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Impact of the timing of invasive mechanical ventilation in patients with sepsis: a multicenter cohort study

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Abstract

Background The potential adverse effects associated with invasive mechanical ventilation (MV) can lead to delayed decisions on starting MV. We aimed to explore the association between the timing of MV and the clinical outcomes in patients with sepsis ventilated in intensive care unit (ICU).

Methods We analyzed data of adult patients with sepsis between September 2019 and December 2021. Data was collected through the Korean Sepsis Alliance from 20 hospitals in Korea. Patients who were admitted to ICU and received MV were included in the study. Patients were divided into 'early MV' and 'delayed MV' groups based on whether they were on MV on the first day of ICU admission or later. Propensity score matching was applied, and patients in the two groups were compared on a 1:1 ratio to overcome bias between the groups. Outcomes including ICU mortality, hospital mortality, length of hospital and ICU stay, and organ failure at ICU discharge were compared.

Results Out of 2440 patients on MV during ICU stay, 2119 'early MV' and 321 'delayed MV' cases were analyzed. The propensity score matching identified 295 patients in each group with similar baseline characteristics. ICU mortality was lower in 'early MV' group than 'delayed MV' group (36.3% vs. 46.4%; odds ratio, 0.66; 95% confidence interval, 0.47–0.93; $p=0.015$). 'Early MV' group had lower in-hospital mortality, shorter ICU stay, and required tracheostomy less frequently than 'delayed MV' group. Multivariable logistic regression model identified 'early MV' as associated with lower ICU mortality (odds ratio, 0.38; 95% confidence interval, 0.29–0.50; $p<0.001$).

Conclusion In patients with sepsis ventilated in ICU, earlier start (first day of ICU admission) of MV may be associated with lower mortality.

Keywords Mechanical ventilation, Sepsis, Intensive care unit, Propensity score, Korean Sepsis Alliance

Background

Mechanical ventilation (MV) is a double-edged sword to critically-ill patients. It improves gas exchange, lowers the work of breathing, and minimizes the risk of patient self-inflicted lung injury [1, 2]. As MV is usually started with sedatives and/or neuromuscular blockers, it may reduce the overall oxygen consumption and, consequently, carbon dioxide production in these patients [3]. In patients with cardiac complications, an increased intrathoracic

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pressure due to MV lowers the venous return and reduces the left ventricular afterload [4], which may improve the heart function. These effects put together can help stabilize the hemodynamics and improve the acid–base disturbances in patients with sepsis. On the other hand, MV is associated with ventilator-induced lung injury [5] or diaphragm dysfunction [6]. Endotracheal intubation for MV can cause laryngeal injuries [7]. Besides, the use of sedatives during MV can lead to delirium and prolonged ICU stay [8, 9]. These drawbacks may deter the decision-making on early intubation and MV. Thus, physicians resort to alternative methods such as noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC) to circumvent hazards of MV. However, this practice tends to delay the use of invasive MV and sometimes leads to worse outcomes [10]. NIV failure rate is reported to be as high as 51% [11], and HFNC failure can occur in about 30% of the patients [12, 13]. Further, MV initiation after more than 48 h of HFNC is associated with a high rate of intensive care unit (ICU) mortality [14].

Existing literature on the timing of intubation in patients with sepsis has inconsistent results. Although some studies have reported beneficial effects of early MV [15, 16], other studies have shown no significant benefits [17]. The aim of this study was to examine the association between the timing of invasive MV and the outcome in a large multicenter cohort of patients with sepsis. We hypothesized that early MV is beneficial in patients with sepsis.

Methods

Study design and patient population

Data of adult patients with sepsis between September 2019 and December 2021 was prospectively collected through the Korean Sepsis Alliance (20 secondary or tertiary hospitals in Korea). Adult patients aged 19 years (legal age for adult in Korea) or older who were diagnosed with sepsis during the study period and admitted to the ICU were included in the study cohort. Sepsis was defined according to the Sepsis-3 definitions [18], including both clinical suspicion of infection and organ dysfunction determined by two or more points scored in the Sequential Organ Failure Assessment (SOFA) score. Patients' hospital journey was followed until hospital discharge or death. Patients' data was collected at ICU admission, on day 1, 2, 3, 7, and the last day of the ICU stay. Patients who were not placed on invasive MV were excluded from this study. The included patients were divided into two groups based on whether they were on MV on the first day of ICU admission ('early MV' group) or later ('delayed MV' group). In this study, MV only included invasive MV and not noninvasive MV. This study was approved by the institutional review boards of all participating hospitals (approval number: IRB-H1808-135-967). All patient data was anonymized.

Study outcomes

Primary outcome: ICU mortality according to 'early MV' vs. 'delayed MV'.

Secondary outcomes: In-hospital mortality, duration of hospital stay, duration of ICU stay, duration for MV, progression to acute respiratory distress syndrome (ARDS), application of renal replacement therapy during ICU stay, need for organ support at ICU discharge including oxygen, MV, HFNC, tracheostomy, and renal replacement therapy in the two study groups.

