0.616
RRT use during hospitalization	1.51 (1.42, 1.61)	<0.001
Duration of mechanical ventilator use	0.97 (0.96, 0.97)	<0.001
Experience of CPR during hospitalization	2.87 (2.72, 3.04)	<0.001
Year of admission for ARDS		
2010	1	
2011	1.13 (1.03, 1.24)	0.011
2012	1.09 (0.99, 1.20)	0.077
2013	1.08 (0.97, 1.19)	0.154
2014	1.04 (0.95, 1.15)	0.391
2015	1.13 (1.03, 1.25)	0.012
2016	1.11 (1.01, 1.22)	0.034
2017	1.12 (1.02, 1.24)	0.019
2018	0.99 (0.89, 1.09)	0.777
2019	0.91 (0.82, 1.00)	0.057

HR, hazard ratio; CI, confidence interval; ARDS, acute respiratory distress syndrome; IM, internal medicine; CCI, Charlson Comorbidity Index; ECMO, extracorporeal membrane oxygenation; NMB, neuromuscular blockade; CPR, cardiopulmonary resuscitation; RRT, renal replacement therapy; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
We performed a subgroup analysis of patients who underwent mechanical ventilatory support for ARDS because the P/F ratio of patients who did not undergo mechanical ventilatory support could not be measured accurately.
CCI at hospital admission for ARDS was included in another separate model to avoid multi-collinearity.

clinical trials have reported conflicting results regarding the relationship between NMB use and mortality in patients with ARDS.[22,23] A recent meta-analysis concluded that although NMB use can improve oxygenation and decrease barotrauma in patients with moderate and severe ARDS, they do not influence mortality risk.[24] However, another meta-analysis concluded that while NMB use may improve short-term mortality, its use does not improve mid- or long-term mortality.[9] Despite these debates regarding the benefits of NMB use in patients with ARDS,[9,24] the current findings indicate that their use has increased in South Korea since 2010.

RRT can aid in maintaining fluid balance in patients with ARDS, and some evidence indicates that early initiation of CRRT can improve oxygenation and shorten the duration of mechanical ventilation in these patients, significantly.[25] However, another study reported that CRRT initiation did not influence mortality in patients with ARDS.[26] Although information regarding the clinical usefulness of RRT in patients with ARDS is limited, our findings indicate that its use has increased in South Korea. Further research is required to verify whether RRT exerts beneficial effects on ARDS outcomes.

Our study also indicates that from 2010 to 2019, the financial burden of ARDS for patients increased. As mentioned previously, the use of ECMO or RRT support is an expensive treatment option. However, the total cost of hospitalization for ARDS in South Korea was found to be generally much lower (mean value: 8844.9 USD) than that in the United States (mean value: 117137 USD).[27] These differences may be explained by differences in the medical insurance systems between the two countries; thus, in our study, the increasing trend in the costs of hospitalization for ARDS was more important than the absolute cost.

We also investigated factors associated with 30-day mortality

https://doi.org/10.3349/ymj.2022.63.5.452

after diagnosis of ARDS. As previously reported, a higher volume of ARDS cases at the treating institution was associated with a lower risk of 30-day mortality.[14] However, findings for other variables should be interpreted with caution, as we did not consider the severity of ARDS using PaO_2/FiO_2 ratio or Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II scores. Therefore, the variables in the multivariable Cox regression model indicate trends among patients with ARDS in South Korea, rather than causal effects.

Our study had some limitations. First, the NHIS database does not contain information regarding important variables, such as the body mass index, P/F ratio, or APACHE II scores at admission for ARDS treatment. Thus, in this study, we were unable to evaluate the effects of these factors. Second, in this study, we used registered ICD-10 codes to calculate CCI values, which may not have accurately represented the underlying diseases. For example, some patients with diabetes mellitus could not be diagnosed using ICD-10 codes given the poor accessibility of healthcare resources. Third, important treatment options, such as prone positioning,[28] were not included in this study because there are no prescription codes for this treatment strategy in South Korea. Fourth, we did not assess the severity of ARDS, and our Cox regression analysis of mortality did not consider patients with ARDS who did not want CPR; thus, our survival analysis should be interpreted with caution. Moreover, as the temporal relationship between CPR and the diagnosis of ARDS was not confirmed in this study, there may have been some cases in which CPR was not related directly to the progression of ARDS. Further, the use of ECMO support, RRT, or NMBs may not have been associated directly with ARDS treatment. Lastly, since most patients did not have ARDS at the time of hospital admission, but developed ARDS during hospitalization, the accuracy of the costs for ARDS management calculated in the current study remains unclear.

In conclusion, our analysis of real-world data between 2010 and 2019 in South Korea indicated that mortality rates, treatment strategies, and healthcare costs have changed among patients with ARDS. These changes included a decrease in mortality and an increase in the use of ECMO support, NMBs, and RRT, as well as an increase in healthcare costs. Our results suggest that, despite the associated increase in financial burden, advances in the management of ARDS have improved mortality rates among patients with ARDS.

