

# Ventilator dependence in critically ill patients with ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*: a multicenter observational study

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## Research

**Keywords:** Ventilator-associated pneumonia, Carbapenem-resistant *Acinetobacter baumannii*, ventilator dependence, mortality

**Posted Date:** May 6th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-479658/v1>

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## Abstract

**Background:** Ventilator-associated pneumonia (VAP) is a leading cause of morbidity and mortality in intensive care units (ICUs). Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is one of the key pathogens associated with VAP. Research on ventilator dependence in patients with VAP caused by CRAB remains limited.

**Methods:** In this retrospective multicenter study, we enrolled ICU-admitted patients with VAP caused by CRAB. The status of ventilator dependence was determined on day 21 after initiating ventilator support, and the clinical factors associated with ventilator dependence as well as the differences in treatment outcomes between patients with and without ventilator dependence were investigated. The impact of VAP-onset time, defined as time between hospitalization and VAP onset, on ventilator dependence and mortality was also explored.

**Results:** A total of 274 patients with VAP caused by CRAB were analyzed. The overall ventilator-dependence rate on day 21 was 63.5% (174/274). Patients with ventilator dependence had longer ICU stays (28.5 [interquartile range (IQR) 21–43] days vs. 16.0 (IQR 12–21) days,  $P < 0.001$ ) and higher day 28 mortality rates (17.2% vs. 5%,  $P = 0.003$ ). Clinical factors associated with ventilator dependence were advanced age (adjusted odds ratio [aOR] 1.02, 95% confidence interval [CI] 1.00–1.04), higher Acute Physiology and Chronic Health Evaluation (APACHE) II score (aOR 1.04, 95% CI 1.00–1.08),  $P_aO_2/FIO_2$  (PF) ratio  $< 200$  (aOR 2.194, 95% CI 1.20–3.99), and late onset VAP (6–10 days: aOR 2.28, 95% CI 1.04–4.99;  $> 10$  days: aOR 3.92, 95% CI 1.86–8.29). Patients with late onset VAP had higher mortality rates.

**Conclusions:** Advanced age, higher APACHE II score, PF ratio  $< 200$ , and late onset VAP were independent factors associated with ventilator dependence in patients with VAP caused by CRAB. Patients with ventilator dependence and late onset VAP were associated with higher mortality rates.

**Trial registration:** This is an observational study; therefore, it has not been registered.

## Background

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a significant nosocomial pathogen among critically ill patients [1]. It was recognized by the World Health Organization as one of the critical-priority pathogens against which research and development of new antibiotics is required [2]. Patients with nosocomial pneumonia caused by CRAB exhibit higher mortality than those with infection caused by carbapenem-susceptible *A. baumannii* [3]. The incidence rates of CRAB infections are higher in intensive care units (ICUs) than in non-ICU settings, ranging from 3.7% in North America to 19.2% in Asia [4]. Further, an outbreak of a CRAB infection in an ICU has been reported previously [5]. In Taiwan, nosocomial infections caused by *A. baumannii* in ICUs declined from 11.0% in 2010 to 5.6% in 2019. However, the proportion of CRAB among *A. baumannii* increased from 67.6% in 2010 to 74.0% in 2019 [6].

Nosocomial pneumonia that occurs in ICUs can be divided into ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP). Previous studies reported that VAP develops in about 10–40% of intubated patients on mechanical ventilation [7]. The incidence rate of VAP is estimated to be about 3% per day during days 2 to 5 of mechanical ventilation, 2% per day during days 6 to 10, and 1% per day after 10 days of mechanical ventilation [8]. Risk factors of VAP include certain patient characteristics, prolonged duration of mechanical ventilation and hospital stay, consciousness-related disorders, burns, comorbidities, prior antibiotic therapy, invasive operations, and gene polymorphisms [9, 10]. Mechanical ventilator dependence is a major complication of VAP. Ventilator weaning is unsuccessful in about 10–20% of critically ill patients during their stay in the ICU, and the mortality rate can be as high as 25–50% [7]. The ventilator dependence rate is even higher among VAP patients; around 60%, as described in a previous report [11].