Propensity score matching

Propensity score matching was used to balance pretreatment characteristics. Variables used for matching included baseline biological information such as age, sex, body mass index (BMI), comorbidities (cardiovascular disease, chronic lung disease, chronic neurologic disease, chronic liver disease, diabetes mellitus, chronic kidney disease, connective tissue disease, immunosuppressed, hematologic malignancy, and solid malignant tumor) and site of infection (respiratory or non-respiratory). Chronic neurologic diseases included a broad range of neurologic diseases including vascular diseases, dementia and movement disorders. Severity information such as initial lactate levels, initial SOFA score, use of vasopressor, and initial vital signs (systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate) were also included. Patients in the 'early MV' and 'delayed MV' groups were matched 1:1 with the nearest neighbor propensity score, estimated using logistic regression, without replacement. The standard pair distance was 0.010. The standardized mean difference (SMD) was used to evaluate adequacy of matching and less than 10% was considered an acceptable balance between the two matched cohorts [19, 20]. The lowest score caliper width that resulted in a sufficient number of subjects and met adequate matching criteria was chosen to produce close matches [21]. Sensitivity analysis was performed using the Hosmer–Lemeshow test, which showed a p value of 0.13 after matching, validating the adequacy of the matching. Matched and unmatched populations were compared within 'early MV' and 'delayed MV' groups separately (Supplementary Tables 1 and 2).

Statistical analysis

Categorical variables were reported as frequency and percentages. Continuous variables were reported as medians and interquartile ranges (IQRs). Between-group differences in baseline characteristics were assessed using Student's t test or Mann–Whitney U

test for continuous variables, and Chi-square test or Fisher exact test for categorical variables. Comparisons between the primary and secondary outcome variables (specified above) were presented as odds ratios (ORs) and 95% confidence intervals (CIs).

Based on the previously reported frequency (77%) of early MV with the same definition as this study [22], the minimum sample size has arrived at 273 participants by considering a confidence level of 95% and a margin of error of 5%.

Multivariable analysis was separately performed to determine variables associated with ICU mortality and early MV application on the unmatched population using logistic regression model with backward elimination method. For ICU mortality model, variables used for propensity score matching were used. For early MV application model, along with most variables used for propensity score matching, additional variables such as admission history of patients at the institution, the types of institution the patients came from (secondary or tertiary), antibiotics use within past 30 days, treatment of wound (an incidence of therapeutic management of a broken skin injury) within past 30 days, dialysis within past 30 days, SOFA score on the first day of ICU admission, Clinical Frailty Scale score, and pathogen type were used for analysis. Continuous variables were categorized into lower abnormal, normal, and upper abnormal values for possibilities of nonlinear relationships. Nagelkerke R^2 was calculated and ORs were displayed on a forest plot. Survival curves were estimated using the Kaplan–Meier method, group differences were compared using the log-rank test. The effect size of unmeasured confounders was estimated using the E-value, calculated with the website for computing E-values [23, 24].

Sensitivity analysis was performed by re-analyzing the propensity score matching using a new set of variables that were composed of the variables used for primary analysis and the variables found associated with the decision of early MV. The added variables included SOFA score on the first day of ICU stay, use of antibiotics within past 30 days, dialysis within past 30 days, and Clinical Frailty Scale score. Propensity score matching using the available data on the day of MV initiation was additionally analyzed (Supplementary Table 3).

All analyses were two-tailed, and p values of < 0.05 were considered statistically significant. Statistical analyses were performed using R Statistical Software (version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

During the study period between September 2019 and December 2021, a total of 11,981 patients with sepsis were registered in the Korean Sepsis Alliance. A total of 4890 patients were admitted to the ICU, of whom 2,527 patients were on MV at some point during their ICU stay (Fig. 1). The 2,527 patients with sepsis who were admitted to the ICU and received MV were included in the study cohort and divided into 'early MV' and 'delayed MV' groups (depending if the patient was put on MV on the first day of ICU stay or later). Patients with missing data (n = 87) on variables used for propensity score matching were excluded, and 2,440 patients without missing data (2119 'early MV' and 321 'delayed MV' cases) were used for analysis.

