Mechanical ventilation associated with worse survival in septic patients: a retrospective analysis of MIMIC-III

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Background: We explored the impact of mechanical ventilation (MV) on hospital mortality in septic patients based on the sepsis-3 criteria.

Methods: We performed a retrospective cohort study of adult Intensive Care Unit (ICU) admissions from 2008 to 2012 of tertiary teaching hospital in Boston, Massachusetts. Multivariate logistic regression explained the relationship between MV and hospital mortality.

Results: In total, 5,783 ICU admissions met for the sepsis-3 criteria with 2,783 (48.1%) receiving invasive ventilation. Compared with sepsis patients without MV, individuals given MV had a higher hospital mortality [odds ratio (OR) 1.6, 95% confidence interval (CI), 1.49–1.75)]. MV was also associated with ICU mortality, 30-day mortality, ICU and hospital length of stay (LOS) for septic patients.

Conclusions: Sepsis patients receiving MV independently tended to have higher in-hospital mortality and other outcomes in admissions of ICU.

Keywords: The sepsis-3 criteria; mechanical ventilation (MV); hospital mortality; MIMIC-III

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Introduction

Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection defined by the Third International Consensus Definitions Task Force (1). It is the most costly disease in the Intensive Care Unit (ICU), covering 23.7 billion dollars (6.2%) of the aggregate costs for all hospitalizations according to the report of Agency for Healthcare Research and Quality (US) (2). The Definitions for Sepsis and Septic Shock (Sepsis-3) (3) updated with criteria for sepsis as suspected infection with associated organ disorders, named Sequential Organ Failure Assessment (SOFA ≥2) (4). The latest version on sepsis identification was certificated to be more effective (5,6).

Sepsis accounts for approximately 70% of clinical disorders from which results in acute respiratory distress syndromes (ARDS) (7), with rapid organ failure, especially for the lung. When the lung was affected, they tended easily to have respiratory failure because of the severe systematic inflammation, and the patients with sepsis are recommended to receive the mechanical ventilation (MV) (8). However, most sepsis patients are more sensitive to MV, and easier to suffer from direct mechanical injury, which could further aggravate the high rates of morbidity and mortality (9,10). Whether we should treat septic patients with protective MV ahead of the respiratory failure coming is still under discussion.

So we studied the deliberated problem based on the latest criteria for septic patients with detailed and specific electronic health records (EHRs) storing in the MIMIC-III database.

The association between MV and the risk of hospital mortality were performed in large sample septic patients.

Methods

Database

Data were obtained from the Medical Information Mart in Intensive Care (MIMIC)-III database v1.4 (11) (https://mimic.physionet.org/). It's an open-access de-identified critical care dataset with 23,620 large ICU admissions. The authors' access to MIMIC-III were approved by Institutional Review Boards of BIDMC and MIT via the training course. The study was reported according to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement (12).

Study population

The study population were extracted from the whole MIMIC-III database, with the including the sepsis-3 (3) criteria for sepsis as suspected infection with associated organ disorders, named Sequential Organ Failure Assessment (SOFA ≥2) (4). We chose patients admitted from 2008 to 2012 as Alistair explained (6): antibiotic prescriptions, explicit sepsis codes, and the new vision of MetaSource are accessible since the year of 2008. And the exclusion criteria were as follows: (I) age below 16 years; (II) experienced cardiac operation; and (III) suspected of infection more than 24 hours before or after ICU admission. The final number of included cohort was 5,783.

Data extraction and management

We fetched the matched data with structure query language (SQL) in PostgreSQL (v10.10) (https://www.postgresql.org/) with the sepsis3 code for MIMIC-III recomposed (13). We precisely replicated the SOFA and Sepsis-3 criteria to define the suitable admissions. And patient demographics (age, gender, ethnicity, fist admission service, admission type and location), diseases (diabetes and metastatic cancer), and clinical outcomes. The primary outcome was hospital mortality of septic patients, and the secondary results were thirty days' mortality, hospital and ICU length of stay (LOS).

Statistical analysis

Demographics for the cohort which was grouped by MV management were analysed. Univariate analysis conducted to figure out the related variables. The *t*-tests were used to compare the continuous data and the results were present as median and 95% confidence internal (CI). For categorical data, we used the Pearson's chi-square test to get the group numbers and percentages. A two-tailed P<0.05 was considered statistically significant. As for the missing data, we assumed they were lost at random, and less than 10% was replicated with multiple imputation to avoid bias when necessary (14).