VAP has been classified into two types: early-onset and late-onset, although their definitions vary in previous studies [8, 12, 13]. Most previous studies focused on the risk of multidrug-resistant (MDR) pathogens and reported that patients with late-onset VAP have a higher chance of acquiring infections caused by MDR pathogens than those with early-onset VAP [14]. The information regarding the impact of VAP-onset time on treatment outcomes, especially ventilator dependence, is very limited. We hypothesized that VAP-onset time is an important factor associated with ventilator dependence and patients with VAP caused by CRAB, on ventilator support, exhibit poor treatment outcomes. To prove our hypothesis, we enrolled ICU-admitted patients with VAP caused by CRAB and investigated the clinical parameters associated with dependence on mechanical ventilation. The impact of VAP-onset time on treatment outcomes and ventilator dependence was further explored.

## Methods

### *Patients and settings*

This is a retrospective cohort study conducted in five tertiary medical centers in Taiwan. All patients admitted to the ICU from January 2016 to December 2016 with documented VAP caused by CRAB were enrolled in the study. The inclusion criteria were as follows: (1) ICU-admitted patients diagnosed with VAP, (2) isolation of CRAB from respiratory specimens. Exclusion criteria were: age  $< 20$  years, community-acquired pneumonia or health-care associated pneumonia, pneumonia before ICU admission, lung cancer or obstructive pneumonia, human immunodeficiency virus infection and CD4 count  $< 200$ . To evaluate ventilator dependence, we also excluded patients who were on mechanical ventilation for  $> 21$  days before the occurrence of VAP and those who died within 21 days of initiation of mechanical ventilator support.

### *Pneumonia diagnosis*

The diagnosis of pneumonia was determined based on the presence of new or progressive radiologic pulmonary infiltrates together with at least two of the following: temperature  $> 38^\circ\text{C}$  or  $< 36^\circ\text{C}$ , leukocytosis (white blood cell [WBC] count  $> 12,000$  cells/ $\text{mm}^3$  or leukopenia (WBC count  $< 4000$  cells/ $\text{mm}^3$ ), or purulent

respiratory secretions. VAP was defined as pneumonia that developed more than 48 hours after intubation and initiation of invasive mechanical ventilator support.

### *Microbiological tests and treatment regimens*

Causative organisms were defined as CRAB that were isolated from respiratory specimens, including sputum, endotracheal aspirates, bronchoalveolar lavage fluid with a concentration of  $>10^4$  colony-forming units (CFU)/mL, and protected specimen brush with a concentration of  $>10^3$  CFU/mL. For sputum and endotracheal aspirate, semi-quantitative methods were used. Carbapenem-resistance was defined as resistance to at least one carbapenem (imipenem, meropenem, doripenem, or ertapenem) on performing the antimicrobial susceptibility test. The results of susceptibility tests of the cultured isolates to carbapenems were determined according to the Clinical and Laboratory Standards Institute recommendations. The collection date of the index culture study was defined as the pneumonia index date. Cases of intravenous antibiotics administration for  $\geq 2$  days, within 7 days of the pneumonia index date, were recorded.

### *Data collection and definitions*

During the treatment period, demographic characteristics and underlying comorbidities were retrospectively collected from complete electronic patient files of the participating hospitals. Disease severity was evaluated by calculating the Acute Physiology and Chronic Health Evaluation (APACHE) II score on ICU-admission day and the Sequential Organ Failure Assessment (SOFA) score on ICU-admission day and the pneumonia index date and considering the presence of organ dysfunction (including septic shock [vasopressor use], renal failure [under dialysis], and respiratory failure [mechanical ventilation and  $P_aO_2/FIO_2$  (PF) ratio  $<200$ ]) on pneumonia diagnosis. VAP-onset time was determined based on the duration from hospital admission to the development of VAP [14]. Patients with VAP-onset time more than 5 days after hospital admission were considered as late onset VAP.

