INTRODUCTION

Acute respiratory distress syndrome (ARDS) is characterized by respiratory failure due to acute hypoxemia, dyspnea, and increased bilateral pulmonary infiltration. A cohort study based on the Berlin criteria reported an ARDS prevalence of 10.4% among intensive care units (ICUs) in 50 countries, and the mortality rates in patients with ARDS ranged from 11%–87%. The global burden of ARDS is the highest in high-and upper-middle-income countries. Moreover, recent evidence has indicated that the global prevalence of ARDS may increase due to the coronavirus disease (COVID-19) pandemic, suggesting that ARDS will become a more important public health issue in the future.
and ECMO support.10 These advances would have likely influenced clinical trends in the management of ARDS.3,11 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, W) and converted subsequently to USD based on an exchange rate of W1080=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, 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
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

| Variable | Value |
|----------|-------|
| ECMO support | 2024 (4.0) |
| Duration of ECMO support, day | 32.2±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

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 | 4555 (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)
ARDS, acute respiratory distress syndrome. [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.
| Variable                                      | HR (95% CI)           | P value |
|-----------------------------------------------|-----------------------|---------|
| Age, male                                     | 1.02 (1.02, 1.02)     | <0.001 |
| Household income level at ARDS treatment      |                       |         |
| Q1 (lowest)                                   | 1.04 (0.97, 1.11)     | 0.250   |
| Q2                                            | 1.02 (0.96, 1.08)     | 0.479   |
| Q3                                            | 0.95 (0.90, 0.99)     | 0.033   |
| Q4 (highest)                                  | 0.84 (0.73, 0.98)     | 0.021   |
| Unknown                                       | 1.27 (1.20, 1.34)     | <0.001 |
| Admitting department: IM (vs. non-IM)         |                       |         |
| Hospital admission                            |                       |         |
| Transfer from other hospital                  | 1.08 (0.99, 1.18)     | 0.068   |
| Admission through Emergency Room              |                       |         |
| Admission through outpatient clinic           | 0.80 (0.73, 0.88)     | <0.001 |
| Annual case volume of ARDS admission          |                       |         |
| Q1 ≤4                                         | 1.09 (1.09, 1.10)     | <0.001 |
| 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)**

| Variable                                      | HR (95% CI)           | P value |
|-----------------------------------------------|-----------------------|---------|
| 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                                          | 1.13 (1.03, 1.24)     | 0.011   |
| 2011                                          | 1.09 (0.99, 1.20)     | 0.077   |

Recent research has indicated that ECMO support can lower mortality risk in patients with severe ARDS. 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, and the influenza pandemic also led to further increases in the use of ECMO support among patients with ARDS. 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. 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. 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. 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 dysynchrony and breathing effort in patients with ARDS, the prolonged use of NMBs may cause side effects, such as neuromuscular weakness. In addition, there is a need for deep sedation during NMB administration. 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, 1.06) | 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   |

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

| Variable                                      | HR (95% CI)            | p value |
|-----------------------------------------------|------------------------|---------|
| 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 (0.88, 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.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.2 Despite these debates regarding the benefits of NMB use in patients with ARDS, 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...
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.\(^1\) 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 Physiology 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,\(^6\) 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.

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