The significant variables were obtained after the univariate analysis, we proceeded the multivariable logistic regression and cox proportional hazard regression analysis (15) with the survival package (16) to study the potential factors influencing the mortality and LOS of septic patients. The visualization was used the ggplot2 package (17). The tables were created with the CBCgrps package (18).

All statistical analysis was conducted on the R platform (v3.6.1) (http://www.R-project.org).

Results

Demographics and clinical characteristics

In total, 2,783 (48.1%) patients with sepsis based on the sepsis-3 criteria received MV therapy, while 3,000 (51.9%) individuals lacked MV. Baseline characteristics of the grouped cohorts are shown in *Table 1*. The MV group was significantly differed with non-MV group in age, gender, ethnicity, body mass index (BMI), and first admission service. Patients' BMI (kg/m^2) with 2,749 missing weight data excluded was categorized into underweight (BMI <18.5), weight (18.5≤ BMI <25), overweight (25≤ BMI <30), obese (BMI ≥30). Compared with patients within non-MV group, these in MV group tended to have a smaller number of the aged of 65–89 (20.9% *vs*. 26.1%, P<0.001), the female (19.5% *vs*. 24.8%, P<0.001), the white (33.4% *vs*. 39.2%, P<0.001) or black (3.3% *vs*. 5.4%, P<0.001) race, metastatic cancer (2.5% *vs*. 3.4%, P<0.05), differed in first service.

Univariate analysis of clinical outcomes

Clinical outcomes based on the different MV groups are presented in *Table 2*. Among the MV group, patients have worse clinical outcomes including the mortality rate and LOS. 10.7% survived less than thirty days after admitted

Table 1 Univariate analysis of demographics and clinical features

Variables, n (%)	Vent =0 (N=3,000), n (%)	Vent =1 (N=2,783), n (%)	P value
Age			<0.001
<45	314 (5.4)	450 (7.8)	0.50
45-64	879 (15.2)	1,002 (17.3)	0.61
65-89	1,508 (26.1)	1,212 (20.9)	<0.001
>90	299 (5.2)	119 (2.1)	0.98
Gender			<0.001
Female	1,435 (24.8)	1,127 (19.5)	
Male	1,565 (27.1)	1,656 (28.6)	
Ethnicity			
White	2,267 (39.2)	1,934 (33.4)	<0.001
Black	311 (5.4)	192 (3.3)	<0.001
Hispanic	94 (1.6)	94 (1.6)	0.65
Other	328 (5.7)	563 (9.7)	<0.001
BMI			<0.001
Underweight	61 (2.0)	29 (1.0)	<0.001
Weight	509 (16.8)	391 (12.9)	<0.001
Overweight	503 (16.6)	485 (16.0)	<0.001
Obese	467 (15.4)	589 (19.4)	<0.001
First service			<0.001
MED	1,924 (33.9)	1,225 (21.1)	
CMED	261 (4.5)	459 (7.9)	
SURG	237 (4.1)	325 (5.6)	
NSURG	199 (3.4)	241 (4.2)	
Others	374 (6.5)	510 (8.8)	
Diabetes			0.28
Yes	864 (14.9)	765 (13.2)	
No	2,136 (37.0)	2,018 (34.9)	
Metastatic cancer			0.02
Yes	199 (3.4)	143 (2.5)	
No	2,801 (48.4)	2,640 (45.7)	

The data were based on the first 24 hours in ICU. BMI, body mass index; MED, medical—general service for internal medicine; CMED, cardiac medical—for non-surgical cardiac related admissions; SURG, surgical—general surgical service not classified elsewhere; NSURG, neurologic surgical—surgical, relating to the brain.

Table 2 Univariate analysis of clinical outcomes

Variables	Vent=0	Vent=1	P value
Mortality, n (%)			
During hospitalization	269 (4.7)	567 (9.8)	<0.001
Thirty days in the ICU	420 (7.3)	621 (10.7)	<0.001
LOS, Median (95% CI)			
Hospitalization	6.24 (3.90, 10.15)	9.13 (5.61, 15.58)	<0.001
ICU stay	1.88 (1.16, 3.11)	4.03 (2.07, 8.40)	<0.001