### *Ventilator dependence and outcome evaluation*

The decisions regarding weaning and extubation were made by the physicians who were in charge, based on clinical judgment. In general, initiation of weaning was considered when symptoms of respiratory failure improved and vital signs were stable. Before extubation, patients underwent a spontaneous breathing trial and weaning parameters were checked. Weaning success in ventilator-dependent patients was defined as extubation without the need for invasive or noninvasive ventilation within the subsequent 3 days in the ICU and complete liberation from mechanical ventilation for 7 consecutive days [15]. The ventilator-weaning status were determined on day 21 after initiation of ventilator support. Ventilator dependence was defined as constituting  $\geq 21$  consecutive days of mechanical ventilation for  $\geq 6$  hours per day [15]. The other treatment outcomes evaluated in this study included overall number of days of ventilator use, hospital stays, ICU stays, and all-cause mortality on day 28 after occurrence of VAP.

### *Statistical analysis*

Demographic characteristics and disease severities were compared using the Mann–Whitney U-test for non-parametric continuous variables or Student's t-test for parametric continuous variables, and Chi-square test and Fisher's exact test for categorical variables. Multivariate logistic regression analysis was used to identify independent factors associated with mechanical ventilator dependence. All variables with P value  $<0.1$  in the univariate analysis were included in the multivariate model. Treatment outcomes were compared between patients with and without ventilator dependence on day 21 after intubation. For survival analysis, patients were stratified into subgroups according to VAP-onset time (2–5 days, 6–10 days, and  $>10$  days) and ventilator-dependence status. The Kaplan–Meier curves were constructed to evaluate the survival status between subgroups of patients. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, NY, USA). All tests were two-tailed and a P value  $<0.05$  was considered statistically significant.

## Results

### *Patient characteristics*

During the study period, a total of 570 cases of VAP caused by carbapenem-resistant gram-negative

bacteria were eligible for enrollment. A flow diagram showing the number of patients and reasons for exclusion is shown in **Figure 1**. Finally, 274 ICU-admitted patients with VAP caused by CRAB were included in the analysis. The baseline demographic characteristics and disease severities of the enrolled patients are presented in **Table 1**. Their mean age was  $72.0 \pm 14.8$  years and 66.1% were men. More than one-third of them had a smoking history, and 64.2% were admitted to the medical ICU. Diabetes was the most common comorbidity (40.9%). The median APACHE II score on ICU admission was 23 (interquartile range [IQR] 17–28) and median SOFA score on the pneumonia index date was 7 (IQR 5–9), and 40.5% of the patients were using vasopressors when VAP was diagnosed. The median number of days on the ventilator before VAP occurrence was 8 (IQR 5–13), and the median number of days in the hospital before VAP occurrence was 10.5 (IQR 7–18).

Among the enrolled patients, 174 (63.5%) were under mechanical ventilation on day 21 after intubation and were categorized as ventilator-dependent patients. When compared with patients who were not ventilator dependent, patients with ventilator dependence were older ( $73.5 \pm 14.2$  years vs.  $69.4 \pm 15.6$  years,  $P=0.037$ ), had higher APACHE II score on ICU admission (24, IQR 19–28 vs. 21, IQR 15–25,  $P=0.002$ ), had higher SOFA score on ICU admission (8, IQR 6–10 vs. 7, IQR 5–9,  $P=0.005$ ), were more likely to use vasopressors (49.4% vs. 25.0%,  $P<0.001$ ), have PF ratio  $<200$  (36.2% vs. 22.0%,  $P=0.014$ ), and undergo dialysis (30.5% vs. 17.0%,  $P=0.014$ ). Moreover, before VAP, ventilator-dependent patients were on mechanical ventilation for a longer duration (10.0, IQR 6.0–14.0 vs. 6.0, IQR 4.0–8.0 days,  $P<0.001$ ), had longer ICU stays (10.0, IQR 7.0–14.2 vs. 6.0, IQR 5.0–9.0 days,  $P<0.001$ ), and longer hospital stays (12.0, IQR 8.0–19.0 vs. 8.0, IQR 5.0–15.0 days,  $P=0.001$ ) than patients who were not ventilator dependent (**Table 1**)