The baseline characteristics of the unmatched cohort are shown in Table 1. 'Early MV' group was older (72 [62–80] vs. 70 [59–78] years of age, $p = 0.01$), had more septic shock (34.2% vs. 27.7%, $p = 0.027$), used more vasopressor (41.0% vs. 33.6%, $p = 0.02$), had higher median lactate levels (3.8 [2.0–6.9] mmol/L vs. 3.1 [1.8–5.9] mmol/L, $p < 0.01$), and had a higher proportion of chronic neurologic disease (25.0% vs. 18.4%, $p = 0.01$) and diabetes mellitus (38.6% vs. 31.8%, $p = 0.02$) than 'delayed MV' group. 'Early MV' group had a median respiratory rate lower than in 'delayed MV' group (22 [18–27] breaths/min vs. 25 [21–31] breaths/min, $p < 0.01$). Initial SOFA score was higher in 'early MV' group than in 'delayed MV' group (8 [5–10] vs. 7 [4–9], $p < 0.01$). Although the study period overlaps with the coronavirus disease 2019 (COVID-2019) pandemics, most patients with COVID-19 were transferred to government-designated special COVID-19 treatment clinics, and only 12 among 2440 (0.49%) patients were reported to have COVID-19. Additionally, 71 out of 2440 (2.9%) patients were on extracorporeal membrane oxygenator during their ICU stay.

Propensity score matching

Using the propensity score matching criteria, 295 patients in 'early MV' group were matched with 295 patients in 'delayed MV' group (Table 1). In 'early MV' group vs. 'delayed MV' group, the median ages were 71 [61–80] years vs. 71 [60–79] years, proportion of male was 62.7% vs. 63.4%, need for vasopressor was 30.8% vs. 34.2%, the median lactate levels were 3.6 [1.7–5.9] mmol/L vs. 3.1 [1.8–6.1] mmol/L, and the median SOFA scores were 6 [5–9] vs. 7 [5–9].

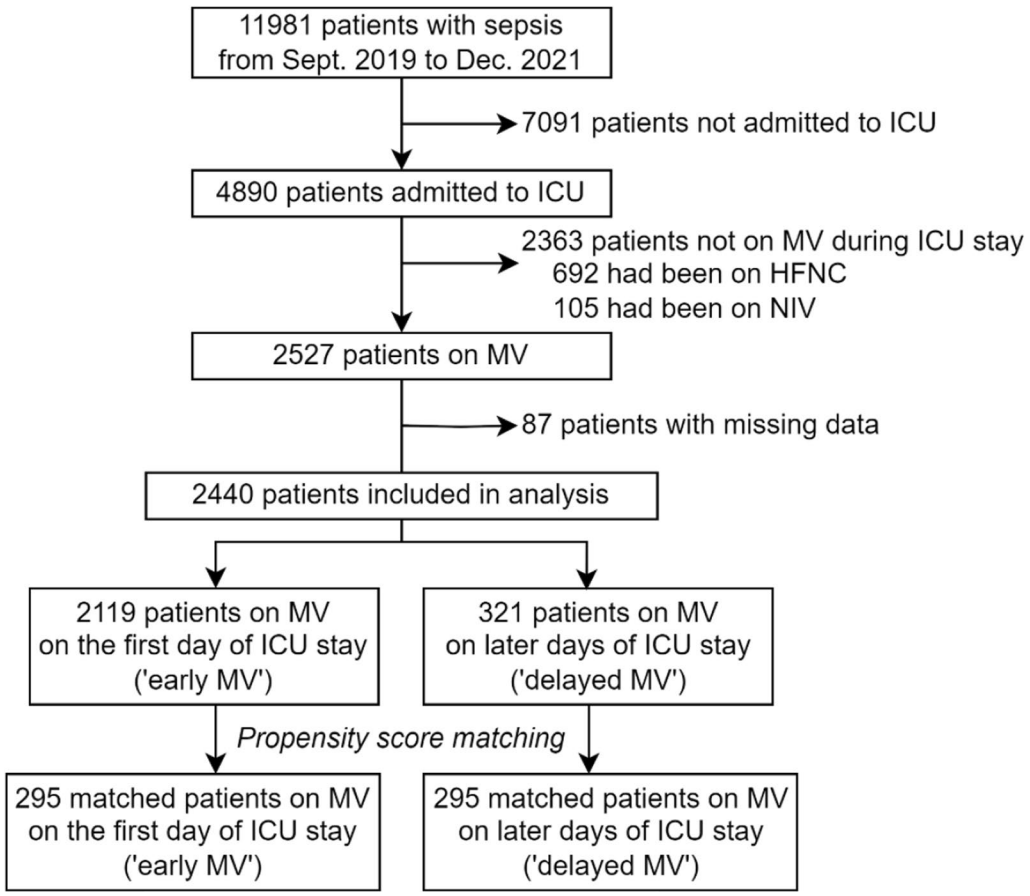

Fig. 1 Study design and patient inclusion

Outcomes

Unmatched cohort

When 'early MV' group was compared with 'delayed MV' group, better outcomes in ICU mortality (38.4% vs. 45.2%, $p=0.025$), in-hospital mortality (47.7% vs. 54.8%, $p=0.020$), hospital duration (19 [8–37] days vs. 24 [12–50] days, $p<0.001$), and duration of ICU stay (7 [3–15] days vs. 12 [6–20] days, $p<0.001$) were observed (Table 2). Duration of MV was similar between in 'early MV' group and 'delayed MV' group (5 [2–12] days vs. 6 [2–14] days, $p=0.249$).