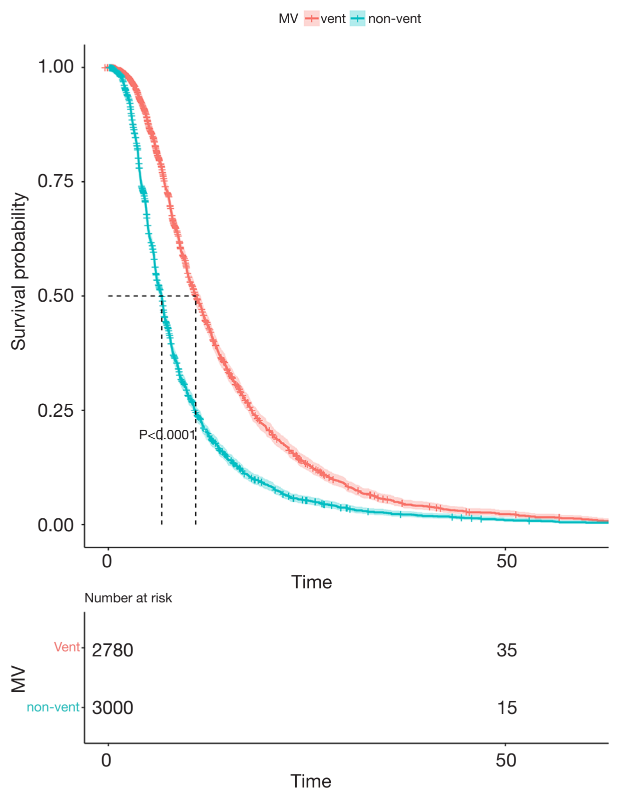

Figure 1 Kaplan-Meier curve. Comparison of hospital mortality between MV and non-MV sepsis patients. MV, mechanical ventilation.

in the ICU, which was significantly much higher than the percentage of non-MV group (7.3%, P<0.001). Moreover, 9.8% patients of MV therapy and 4.7% patients of non-MV therapy died during hospitalization (P<0.001).

As regard to the LOS, the MV group with sepsis tended to have longer days with the median length of hospitalization and ICU stay was 9.13 and 4.03 days, respectively, while that for the non-MV sepsis patients was 6.24 and 1.88 (P<0.001 for both). The Kaplan-Meier curve for hospitalization survival by MV is shown in *Figure 1*, indicating the obvious advantage in the non-MV group compared with the MV (log-rank test P<0.0001).

Survival analysis and multivariate logistic regression model

We performed the univariate analysis between survival and death patients with sepsis on the duration of hospitalization and thirty-day status to figure out the mortality-related factors (*Table 3*). We further conducted the Cox proportional-hazards model and selected MV, gender, age (<45 as younger age, 45–64 as middle age, 65–89 as aged age, >90 as older age), BMI, the white race as the chosen factors. The multivariate regression model revealed relation among non-ventilation (P<0.001, OR =1.62, 95% CI, 1.50–1.70), the older (P<0.001, OR =1.55, 95% CI, 1.28–1.90), female (P<0.05, OR =1.10, 95% CI, 1.01–1.20) and the high risk of death during sepsis patients' hospitalization (*Figure 2*).

Discussion

Little studies discussed the relationship between MV and clinical outcomes in patients meeting the criteria sepsis-3, mostly focused on the ventilation mode and parameters. Understanding how invasive ventilation could hurt lungs has developed over years (19), however, the results of whether septic patients should receive invasive ventilation are still controversial. We obtained the 5,783 patients meeting the sepsis-3 criteria for the further retrospective cohort analysis. To ensure the reliability, we grouped patients into the MV group and non-MV group from considerably large number of population. Interestingly, the study recruited patients who required MV for 48 hours or more but did not have ARDS at the onset of MV from the

Table 3 Univariate analysis of demographic and clinical features by sepsis patients outcomes

