The Impact of Ventilator-Associated Events in Critically Ill Patients with Prolonged Mechanical Ventilation

Hidetsugu Kobayashi[1], MD, Shigehiko Uchino[1], MD, Masanori Takinami[1], MD, Shoichi Uezono[2], MD.

1: Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan

2: Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan

Address correspondence to:

Hidetsugu Kobayashi

Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine

3-19-18, Nishi-Shinbashi, Minato-ku, Tokyo, Japan, 105-8471.

TEL: 81-3-3433-1111, FAX: 81-3-5401-0454

E-mail: hidetsugu-evfr@jikei.ac.jp

Contributorship

Literature search: HK, SUc

Data collection: HK, SUc

Study design: HK, SUc, MT

Analysis of Data: HK, SUc

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Abstract

BACKGROUND: The Centers for Disease Control and Prevention (CDC) recently released a novel surveillance definition for respiratory complications in ventilated patients, ventilator-associated event (VAE), to replace ventilator-associated pneumonia (VAP). VAE consists of a ventilator-associated condition (VAC), an infection-related ventilator-associated complication (IVAC), and a possible VAP (PVAP). A duration of mechanical ventilation (MV) of at least four calendar days is required to diagnose VAE. However, the observed duration of MV was shorter than four calendar days in many previous studies. We aimed to evaluate the impact of VAE on clinical outcomes in critically ill patients who required MV for equal to or greater than four calendar days.

METHODS: This single-center retrospective cohort study was conducted in the general intensive care unit (ICU) of an academic hospital. We included 407 adult subjects who were admitted to the ICU and required MV for at least four calendar days. VAC and IVAC were identified from the electronic medical records. VAP was defined according to the 2008 CDC's criteria and was identified from the surveillance data of the Infection Control Team of our

hospital. Clinical outcomes were studied in the VAC, IVAC, and VAP groups. PVAP was not investigated.

RESULTS: Higher mortality was seen in VAC and IVAC subjects, but not in VAP subjects, compared with those without VAEs and VAP. By multivariable hazard model for hospital mortality, IVAC was independently associated with hospital mortality (HR: 2.42, 95%CI: 1.39-4.20, P= .002). VAC also tended to show a similar association with hospital mortality (HR: 1.45, 95%CI: 0.97- 2.18, P= .07). On the other hand, VAP did not increase a hazard of hospital death (HR: 1.08, 95%CI: 0.44- 2.66, P= .87).

CONCLUSIONS: We found that VAE was related to hospital mortality in critically ill patients with prolonged mechanical ventilation and that VAP was not.

Key Words: mechanical ventilation, complication, ventilator-associated pneumonia, ventilator-associated event, prolonged mechanical ventilation

Introduction

Ventilator-associated pneumonia (VAP) is a major morbidity in patients with mechanical ventilation (MV), and many hospitals regard VAP as an important nosocomial infection.[1-3] However, it is difficult to diagnose VAP accurately because the diagnostic criteria include subjective and non-specific measures such as chest radiography and sputum conditions.[1] Therefore, alternative quality benchmarking for mechanically ventilated patients has been sought in the past decade.[4-8] In 2013, the US Centers for Disease Control and Prevention (CDC) established a novel surveillance definition, the ventilator-associated event (VAE).[8,9] VAE consists of a ventilator-associated condition (VAC), an infection-related ventilator-associated complication (IVAC, a subset of VAC with infectious signs), and a possible VAP (PVAP, IVAC with microbiological evidence of pneumonia). Several studies have shown that VAC and IVAC were associated with morbidity and mortality, and that the relationship between VAC (or IVAC) in new VAE criteria and VAP in the previous 2008 CDC's definition was poor.[10-14]

To diagnose a VAE, sustained deterioration of oxygenation for at least two calendar days after stability or improvement on the ventilator for two or more consecutive days is needed.