ARDS occurrence during the ICU stay did not differ between the two groups. During ICU stay, a higher number of patients in 'early MV' group required renal replacement therapy than 'delayed MV' group (26.7% vs. 18.1%, $p=0.001$), but at ICU discharge a smaller number of patients in 'early MV' group required renal replacement therapy (7.1% vs. 13.6%, $p=0.004$). 'Early MV' group less frequently required tracheostomy (22.2% vs. 30.1%, $p=0.025$) than 'delayed MV' group.

Propensity score-matched cohort

ICU mortality was significantly lower in 'early MV' vs. 'delayed MV' group (36.3% vs. 46.4%) with an OR of 0.66 (95% CI, 0.47–0.93; $p=0.015$) (Table 2). 'Early MV' group also showed a better outcome in 28-day ICU mortality (33.6% vs. 42.4%, $p=0.034$). In-hospital mortality was lower in 'early MV' vs. 'delayed MV' group (44.7% vs. 55.9%) with an OR of 0.64 (95% CI, 0.46–0.89; $p<0.001$). ICU duration was also shorter in 'early MV' vs. 'delayed MV' group (7 [3–14] days vs. 12 [6–20] days, $p<0.001$). The median MV duration was 4 [2–10.5] days and 6 [2–13.5] days, respectively ($p=0.060$).

During ICU stay, ARDS occurrence during the ICU stay did not differ between the two groups. A higher number of patients in 'early MV' group required renal replacement therapy than 'delayed MV' group (28.1% vs. 18.6%, $p=0.009$). At ICU discharge, however, no significant differences were observed in the proportion of patients who required renal replacement therapy. At ICU discharge, a smaller number of patients in 'early MV'

Table 1 Baseline characteristics of study population (numbers in parentheses represent percentages)

	(A) Unmatched cohort				(B) Propensity score-matched cohort			
	Early MV n = 2119	**Delayed MV n = 321**	***p* value**	**SMD (%)**	**Early MV n = 295**	**Delayed MV n = 295**	***p* value**	**SMD (%)**
Age	72 [62, 80]	70 [59, 78]	0.01	16.2	71 [61, 80]	71 [60, 79]	0.43	7.2
Sex			0.76	2.2			0.93	1.4
Male	1349 (63.7)	201 (62.6)			185 (62.7)	187 (63.4)		
Female	770 (36.3)	120 (37.4)			110 (37.3)	108 (36.6)		
BMI	21.9 [19.2, 24.8]	21.9 [18.9, 24.8]	0.94	1.8	21.7 [18.7, 24.8]	22.0 [18.8, 24.8]	0.64	4.9
Septic shock								
Vasopressor	868 (41.0)	108 (33.6)	0.02	15.2	91 (30.8)	101 (34.2)	0.43	7.2
Lactate > 2 mmol/L	1530 (72.2)	206 (64.2)	< 0.01	17.3	202 (68.5)	189 (64.1)	0.30	9.3
Comorbidities								
Cardiovascular disease	513 (24.2)	73 (22.7)	0.61	3.5	78 (26.4)	70 (23.7)	0.51	6.3
Chronic lung disease	350 (16.5)	39 (12.1)	0.06	12.5	30 (10.2)	38 (12.9)	0.37	8.5
Chronic neurologic disease	530 (25.0)	59 (18.4)	0.01	16.1	67 (22.7)	56 (19.0)	0.31	9.2
Chronic liver disease	206 (9.7)	38 (11.8)	0.28	6.8	32 (10.8)	35 (11.9)	0.80	3.2
Diabetes mellitus	818 (38.6)	102 (31.8)	0.02	14.3	108 (36.6)	100 (33.9)	0.55	5.7
Chronic kidney disease	311 (14.7)	48 (15.0)	0.96	0.8	48 (16.3)	47 (15.9)	1.00	0.9
Connective tissue disease	58 (2.7)	13 (4.0)	0.26	7.3	9 (3.1)	12 (4.1)	0.66	5.5
Immunosuppressed	83 (3.9)	16 (5.0)	0.45	5.2	18 (6.1)	15 (5.1)	0.72	4.4
Hematologic malignancy	156 (7.4)	33 (10.3)	0.09	10.3	23 (7.8)	29 (9.8)	0.47	7.2
Solid malignant tumor	643 (30.3)	91 (28.3)	0.51	4.4	81 (27.5)	86 (29.2)	0.72	3.8
Site of Infection			< 0.01	40.9			0.51	6.2
Respiratory	1256 (59.3)	126 (39.3)			116 (39.3)	125 (42.4)		
Other than respiratory	863 (40.7)	195 (60.7)			179 (60.7)	170 (57.6)		
Vital signs								
SBP (mmHg)	105 [86, 126]	105 [91, 124]	0.29	4.7	102 [88, 120]	105 [91, 123]	0.16	8.5
DBP (mmHg)	60 [51, 73]	62.0 [53, 72]	0.11	11.3	60 [50, 72]	62 [53, 71]	0.23	7.2
HR (beats/min)	109 [91, 126]	109 [93, 124]	0.94	0.1	110 [91, 124]	109 [94, 124]	0.70	3.3
RR (breaths/min)	22 [18, 27]	25 [21, 31]	< 0.01	41.7	24 [20, 29]	25 [20, 30]	0.19	6.0
Lactate (mmol/L)	3.6 [1.7, 5.9]	3.1 [1.8, 6.1]	< 0.01	20.5	3.6 [1.7, 5.9]	3.1 [1.8, 6.1]	0.62	1.4
SOFA score	8 [5, 10]	7 [4, 9]	< 0.01	32.0	6 [5, 9]	7 [5, 9]	0.59	1.7