Variables	Hospital survival, n (%)			Survival in 30 days, n (%)		
	Survival	Death	P value	Survival	Death	P value
Vent	2,216 (38.3)	567 (9.8)	<0.001	2,162 (37.4)	621 (10.7)	<0.001
Age			<0.001			<0.001
<45	707 (12.2)	57 (1.0)	0.41	700 (12.1)	64 (1.1)	0.10
45–64	1,656 (28.6)	225 (3.9)	0.37	1,619 (28.0)	262 (4.5)	0.18
65–89	2,240 (38.7)	480 (8.3)	<0.001	2,126 (36.8)	594 (10.3)	<0.001
>90	344 (5.9)	74 (1.3)	0.99	297 (5.1)	121 (2.1)	0.98
Gender			0.32			0.14
Female	2,178 (37.7)	384 (6.6)		2,079 (36.0)	483 (8.4)	
Male	2,769 (47.9)	452 (7.8)		2,663 (46.0)	558 (9.6)	
Ethnicity						
White	3,626 (62.7)	575 (10.0)	0.0076	3,468 (60.0)	733 (12.7)	0.08
Black	451 (7.8)	52 (0.9)	0.0073	437 (7.6)	66 (1.1)	0.0035
Hispanic	170 (2.9)	18 (0.3)	0.07	167 (2.9)	21 (0.4)	0.02
Other	700 (12.1)	191 (3.3)	<0.001	670 (11.6)	221 (3.8)	<0.001
BMI			0.11			0.0059
Underweight	855 (21.7)	133 (3.4)	0.43	70 (2.3)	20 (0.7)	0.35
Weight	763 (19.4)	137 (3.5)	0.005	725 (23.9)	175 (5.8)	0.02
Overweight	855 (21.7)	133 (3.5)	0.92	827 (27.3)	161 (5.3)	0.24
Obese	930 (23.7)	126 (3.2)	0.55	908 (30.0)	148 (4.9)	0.48
First service			<0.001			<0.001
MED	2,629 (45.5)	525 (9.1)		2,475 (42.8)	679 (11.7)	
CMED	628 (10.9)	92 (1.6)		618 (10.7)	102 (1.8)	
SURG	510 (8.8)	52 (0.9)		510 (8.8)	52 (0.9)	
NSURG	385 (6.7)	55 (1.0)		368 (6.4)	72 (1.2)	
Other	765 (13.2)	112 (2.3)		771 (13.3)	136 (2.4)	
Diabetes			0.74			0.66
Yes	1,398 (24.2)	231 (4.0)		1,342 (23.2)	287 (5.0)	
No	3,549 (61.4)	605 (10.4)		3,400 (58.8)	754 (13.0)	
Metastatic cancer			<0.001			<0.001
Yes	249 (4.3)	93 (1.6)		207 (3.6)	135 (2.3)	
No	4,689 (81.3)	743 (12.8)		4,535 (78.4)	906 (15.7)	

MED, medical—general service for internal medicine; CMED, cardiac medical—for non-surgical cardiac related admissions; SURG, surgical—general surgical service not classified elsewhere; NSURG, neurologic surgical—surgical, relating to the brain.