However, in most previous studies validating the VAE definition, the duration of MV was defined as more than 48 hours,[10,11,14,15] or at least two calendar days.[12,13,16] The duration of MV in those studies did not meet the minimal requirement of the VAE definition (at least four calendar days in total). We speculated that the shorter duration of MV in those studies than that of VAE criteria might affect the results. Therefore, in the present study, we included only patients who required prolonged MV (equal to or greater than four calendar days) to strictly follow the VAE definition, and investigated the impact of VAC, IVAC, and VAP in 2008 CDC's criteria on patient outcome. We also examined the relationship between VAC, IVAC, and VAP.

Methods

This is a single-center retrospective cohort study, conducted in a 20-bed general intensive care unit (ICU) of an academic hospital in Tokyo, Japan. The Investigational Review Board of Jikei University hospital reviewed the study protocol, and the need for informed consent was waived because of the anonymous and retrospective design.

Study Population

All patients who were admitted to the ICU between January 1st 2010 and December 31st 2013 were screened retrospectively. We included subjects who were equal to or older than 18 years of age and required MV for four or more calendar days. Subjects treated with extracorporeal membrane oxygenation (ECMO) or high-frequency oscillatory ventilation (HFOV) were excluded. We identified VAC and IVAC in the study population according to the new VAE definition and PVAP was not examined in this study.[9] Our laboratory reports only semi-quantitative results without a count of neutrophils and squamous epithelial cells for sputum culture, which made us difficult to diagnose PVAP. VAP subjects during the study period were identified in the VAP surveillance database maintained by the Infection Control Team of our hospital, based on previous 2008 CDC criteria, usually PNU1. The 2008 CDC PNU1 definition consists of X-ray findings, clinical signs or symptoms and laboratory data (leukopenia or leukocytosis). Microbiological tests are not needed to diagnose clinical pneumonia.[1] Therefore, cut-off values in semi-quantitative sputum culture to diagnose VAP were not established in our VAP surveillance. In our usual practice, we requested the chest X-

ray once a day in ventilated patients because of the confirmation of the tracheal tube and catheters. Furthermore, regardless of the surveillance protocol (2008 VAP definition or 2013 VAE criteria), microbiological tests (tracheal aspirate was usually used) were examined when we suspected of respiratory infection in ventilated subjects by worsening gas exchange, the change of sputum condition, chest X-ray findings, white blood cell count, body temperature and so on.

Data Collection

From the computerized ICU database, we retrieved following subject characteristics: age, gender, height, weight, Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[17] duration from hospital admission to ICU admission, ICU admission type, ICU readmission within consecutive hospitalization, comorbidities, requirement of tracheostomy and renal replacement therapy (RRT) in the ICU, and clinical outcomes. To identify VAC and IVAC, we also collected the following data from the electronic medical records: daily minimum F_{IO_2} and PEEP, body temperature, white blood cell count, and antimicrobial agent use.[9]

Primary outcome was hospital mortality. We took time-varying confounding of ventilated patients and competing events (liberation from MV, discharge alive or dead within 3 days from ICU admission) into account to evaluate the impact of ventilator-associated complication to hospital mortality. Secondary outcomes included ICU mortality, duration of MV, and length of stay (LOS) in ICU and hospital.

Statistical Analysis

The characteristics and outcomes of VAEs (VAC and IVAC) and VAP subjects were studied by descriptive statistics and were presented as medians and interquartile ranges (25^{th} to 75^{th} percentiles) in continuous variables or percentages in categorical data. Because subjects with VAEs or VAP were not mutually exclusive, for example, subjects in the IVAC group were all included in VAC, pairwise comparisons of subjects with VAC, IVAC and VAP to the "without VAEs and VAP" (the rest of VAEs and VAP) group were explored, respectively. The Fisher's exact test and t-test were used for comparisons of categorical data and continuous data, respectively. Since survival and death at hospital discharge are competing events, a cause-