group were tracheostomized compared with 'delayed MV' group (16.5% vs. 31.0%, $p = 0.002$).

Kaplan–Meier curves of mortality showed similar 28-day ICU mortality between 'early MV' and 'delayed MV' groups (Supplementary Fig. 1). The log-rank test did not show significant differences.

Logistic regression model for ICU mortality

A multivariable logistic regression model using the backward elimination method was performed. The resulting model, predicting ICU mortality in the unmatched MV cohort, showed that 'early MV' was associated with ICU mortality, with an OR of 0.38 (95% CI, 0.29–0.50; $p < 0.001$) (Fig. 2). The amount of variance explained as estimated by Nagelkerke R^2 was 0.22 suggesting that 22% of differences contributed to the outcome.

Factors associated with early MV application

As the timing of MV depends on many variables, we performed multivariable analysis using logistic regression to investigate the determinants of 'early MV' application (Fig. 3). The best model was composed of comorbidities, respiratory rate, SOFA score on the first day of ICU admission, antibiotics treatment within past 30 days, dialysis treatment within past 30 days, and Clinical Frailty Scale score as contributors. Chronic lung disease, chronic neurologic disease, SOFA score on the first day of ICU stay, and Clinical Frailty Scale score were associated with 'early MV' implementation. Whereas chronic liver disease, immunodeficiency, and dialysis within past 30 days were associated with 'delayed MV'. Statistical significance at conventional level was found in comorbidities, SOFA score on the first day of ICU admission, dialysis treatment within

Table 2 Outcomes of study population (numbers in parentheses represent percentages)

	(A) Unmatched cohort			(B) Propensity score-matched cohort			
	Early MV n = 2119	**Delayed MV n = 321**	***p* value**	**Early MV n = 295**	**Delayed MV n = 295**	**OR (95% CI)**	***p* value**
ICU mortality	814 (38.4)	145 (45.2)	0.025	107 (36.3)	137 (46.4)	0.66 (0.47–0.93)	0.015
In-hospital mortality	1010 (47.7)	176 (54.8)	0.020	132 (44.7)	165 (55.9)	0.64 (0.46–0.89)	0.008
Hospital duration (days)	19 [8, 37]	24 [12, 50]	< 0.001	18 [8, 35.5]	23 [12, 48.5]		0.001
ICU duration (days)	7 [3, 15]	12 [6, 20]	< 0.001	7 [3, 14]	12 [6, 20]		< 0.001
MV duration (days)	5 [2, 12]	6 [2, 14]	0.249	4 [2, 10.5]	6 [2, 13.5]		0.060
During ICU stay							
ARDS	150 (7.1)	26 (8.1)	0.587	13 (4.4)	25 (8.5)	0.50 (0.23–1.04)	0.065
Renal replacement therapy	566 (26.7)	58 (18.1)	0.001	83 (28.1)	55 (18.6)	1.71 (1.14–2.57)	0.009
At ICU discharge							
Oxygen requirement	737 (56.5)	93 (52.8)	0.406	104 (55.3)	83 (52.5)	1.12 (0.72–1.75)	0.682
MV	186 (14.3)	22 (12.5)	0.608	22 (11.7)	19 (12.0)	0.97 (0.48–1.98)	1.000
HFNC	175 (13.4)	27 (15.3)	0.559	23 (12.2)	26 (16.5)	0.71 (0.37–1.36)	0.333
Tracheostomized	290 (22.2)	53 (30.1)	0.025	31 (16.5)	49 (31.0)	0.44 (0.25–0.75)	0.002
Renal replacement therapy	93 (7.1)	24 (13.6)	0.004	16 (8.5)	22 (13.9)	0.58 (0.27–1.20)	0.152