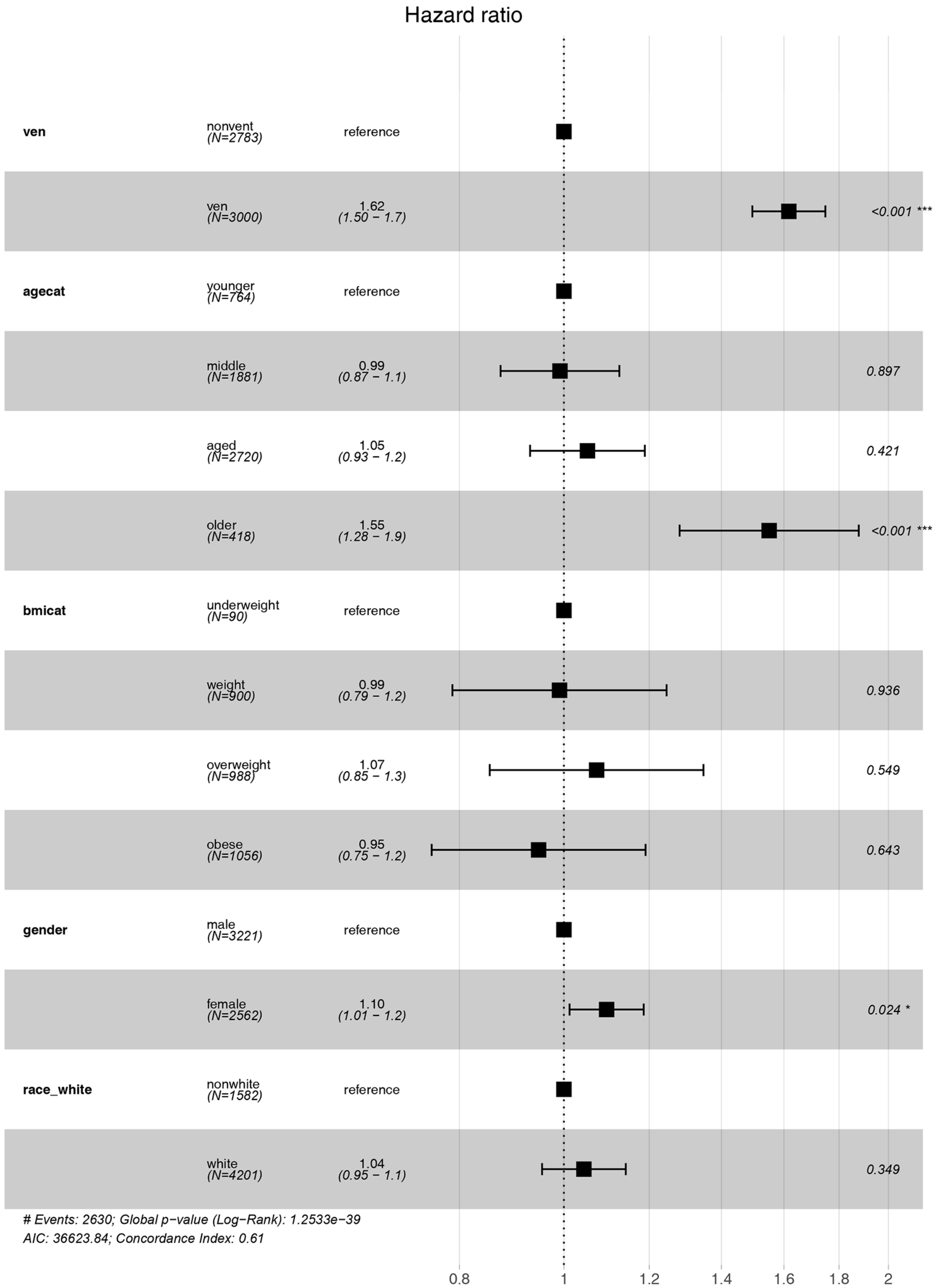

Figure 2 Results of the Cox proportional hazard regression analysis. Ven as mechanical ventilation (including the two groups of ventilation and non-ventilation); agecat as age categories including the four age groups of younger as <45, middle as 45–64, aged as 65–89, older as >90); bmicat as BMI categories (including the four BMI groups of underweight as <18.5, weight as 18.5–25), overweight as 25–30, obese as ≥30); * is a symbol of P value <0.05, *** is a symbol of P value <0.001.

International Mechanical Ventilation Study database, and found that is the initial ventilator settings, in particular large tidal volumes, had potential harm (20). In addition, high MV power was independently associated with higher in-hospital mortality in ICU patients receiving invasive ventilation for at least 48 hours (6). They suggested that ARDS in mechanically ventilated patients is a partial preventable complication. There was a systematic analysis about the patients without ARDS receiving lower tidal volume of invasive ventilation, and the results got greater clinical outcomes (21). Similarly, another claimed that mechanically ventilated patients without ARDS benefited from the lower tidal volume to alleviate ARDS (22).

Female had a higher risk on sepsis development, which conflicted with a study specialized in the sex impact (23). The study reported male patients with sepsis had higher mortality rate and LOS of hospital and ICU, however, the male were tended to have more treatments. Sepsis patients with metastatic cancer was related with the worse clinical outcomes, while the disease state of diabetes had no significant influence.

Our limitations still existed. We obtained from the two large cohort derived from a retrospective and single-center database. The population met the novel sepsis-3criteriawhich is still under uncertificated proof. The criterion is strongly advised SOFA and quick SOFA (qSOFA) instead of lactate based on the mortality of the patients, and it is proven that SOFA has better predictive validity for in-hospital mortality than SIRS and qSOFA in ICU from 148,907 patients and 184,875 patients respectively (5,24). Meanwhile, compared with Sepsis-2 shock, there has a much higher Acute Physiology And Chronic Health Evaluation II (APACHE II) score, with greater mortality on Sepsis-3 septic shock (25). Systematic interpretation could not be merely involved in one single dependent factor, and it is inevitable to ignore other mixed variables. The results indicated the physician must be very cautious about the need for MV in patients under the sepsis-3 criteria. To discover more exactly, we are on procession on following up the patients who has not yet progressed to respiratory failure or ARDS to predict their lung involvement severity and mortality.

Conclusions

The clinical outcome in mechanically ventilated patients met the sepsis-3 criteria is worse than that in non-MV sepsis patients as regard to the mortality and length of hospital and ICU stay.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors' access to MIMIC-III were approved by Institutional Review Boards of BIDMC and MIT via the training course.

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