specific hazard (CSH) for hospital death were explored by the Cox proportional hazards model with multivariate baseline variables as fixed covariates and VAC as time-dependent covariate. Firstly, candidate confounding baseline variables (age, sex, height, weight, APACHE II score, ICU admission type, comorbidities) to CSH for hospital death were selected by backward variables selection using the Cox proportional hazards model where both removing and staying criteria were set at P value < 0.05. Next, CSH for hospital death was modelled with statistically significant variables (fixed covariates) and VAC as a time-dependent covariate and hazard ratios and their 95% confidence intervals were estimated. An unadjusted hazard ratio of VAC (time-dependent covariate) was also estimated. Similar analyses were done for IVAC and VAP. The association between VAE/VAP and ICU events (ICU readmission within consecutive hospitalization, RRT, tracheostomy) was explored by odds ratios. Furthermore, the association between characteristics of VAE/VAP subjects and hospital mortality was also investigated by odds ratios. In the two-by-two contingency table including zero-cell, we used modified odds ratios by the addition of 0.5 to each cell of the study table. [18] For all statistical analyses, a commercially available statistical software (SAS®, Version 9.4) was used.

Results

During the study period, 2054 subjects were intubated and received MV in the ICU. Of these, 407 were ventilated for four or more calendar days, and three subjects were excluded because of the ECMO use. No subjects were treated with HFOV during the study period. All subjects were followed up to hospital discharge and there was no censoring in this study. Flow chart of study subjects was shown in Figure 1. A total of 54 and 23 subjects were identified as having VAC and IVAC, respectively (IVACs were a subset of the VACs). Twenty-one subjects were received a diagnosis of VAP by the Infection Control Team during the study period, among whom one was excluded because the duration of MV was shorter than four calendar days. There were 20 VAP subjects (5.0%) in 404 study population. Eight subjects (8/404, 2.0%) met both of VAC according to the VAE criteria and VAP according to the previous CDC's definition. Twenty-three IVACs included only 4 VAPs. There was no strong correlation between VAE and VAP.

The median and mean days from the initiation of MV to the onset of VAC (or IVAC) were 4.5

days (25^{th} to 75^{th} percentiles: 3 to 9) and 9.2 (standard deviation: 17.3) days. Table 1 summarizes the characteristics of subjects with VAEs (VAC including IVAC, IVAC), VAP and without VAEs and VAP. The median age was 68 years and 70 percent of subjects were male. Approximately half of subjects was admitted to ICU after elective or emergent surgery. The APACHE II score was significantly lower in VAP subjects than without VAEs and VAP (P= .018). The clinical courses and outcomes for subjects with VAEs, VAP and without VAEs and VAP are summarized in Table 2. Median ventilation day and LOS of ICU were approximately seven and 11 days, respectively. Overall ICU and hospital mortality were 18% and 37%. Indication of RRT within ICU stay was more frequent and mortality was higher in VAC and IVAC subjects compared with subjects without VAEs and VAP. Table 3 shows the association between VAE/VAP and incidences of ICU readmission, requirement of tracheostomy/RRT in the ICU. RRT requirement in the ICU was significantly associated with VAC and IVAC, but not VAP.

Results of multivariable Cox proportional hazards model analysis for hospital mortality are shown in Table 4. After adjustment of confounding variables (body weight, sex male, APACHE

II score, liver failure and metastatic cancer), IVAC was independently associated with hospital mortality (HR: 2.42, 95%CI: 1.39- 4.20, P= .002). VAC also tended to show a similar association with hospital mortality (HR: 1.45, 95%CI: 0.97- 2.18, P= .07). VAP was not associated with hospital death (HR: 1.08, 95%CI: 0.44- 2.66, P= .87). The association between characteristics of VAE/VAP subjects and hospital mortality is summarized in Table 5. In non-operative subjects, VAC and IVAC were significantly associated with hospital mortality, while VAP was not. In subjects with comorbidities, although there was no statistically significance, odds ratios for hospital mortality tended to be higher in VAC and IVAC compared with VAP.