We further compared the treatment outcomes of enrolled patients with and without ventilator dependence. As shown in **Table 2**, patients with ventilator dependence were under mechanical ventilation for longer time (41.0, IQR 29.0–58.2 vs. 12.0, IQR 9.0–17.0 days,  $P<0.001$ ), spent longer time in the hospital (56.0, IQR 43.7–84.0 vs. 36.0, IQR 27.0–56.7 days,  $P<0.001$ ) and ICU (28.5, IQR 21.0–43.0 vs. 16.0, IQR 12.0–21.0 days,  $P<0.001$ ); they also exhibited higher all-cause mortality rate on day 28 (17.2% vs. 5.0%,  $P=0.003$ ) and higher hospital mortality rate (38.5% vs. 12.0%,  $P<0.001$ ). Kaplan–Meier analysis demonstrated that patients with ventilator dependence had significantly higher mortality rates than those without it (**Figure 2**). The curves separated early after day 21 of intubation.

#### *Independent factor associated with ventilator dependence*

Univariate and multivariate logistic regression analyses were performed to identify clinical factors associated with ventilator dependence in VAP patients. In univariate analysis as shown in **Table 3**, clinical factors associated with ventilator dependence included advanced age, higher APACHE II score on ICU admission, PF ratio  $<200$ , dialysis requirement, albumin  $\leq 3$  mg/dL, intravenous colistin administration, and late onset VAP. In multivariate analysis, independent clinical factors associated with ventilator dependence included advanced age (adjusted odds ratio [aOR] 1.02, 95% confidence interval [CI] 1.00–1.04), higher APACHE II score on ICU admission (aOR, 1.04; 95% CI, 1.00–1.08;  $P=0.017$ ), PF ratio  $<200$  (aOR, 2.19; 95% CI, 1.20–3.99;  $P=0.010$ ), and late onset VAP (6–10 days: aOR, 2.28, 95% CI, 1.04–4.99;  $P=0.039$ ,  $>10$  days: aOR, 3.92, 95% CI, 1.86–8.29;  $P<0.001$ ).

#### *Impact of VAP-onset times on ventilator dependence and treatment outcomes*

To explore the impact of VAP-onset times on treatment outcomes, we categorized the patients into subgroups according to the hospital days before VAP occurrence (2–5 days, 6–10 days,  $>10$  days). The demographic characteristics of patients with various VAP-onset times are shown in **Supplementary Table 1**.

As shown in **Figure 3A**, the day 21 ventilator-weaning rates in patients with VAP-onset times of 2–5 days, 6–10 days, and  $>10$  days were 58.7%, 43.8%, and 28.8% respectively; the overall ventilator-weaning rate upon discharge was 73.9%, 73.0%, and 61.9% respectively. The day 21 ventilator-weaning rate was significantly higher in patients with shorter VAP-onset times. The day 28 mortality rates were 4.3%, 9.0%, and 18.0% in patients with ventilator-onset times of 2–5 days, 6–10 days, and  $>10$  days, respectively, while the hospital-mortality rates were 23.9%, 19.1%, and 36.7% in patients with ventilator-onset times of 2–5 days, 6–10 days, and  $>10$  days, respectively (**Figure 3B**). Patients with longer VAP-onset times had significantly higher mortality. The Kaplan–Meier analysis demonstrated that patients with longer VAP-onset times had significantly higher mortality rates ( $P=0.023$ ) (**Figure 4A**). The curves separated early after day 21 of intubation. The Kaplan–Meier analysis also suggested that patients with longer VAP-onset times had significantly lower ventilator-weaning rates ( $P=0.013$ ) (**Figure 4B**).

## Discussion

This multicenter study included 274 critically ill patients with VAP caused by CRAB. Nearly two-thirds of the enrolled patients had ventilator dependence, which was defined as failed weaning on day 21 after intubation. Patients with ventilator dependence had longer ICU stays, longer hospital stays, and higher mortality rates. Patients with late onset VAP were more likely to be ventilator dependent and had higher mortality rates. Independent clinical factors associated with ventilator dependence included advanced age, higher APACHE II scores on admission, lower PF ratio on VAP presentation, and late onset VAP.