AUTHOR CONTRIBUTIONS

Conceptualization: Tak Kyu Oh and In-Ae Song. Data curation: In-Ae Song. Formal analysis: Tak Kyu Oh. Funding acquisition: In-Ae Song. Investigation: Tak Kyu Oh and In-Ae Song. Methodology: Tak Kyu Oh and In-Ae Song. Project administration: Tak Kyu Oh and In-Ae Song. Resources: In-Ae Song. Software: Tak Kyu Oh and In-Ae Song. Supervision: Tak Kyu Oh and In-Ae Song. Validation: Tak Kyu Oh and In-Ae Song. Visualization: Tak Kyu Oh and In-Ae Song. Writing—original draft: Tak Kyu Oh. Writing—review & editing: In-Ae Song. Approval of final manuscript: Tak Kyu Oh and In-Ae Song.

ORCID iDs

Tak Kyu Oh https://orcid.org/0000-0002-4027-4423
In-Ae Song https://orcid.org/0000-0002-7814-4253

REFERENCES

1. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307:2526-33.
2. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315:788-800.
3. Máca J, Jor O, Holub M, Sklienka P, Burša F, Burda M, et al. Past and present ARDS mortality rates: a systematic review. Respir Care 2017;62:113-22.
4. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. Lancet 2010;376:1339-46.
5. Riviello ED, Kiviri W, Twagirumugabe T, Mueller A, Banner-Goodspeed VM, Officer L, et al. Hospital incidence and outcomes of the acute respiratory distress syndrome using the Kigali modification of the Berlin definition. Am J Respir Crit Care Med 2016;193:52-9.
6. Tzotzos SJ, Fischer B, Fischer H, Zeitlinger M. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: a global literature survey. Crit Care 2020;24:516.
7. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. JAMA 2018;319:698-710.
8. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372:747-55.
9. Zheng Z, Jiang L, Zhang S, Guervilly C, Zhang M, Feng X, et al. Neuromuscular blocking agents for acute respiratory distress syndrome: an updated meta-analysis of randomized controlled trials. Respir Res 2020;21:23.
10. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965-75.
11. Peck TJ, Hibbert KA. Recent advances in the understanding and management of ARDS. F1000Res 2019;8:1959.
12. Li G, Malinchoc M, Cartin-Ceba R, Venkata CV, Kor DJ, Peters SG, et al. Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. Am J Respir Crit Care Med 2011;183:59-66.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495-9.
14. Ike JD, Kempker JA, Kramer MR, Martin GS. The association between acute respiratory distress syndrome hospital case volume and mortality in a U.S. cohort, 2002-2011. Crit Care Med 2018;46:764-73.
15. Combes A, Peek GJ, Hajage D, Hardy P, Abrams D, Schmidt M, et al. ECMO for severe ARDS: systematic review and individual patient data meta-analysis. Intensive Care Med 2020;46:2048-57.
16. Natt BS, Desai H, Singh N, Poongkunran C, Parthasarathy S, Bime C. Extracorporeal membrane oxygenation for ARDS: national trends in the United States 2008-2012. Respir Care 2016;61:1293-8.
17. Roch A, Lepaul-Ercole R, Grisoli D, Bessereau J, Brissy O, Castanier M, et al. Extracorporeal membrane oxygenation for severe influ-

enza A (H1N1) acute respiratory distress syndrome: a prospective observational comparative study. Intensive Care Med 2010;36: 1899-905.
18. Cho HW, Song IA, Oh TK. Trends in extracorporeal membrane oxygenation treatment from 2005 to 2018 in South Korea. Perfusion 2021 May 20. [Epub]. Available at: https://doi.org/10.1177/02676591211018130.
19. Slutsky AS. Neuromuscular blocking agents in ARDS. N Engl J Med 2010;363:1176-80.
20. Puthucheary Z, Rawal J, Ratnayake G, Harridge S, Montgomery H, Hart N. Neuromuscular blockade and skeletal muscle weakness in critically ill patients: time to rethink the evidence? Am J Respir Crit Care Med 2012;185:911-7.
21. Wongtangman K, Grabitz SD, Hammer M, Wachtendorf LJ, Xu X, Schaefer MS, et al. Optimal sedation in patients who receive neuromuscular blocking agent infusions for treatment of acute respiratory distress syndrome-a retrospective cohort study from a New England Health Care Network. Crit Care Med 2021;49:1137-48.
22. Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, Gong MN, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 2019;380:1997-2008.
23. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
24. Ho ATN, Patolia S, Guervilly C. Neuromuscular blockade in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. J Intensive Care 2020;8:12.
25. Han F, Sun R, Ni Y, Hu X, Chen X, Jiang L, et al. Early initiation of continuous renal replacement therapy improves clinical outcomes in patients with acute respiratory distress syndrome. Am J Med Sci 2015;349:199-205.
26. Dill J, Bixby B, Ateeli H, Sarsah B, Goel K, Buckley R, et al. Renal replacement therapy in patients with acute respiratory distress syndrome: a single-center retrospective study. Int J Nephrol Renovasc Dis 2018;11:249-57.
27. Wu N, Hanrahan J, Bornstein J, Chen SY. Healthcare costs utilization and costs of patients hospitalized with acute respiratory distress syndrome (ARDS) in US commercially-insured individuals and medicare beneficiaries. Eur Respir J 2015;46:PA2139.
28. Scholten EL, Beitler JR, Prisk GK, Malhotra A. Treatment of ARDS with prone positioning. Chest 2017;151:215-24.