Discussion

Key Findings

We have studied the clinical impact of VAC, IVAC in the VAE criteria and VAP in the 2008 CDC's definition in 404 subjects who required MV for equal to or greater than four calendar days. IVAC was independently associated with hospital mortality. Although not statistically significant, VAC also tended to show a similar association with hospital mortality. On the other

hand, VAP was not associated with hospital death.

Relationship to Previous Studies

There are several previous studies on the epidemiology and clinical impact of VAEs.[10-16,19] The incidence of VAC and IVAC was reported approximately 5 to 10% and 3 to 5%, respectively, similar to our results (VAC: 13.4%, IVAC: 5.7%).[10,12,13,19] These previous studies consistently found that the relationship among VAC, IVAC and conventional VAP was poor, and that VAE was associated with adverse outcomes. However, the duration of MV in these studies was shorter than the minimal requirement in the VAE definition (four calendar days). The shorter duration of MV in those studies might have affected the assessment of clinical outcomes of VAEs.

To the best of our knowledge, there are only a few studies in which study cohorts met the minimal requirement of the duration of MV to diagnose VAE. Lilly and colleagues studied the prevalence and characteristics of VAEs in 8408 adult patients who required MV for at least 10 minutes in seven ICUs.[20] They included 2857 patients who required MV for four or more days

to identify VAC and IVAC, and included 3313 patients who required MV for three or more days to identify VAP. They demonstrated that the odds ratios for in-hospital mortality for VAC, IVAC, and VAP after adjustment for disease severity and type of ICU were not statistically significant (OR: VAC 1.84, IVAC 1.32, VAP 1.03). However, in the analysis for in-hospital mortality, all mechanically ventilated patients who required MV for at least 10 minutes were used as the reference. We think that the shorter duration of MV than four days in the reference in their analysis possibly affected their results. The OUTCOMEREA Study Group studied VAE epidemiology and clinical outcomes in 3028 critically ill adult patients with MV for at least five consecutive days.[21] They found that VAC and IVAC were associated with longer ventilation days, prolonged ICU and hospital stay, and increase in the total antimicrobial consumption. The crude rates of hospital mortality for VAC, IVAC, and Non-VAC were similar among the three groups (VAC 36.7%, IVAC 44.4%, Non-VAC 39.9%). However, they modified the VAE definition presented by CDC for the deterioration of oxygenation (P_{aO_2}/F_{IO_2} ratio and PEEP level instead of increase in daily minimum F_{IO_2} and PEEP values).[9] This modification makes the comparison of their results with other studies (including ours) difficult. Furthermore, several

studies decreased the time-related selection bias by their statistical methods. Klompas and colleagues matched the duration of MV in ventilated control subjects for as long as the time to VAE onset to reduce the impact of the different duration of MV on the clinical outcomes.[5,6,22] Other studies used the time varying statistical methods to account for time to onset of VAE.[11,13] In our study, we not only limited study subjects to those who met the minimal requirement of the MV duration for VAE diagnosis but also used the time varying statistical method to account for time to onset of VAE/VAP for the impact on hospital mortality.

Significance and Implications

In subjects with MV for at least four calendar days, IVAC was associated with hospital mortality, while VAP was not (Table 4). The more critically ill subjects might be picked up by the VAE surveillance than that of VAP (Table 1, 2, 5). Furthermore, the VAE definition can facilitate automated surveillance because of the requirement for objective data.[8,9] We believe that VAE is more appropriate for a surveillance tool than previous 2008 VAP in critically ill patients who require prolonged MV.

However, it is uncertain whether VAE is a remarkable quality indicator or merely a marker of disease severity in ventilated patients. In general, a quality indicator is necessary to evaluate preventability of a certain intervention. The preventability of VAE has been investigated in recent studies, and early liberation from MV has been suggested for preventing VAE.[23-25] Further studies for the preventability of VAE are needed to develop new bundles of care for ventilated patients.