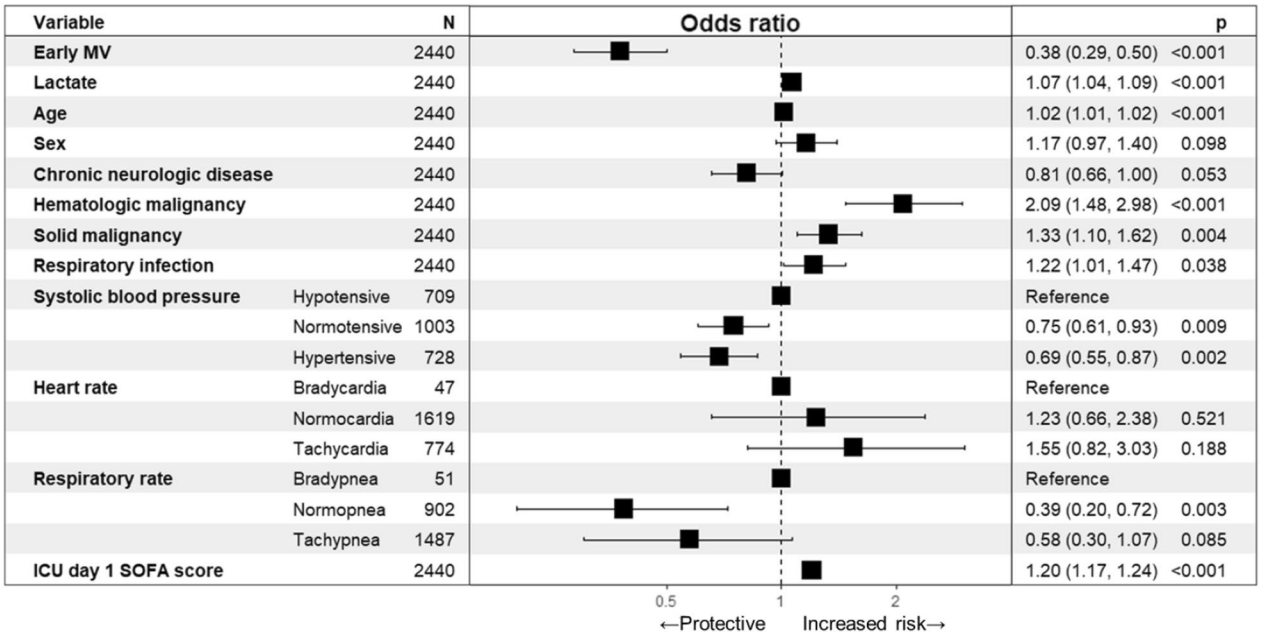

Fig. 2 Multivariable logistic regression model among unmatched cohort for predicting ICU mortality. OR and *p* value of each variable are shown

past 30 days, and Clinical Frailty Scale score. The amount of variance explained as estimated by Nagelkerke R^2 was 0.23 suggesting that 23% of differences contributed to the outcome. Sensitivity analysis was performed by adding the variables associated with early MV application in propensity score matching, and ICU mortality was consistently lower in 'early MV' group than in 'delayed MV' group (33.7% vs. 49.4; OR, 0.52; 95% CI, 0.33–0.83; $p = 0.005$).

Discussion

This multicenter cohort study using the Korean Sepsis Alliance registry data showed that in sepsis patients ventilated in ICU, 'early MV' initiation by the first day of ICU admission was associated with a lower mortality (both ICU mortality and in-hospital mortality) and a decreased length of ICU stay. The outcome benefits were consistent after propensity score matching with patients who received 'delayed MV'.

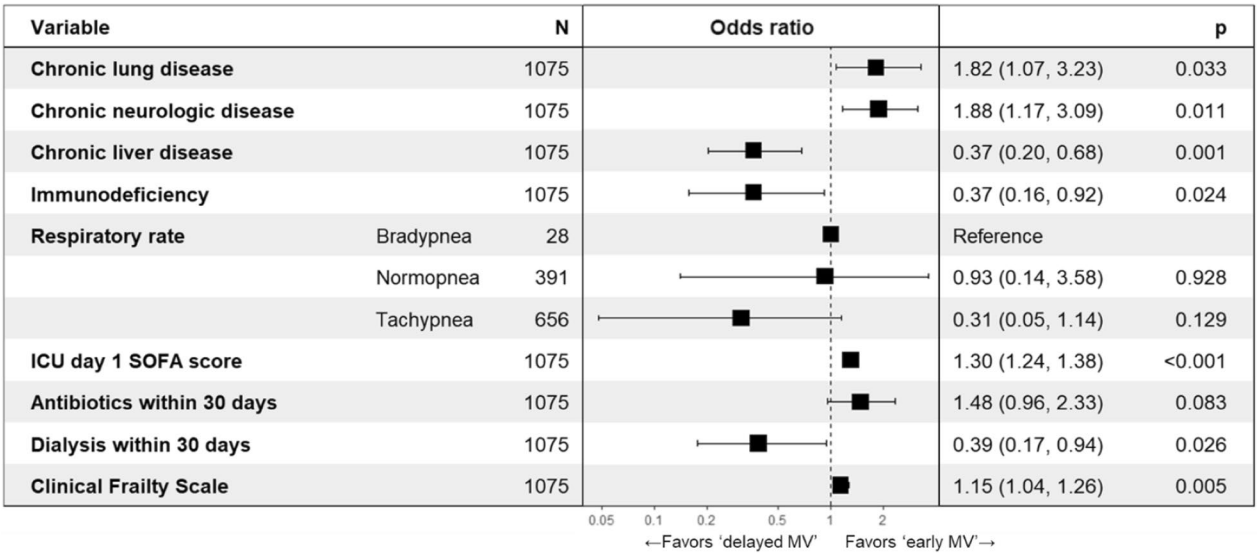

Fig. 3 Multivariable analysis for 'early MV' on the unmatched study population, and ORs for the selected variables of the best model