Strengths and Limitations

Different from many previous studies,[10-16] all subjects in the present study met the minimal requirement of four calendar days on MV to diagnose VAE. We also used the time varying statistical method to reduce a major source of confoundings that longer a subject was on MV, the greater their risk of poor outcomes was. Furthermore, there was no censoring and all subjects were followed-up until hospital discharge in this study. To our knowledge, the finding that RRT requirement was strongly associated with VAC and IVAC in this study (Table 3) has not been studied in previous studies. Further prospective studies are needed to evaluate a

causal relationship between VAE and RRT requirement.

The present study also has several limitations. First, the generalizability of our findings could be limited because of retrospective research conducted in a single center in Japan. However, all subjects in our study met the minimal requirement of the duration of MV to diagnose VAE and we used the time-varying statistical method for the impact of VAE/VAP on mortality. Although this is a small single-center study, we believe that the current study also provides useful information for epidemiology and outcomes of VAE as well as prior studies. [5,6,11,13,20,21,22] Second, PVAP in the VAE criteria was not investigated due to semi-quantitative microbiological data without a count of neutrophils and squamous epithelial cells for sputum culture in our laboratory. Furthermore, not all VAE subjects were screened for microbiological cultures. These limitations made us difficult to diagnose PVAP and compare with VAP in 2008 CDC criteria. Third, we did not investigate the detailed causes of VAE. The various causes of deterioration of oxygenation in patients with VAE have been reported in previous studies.[12,13,20,21] Although it is important to detect causes of respiratory deterioration to treat patients in the clinical settings, it is not known what interventions can lead to VAE prevention.

Further studies are necessary to identify the causes of VAE.

Conclusions

We have found that VAE was related to hospital mortality in critically ill patients with prolonged mechanical ventilation and that VAP was not. VAE, especially IVAC, is a reasonable novel marker for surveillance in mechanically ventilated patients.

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Figure 1

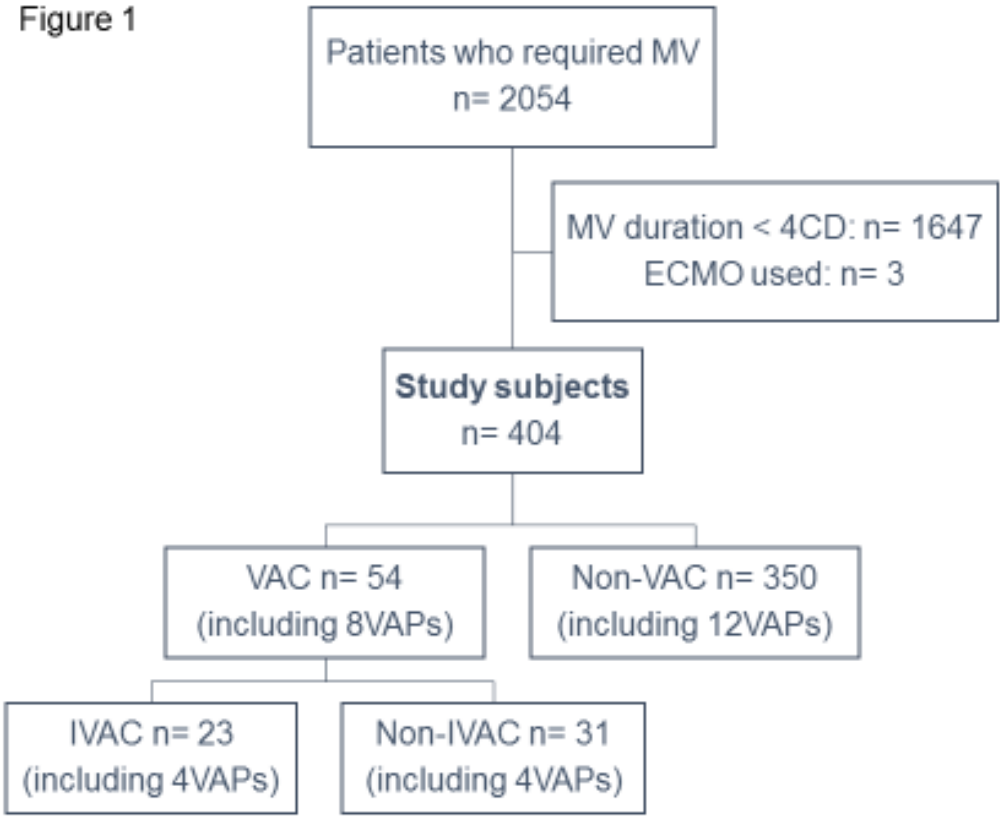

Figure 1: Flow chart of subjects who required mechanical ventilation. MV: mechanical ventilation, CD: calendar days, ECMO: extracorporeal membrane oxygenation, VAC: ventilator-associated condition, IVAC: infection-related ventilator-associated complication, VAP: ventilator-associated pneumonia by 2008 CDC's criteria.

Table 1. Characteristics of VAEs and VAP subjects

	All subjects	VAC	IVAC	VAP	Without VAEs and VAP
Number of subjects	404 (100%)	54 (13.4%)	23 (5.7%)	20 (5.0%)	338 (83.7%)
Age, years	68 (58-75)	70 (61-78)	70 (64-76)	67 (61-72)	68 (58-75)
Male	283 (70.0%)	38 (70.4%)	17 (73.9%)	14 (70.0%)	237 (70.1%)
Height, cm	164 (156-169)	164 (156-171)	163 (156-174)	164 (158-174)	164 (156-169)
Weight, kg	57 (49-67)	60 (50-70)	60 (52-65)	54 (51-69)	56 (48-65)
APACHE II score	23 (18-29)	24 (19-32)	24 (19-30)	17 (14-27)*	23 (18-29)
Admission type					
Emergency surgery	91 (22.5%)	8 (14.8%)	4 (17.4%)	3 (15.0%)	81 (24.0%)
Elective surgery	120 (29.7%)	23 (42.6%) *	9 (39.1%)	13 (65.0%) *	90 (26.6%)
Non-operative	193 (47.8%)	23 (42.6%)	10 (43.5%)	4 (20.0%) *	167 (49.4%)
Comorbidities					
Immunocompromised	46 (11.4%)	9 (16.7%)	4 (17.4%)	1 (5.0%)	36 (10.7%)
Metastatic cancer	11 (2.7%)	1 (1.9%)	0 (0%)	0 (0%)	10 (3.0%)
Hematologic malignancy	22 (5.4%)	4 (7.4%)	2 (8.7%)	0 (0%)	19 (5.6%)
ESKD	44 (10.9%)	7 (13.0%)	4 (17.4%)	3 (15.0%)	37 (10.9%)
Liver failure	9 (2.2%)	2 (3.7%)	2 (8.7%)	0 (0%)	7 (2.1%)

VAC: ventilator-associated condition, including IVAC, IVAC: infection-related ventilator-associated complication, VAP: ventilator-associated pneumonia in 2008 CDC's criteria, VAE: ventilator-associated event, APACHE II score: acute physiology and chronic health evaluation score II, ESKD: end-stage kidney disease.

Continuous data are presented as median and interquartile range (25^{th} to 75^{th} percentiles) and categorical data are summarized by percentage.
Fisher's exact test and t-test were performed in the comparison of categorical data and continuous data, respectively.
* P value < .05 compared to "Without VAEs and VAP" group.