Although several studies have compared the timing of invasive MV in critical care, there exist only a few studies that have investigated a homogeneous group of sepsis. A post hoc analysis of a randomized controlled trial of 776 septic shock patients showed that delayed MV was associated with fewer days alive without organ support [15]. Another retrospective analysis of 358 septic shock patients showed that intubation within 24 h of sepsis onset was associated with reduced hospital-free days through 28 days [16]. These studies, however, did not show any mortality benefits of early MV. Another secondary analysis of multicenter prospective study involving 735 septic shock patients did not show any significant differences in the hospital mortality or length of hospital stay in the early MV group compared to the delayed MV group [17].

Findings from MV timing studies conducted in different disease settings showed different results. Studies in patients with acute respiratory failure (ARF) have shown mortality benefits of early MV. A prospective cohort study investigating 60-day mortality of 457 patients with ARDS (of whom 40% had sepsis) demonstrated that patients in delayed intubation group had higher mortality than patients in early intubation group [19]. Similarly, another pooled analysis of 11,087 immunocompromised patients with ARF showed low mortality in those who received early invasive MV [25]. Studies of patients with COVID-19 also reported compromised mortality with delayed intubation [26–28]. The results of our present study on sepsis patients are more consistent with these results from ARF, ARDS, and COVID-19.

In our results, 'early MV' was also associated with a shorter ICU stay. Clinicians may be inclined to circumvent MV in septic patients due to the concern over prolonged ICU stay. MV often necessitates the use of sedatives and paralyzing agents, which are known to delay extubation and to increase ICU stay [9]. Contrary to this popular belief, early application of MV was associated with reduced length of ICU stay in our propensity score-matched cohorts. Shorter ICU stay in patients undergoing early MV was also observed in other studies investigating the timing of MV [29, 30]. Reducing the length of ICU stay has emerged as an important issue for optimizing ICU resource utilization, especially in the era of pandemics such as COVID-19. Our study, along with the previous studies, suggests the prompt cardiorespiratory stabilization provided by early MV may outweigh potential disadvantages in terms of ICU stay.

Physiologic benefits of timely MV may not be limited to the pulmonary system. In our results, renal replacement therapy during ICU stay was more frequent in 'early MV' group than in 'delayed MV' group (Table 2). At ICU discharge, however, 'early MV' group was associated with a smaller (albeit statistically insignificant) proportion of patients requiring renal replacement therapy than 'delayed MV' group. MV is known to exert unpredictable effects on renal function. According to a few studies, MV has negative effects on kidney function [31–33], which could be attributed to decreased cardiac output, compromised renal blood flow, increased inflammation, and elevated sympathetic tone. Nevertheless, there exist a few studies that showed positive effects of MV on renal function. In a study by Delbove et al., the proportion of

patients without renal replacement therapy on day 28 was significantly higher in the early intubation group [15]. Similar trend was observed in a cohort study [34]. In line with these reports, our results suggest 'early MV' may favor the overall risk–benefit of the renal function in critically ill patients with sepsis.

ARDS from sepsis is known to carry a higher mortality rate compared with ARDS from other causes [35]. Direct and indirect lung injuries entering airspace and circulation interrupt alveolar-capillary barrier, leading to sepsis-induced ARDS. We hypothesized that 'early MV' can be associated with less ARDS progression due to early stabilization of the lungs. However, our results showed that progression to ARDS was similar between 'early MV' and 'delayed MV' groups, suggesting that the timing of MV did not significantly affect the progression to ARDS (Table 2). The need for respiratory support at ICU discharge was investigated to estimate the respiratory sequelae at ICU discharge. The proportion of patients requiring tracheostomy at ICU discharge was significantly lower in 'early MV' group. Physicians, whether novice or experienced, may prefer to manage respiratory distress of patients without resorting to invasive airways, such as endotracheal intubation and tracheostomy. Nevertheless, previous reports have shown early MV resulted in decreased MV duration or increased MV-free days [15, 29], suggesting a decreased need for tracheostomy with early intubation. Our result adds to these reports that timely intubation in patients with sepsis may reduce the likelihood of requiring a tracheostomy.