Table 2. Clinical course and outcomes of VAEs and VAP subjects

	All subjects	VAC	IVAC	VAP	Without VAEs and VAP
Number of subjects	404 (100%)	54 (13.4%)	23 (5.7%)	20 (5.0%)	338 (83.7%)
Hosp-ICU, days	5 (0-16)	5.5 (2-15) †	4 (2-18) †	6.5 (1.3-7.8) †	5 (0-18)
ICU readmission	77 (19.1%)	8 (14.8%)	4 (17.4%)	3 (15.0%)	67 (19.8%)
Tracheostomy	132 (32.7%)	18 (33.3%)	7 (30.4%)	7 (35.0%)	109 (32.2%)
Renal replacement therapy	113 (28.0%)	25 (46.3%) *	14 (60.9%) *	5 (25.0%)	88 (26.0%)
Duration of MV, days	7 (5-12)	15 (7-23) †	13 (9-21) †	11 (8-17) †	6 (4-9)
(ICU discharge alive)	7 (5-10)	14 (8-20) *	10 (9-15)	9 (8-12) *	5 (4-8)
(ICU discharge dead)	11 (6-21)	15 (7-24)	13 (8-23)	27 (23-35)	8 (5-20)
ICU LOS, days	11 (7-17)	17 (11-23) †	15 (12-22) †	14 (13-22) †	10 (7-15)
(ICU discharge alive)	11 (7-15)	17 (12-24) *	17 (13-20) *	13 (11-16) *	10 (7-15)
(ICU discharge dead)	12 (6-23)	15 (10-23)	14 (11-21)	26 (23-34)	10 (5-21)
Hospital LOS, days	63 (33-119)	47 (31-122) †	47 (16-88) †	74 (41-123) †	63 (33-120)
(Hospital discharge alive)	72 (42-126)	95 (59-224) *	102 (63-219)	82 (62-129)	68 (41-121)
(Hospital discharge dead)	43 (17-98)	38 (16-65)	38 (14-65)	36 (30-39)	53 (20-103)
ICU mortality	74 (18.3%)	26 (48.1%) *	14 (60.9%) *	5 (25.0%)	47 (13.9%)
Hospital mortality	150 (37.1%)	31 (57.4%) *	15 (65.2%) *	5 (25.0%)	118 (34.9%)

VAC: ventilator-associated condition, including IVAC, IVAC: infection-related ventilator-associated complication, VAP: ventilator-associated pneumonia in 2008 CDC's criteria, VAE: ventilator-associated event, Hosp-ICU: duration from hospital admission to ICU admission, ICU readmission: ICU readmission within consecutive hospitalization, MV: mechanical ventilation, LOS: length

of stay.
Continuous data are presented as median and interquartile range (25^{th} to 75^{th} percentiles) and categorical data are summarized by percentage.
Fisher's exact test and t-test were performed in the comparison of categorical data and continuous data, respectively.
* P value < .05 in the comparison to "Without VAEs and VAP" group.
† The comparison to without VAEs and VAP group was not performed, because the interpretation depends on the status of discharge (alive or dead).

Table 3. Association between ICU events and VAEs and VAP

All subjects, n= 404	VAC, n= 54	IVAC, n= 23	VAP, n= 20
ICU event	Number of event (proportion), Odds ratio (95% CI)		
ICU readmission, n= 77	8 (15%), 0.71 (0.32- 1.57)	4 (17%), 0.89 (0.29- 2.69)	3 (15%), 0.74 (0.21- 2.59)
Tracheostomy, n= 132	18 (33%), 1.04 (0.56- 1.90)	7 (30%), 0.90 (0.36- 2.23)	7 (35%), 1.12 (0.43- 2.87)
Renal replacement therapy, n= 113	25 (46%), 2.57 (1.43- 4.62)	14 (61%), 4.43 (1.86- 10.56)	5 (25%), 0.85 (0.30- 3.13)

VAE: ventilator-associated event, VAC: ventilator-associated condition, including IVAC, IVAC: infection-related ventilator-associated complication, VAP: ventilator-associated pneumonia in 2008 CDC's criteria, ICU readmission: ICU readmission within consecutive hospitalization.

Table 4. Multivariable hazards model for hospital mortality

	VAC	P value	IVAC	P value	VAP	P value
Crude mortality	31/54 (57.4%)		15/23 (65.2%)		5/20 (25.0%)	
Hazard Ratio (95% CI)	1.61 (1.08- 2.40)	.02	2.27 (1.33- 3.88)	.003	0.70 (0.29-1.71)	.43
Adjusted Hazard Ratio by confounders (95% CI)	1.45 (0.97- 2.18)	.07	2.42 (1.39- 4.20)	.002	1.08 (0.44- 2.66)	.87
Confounding variables						
Weight, kg	0.99 (0.98- 1.00)	.02	0.98 (0.97- 1.00)	.01	0.99 (0.98- 1.00)	.03
Male (vs. female)	1.55 (1.05- 2.29)	.03	1.52 (1.03- 2.25)	.036	1.54 (1.04- 2.28)	.03
APACHE II score, point	1.08 (1.06- 1.10)	<.001	1.09 (1.06- 1.11)	<.001	1.09 (1.06- 1.11)	<.001
Liver failure	3.91 (1.80- 8.52)	<.001	3.66 (1.68- 8.00)	.001	3.49 (1.52- 8.04)	<.001
Metastatic cancer	3.64 (1.58- 8.38)	.002	3.72 (1.62- 8.58)	.002	3.70 (1.60- 8.53)	.003

VAC: ventilator-associated condition, including IVAC, IVAC: infection-related ventilator-associated complication, VAP: ventilator-associated pneumonia in 2008 CDC's criteria, APACHE II score: acute physiology and chronic health evaluation score II. Statistical significant confounder was defined that P value was < .05.

Table 5. Association between hospital mortality and characteristics of VAEs and VAP subjects

Characteristics, Hospital mortality	Hospital mortality, Odds ratio (95% CI)		
All subjects, 150/404 (37.1%)	VAC, 31/54 (57.4%)	IVAC, 15/23 (65.2%)	VAP, 5/20 (25.0%)
Admission type			
Emergency surgery, 30/91 (33.0%)	2/8 (25.0%)	1/4 (25%)	0/3 (0%)
	0.66 (0.12- 3.46)	0.67 (0.07- 6.70)	0.27 (0.014- 5.48) *
Elective surgery, 26/120 (21.7%)	8/23 (34.8%)	4/9 (44.4%)	3/13 (23.1%)
	2.34 (0.86- 6.36)	3.24 (0.80- 13.1)	1.10 (0.28- 4.31)
Non-operative, 94/193 (48.7%)	21/23 (91.3%)	10/10 (100%)	2/4 (50.0%)
	14.0 (3.17- 61.4)	24.7 (1.43- 428) *	1.05 (0.15- 7.64)
Comorbidities			
Immunocompromised, 29/46 (63.0%)	7/9 (77.8%)	4/4 (100%)	0/1 (0%)
	2.39 (0.43- 13.1)	6.18 (0.31- 41.3) *	0.19 (0.007- 4.84) *
Metastatic cancer, 6/11(54.5%)	1/1 (100%)	- †	- †
	3.00 (0.10- 91.0) *	0.85 (0.01- 50.1) *	0.85 (0.01- 50.1) *
Hematologic malignancy, 19/22 (86.4%)	4/4 (100%)	2/2 (100%)	- †
	2.03 (0.09- 47.1) *	1.00 (0.04- 25.7) *	0.18 (0.003- 10.6) *
ESKD, 20/44 (45.5%)	4/7 (57.1%)	2/4 (50.0%)	1/3 (33.3%)
	1.75 (0.34- 8.95)	1.22 (0.16- 9.56)	0.58 (0.05- 6.90)
Liver failure, 7/9 (77.8%)	2/2 (100%)	2/2 (100%)	0 (0%)
	2.27 (0.08- 67.1) *	2.27 (0.08- 67.1) *	0.33 (0.005- 21.6) *

VAE: ventilator-associated event, VAC: ventilator-associated condition, including IVAC, IVAC: infection-related ventilator-

associated complication, VAP: ventilator-associated pneumonia in 2008 CDC’s criteria, ICU readmission: ICU readmission within consecutive hospitalization, ESKD: end-stage kidney disease.

* Modified odds ratio was presented because of zero-cell counts in two-by-two contingency table.

† No subjects were identified IVAC or VAP.