The present study showed that early MV was associated with decreased ICU and in-hospital mortality in patients with sepsis from the results of Chi-square test and logistic regression model. Our results showed an effect size (OR) of 0.66 (95% CI, 0.47–0.93) for ICU mortality, and multivariable analysis performed for unmatched MV cohort also showed an OR of 0.38 (95% CI, 0.29–0.50) for 'early MV' (Fig. 2). However, the survivals did not vary between the groups in survival analysis performed with log-rank test and Cox proportional hazards model (Supplementary Fig. 1). The discrepancies in the results can be due to different factors. Reduced power can be one of the factors. A relatively small number of patients were in 'delayed MV' group, resulting in reduced size of propensity score matched cohort. With mortality approaching 50% and the presence of discharged patients leading to censored data, the reduced power of survival analysis may result in less accurate comparisons of survival curves between the 'early MV' and 'delayed MV' groups. Non-proportional hazards can affect the results of the log-rank test, which might have influenced our results. To address these inconsistencies, a larger number of patients in the 'delayed MV' group would be necessary.

We aimed to explore factors favoring 'early MV' application. According to the logistic regression model of best fit, we produced a model composed of comorbidities, respiratory rate, SOFA score on day 1 of ICU admission, antibiotics therapy and dialysis within past 30 days, and Clinical Frailty Scale score to be associated with early MV (Fig. 3). Based on the model, chronic lung disease, chronic neurologic disease, high SOFA score on day 1 of ICU, and high Clinical Frailty Scale score were associated with 'early MV'. On the other hand, chronic liver disease, immunodeficiency, and dialysis treatment within past 30 days were associated with 'delayed MV'. Only 23.5% of 'early MV' decisions can be explained through this model suggesting that there might be other factors associated with the decision for early intubation. This obviously warrants further investigation in future studies.

Decision to intubate and start invasive MV is a complex process involving many factors such as clinical parameters, personal biases, and institutional policies/resources. An observational study demonstrated that factors such as Glasgow Coma Scale score, center effect, use of accessory respiratory muscles, lactate level, vasopressor dose, pH, and inability to clear tracheal secretions explained 60% of the model fit associated with early intubation [29]. A mixed methods study of critical care team members indicated that factors such as patients, clinicians, and other system factors influence the decision-making process of intubation of patients with sepsis [36]. While the severity of ARF is a crucial factor in deciding on MV, over 50% of participants believed that both the severity of the disease and the anticipated disease course should be considered, rather than severity alone. An interesting observational study showed a higher intubation rate and worse outcome in sepsis patients associated with weekend admission [37]. Put together, clinicians need to be aware of various factors interfering with the decision to initiate MV and take caution not to delay intubation due to non-medical factors. Further investigation may be needed to elucidate the determinants of the timing of MV.

Our study has limitations. First, as the study was not a randomized study, selection bias can be present. Notably, patients who were not admitted to ICU or were not on MV were excluded from the study. This study aimed to review those who have a high possibility of necessitating MV and compared 'early MV' and 'delayed MV' in patients who eventually required MV in a retrospective manner. Although we used propensity score matching to minimize the bias, other characteristics that were not matched also could have an effect. E-value estimation showed the observed effects may be overcome by unmeasured confounders by a risk ratio of 1.76-fold. Second, as only calendar day of MV application was available on the registry data, hourly investigation of the timing

of MV application was not possible. Third, time zero of ICU admission may not reflect the exact physiological state of the patient across the population. Fourth, there was a substantial difference in the number of patients between the 'early MV' and 'delayed MV' groups. This may have contributed to the selection bias during the process of propensity score matching, and to the reduced power especially for the log-rank test. A different study design to generate less skewed population numbers may improve the robustness. Fifth, information regarding withdrawing life-sustaining treatments, including MV, was not available on the registry data. Advance directives and physician orders for life-sustaining treatment are still in their infancy in Korea, primarily due to conservative culture. Last, although our study included a large population, the study findings cannot be generalized as the data is from selected centers in a single country.

Conclusions

In patients with sepsis admitted to ICU and received invasive MV, early MV was associated with lower ICU and in-hospital mortality and a shorter ICU stay. Additionally, at ICU discharge, early MV was linked to a reduced need for tracheostomy and a relatively lower frequency of renal replacement therapy.

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
HFNC	High-flow nasal cannula
HR	Hazard ratio
ICU	Intensive care unit
IQR	Interquartile range
KSA	Korean Sepsis Alliance
MV	Mechanical ventilation
NIV	Noninvasive ventilation
SMD	Standardized mean difference
SOFA	Sequential Organ Failure Assessment
OR	Odds ratio

Supplementary Information

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Additional file1

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Author contributions

GK performed statistical analysis and wrote the manuscript. DKO, SYL, and MHP wrote the electronic case report form and managed the database. CML conceptualized and supervised the research. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed in this article are from the KSA registry and are not publicly available due to health privacy concerns but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review boards (IRB) of all participating hospitals (approval number: IRB-H1808-135-967). Informed consent was obtained from all participants or legally authorized representatives for all participating patients who lacked decisional capacity. All patient data was anonymized.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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