Although VAP is a common and important nosocomial infection, studies evaluating the weaning rate in cases of VAP are limited. In a single-center retrospective cohort study that included 90 cases of VAP, Tseng et al. reported that the ventilator-dependence rate among VAP patients at the time of discharge from hospital was 60% [11]. In our study, the ventilator-dependence rate was 63.5% on day 21 after initiation of ventilator support. To the best of our knowledge, this is the first study investigating ventilator weaning in patients with VAP caused by CRAB. Considering the difference in the definition of ventilator dependence and the study design, it would be difficult to compare our findings with those of the previous study. However, the high ventilator-dependence rates noted in both studies demonstrates the high morbidity rates associated with VAP, which deserves aggressive investigation and treatment. The outcomes could be even worse when VAP is caused by highly resistant microorganisms. Meanwhile, we found that patients with ventilator dependence had longer hospital stays and higher mortality rates, which suggests that failed weaning in VAP patients should be viewed as an important indicator of poor prognosis.

Several clinical factors have been reported to be associated with unsuccessful weaning in ICU patients with respiratory failure, including advanced age ( $>70$  years), duration of mechanical ventilation before weaning, underlying comorbidities, severity of illness at the time of weaning, semi-recumbent positioning after extubation, use of continuous intravenous sedation, pneumonia as the reason to start ventilator support, and the level of positive end-expiratory pressure (PEEP) used before weaning [16–21]. On the contrary, investigations of the clinical factors associated with ventilator dependence in patients with VAP are scarce. Tseng et al. reported that previously impaired cardiac function, high oxygenation index, APACHE II scores, and SOFA scores during the occurrence of VAP were independent factors in predicting ventilator dependence of VAP patients in ICUs [11]. In line with a previous study, we found that advanced age, higher disease severities, and poor oxygenation were independent factors associated with ventilator dependence. However, selection of antibiotics had limited impact on ventilator dependence in our VAP patients infected by CRAB. Our findings highlight that demographic characteristics and disease severity are important parameters that affect ventilator weaning in VAP patients. It also indicates that VAP patients with high risk of ventilator dependence can be identified early at VAP onset and should be managed aggressively to improve their treatment outcomes.

Another important goal of the present study was to explore the clinical impact of VAP-onset time on ventilator dependence and treatment outcomes. The method used to distinguish between early-onset and late-onset VAP remains controversial. Some studies suggested that late-onset VAP was more likely to be caused by high-level antibiotic-resistant pathogens [14, 22]. The latest HAP/VAP guidelines also listed late-onset VAP that occurs after  $>5$  days of

hospitalization as a risk factor for infection with MDR organisms [14]. However, many studies reported infections by similar pathogens in early-onset and late-onset VAP [23-25]. Meanwhile, investigations regarding the impact of VAP-onset times on treatment outcomes, including ventilator weaning, are very limited. In the present study, we categorized our VAP patients based on their VAP-onset times into the following subgroups: 2–5 days, 6–10 days, and >10 days, which was determined based on hospital admission. We found that patients with late onset VAP were more likely to be ventilator dependent and had higher mortality. As all the patients enrolled in the present study were infected by CRAB, the different treatment outcomes between patients with various VAP-onset times cannot be explained by microbiological factors. We found that patients with late onset VAP exhibited greater disease severity and organ dysfunction. However, late onset VAP remains an independent factor associated with ventilator dependence in multivariate analysis with adjustment for disease severity. Our findings suggest that the concept of early-onset and late-onset VAP is an important factor in clinical practice, and VAP-onset time should be taken into consideration when managing such patients.

This study has several limitations. First, as a retrospective study, some important parameters were not considered, such as the application of lung protective strategy and setting of PEEP in patients with acute respiratory distress syndrome (ARDS) during the VAP episode; these could not be adjusted in our analysis. Second, the time at which to start weaning and the weaning protocols were not unified and were dependent on the doctor who determined them. Third, the antibiotic regimen for the treatment of CRAB-related VAP was not standardized. However, we have included key antibiotics in the multivariate analysis and none of them were independent factors associated with ventilator dependence. Finally, this study included patients from referral medical centers that specialized in management of critically ill patients. Therefore, it may not be possible to apply our study findings to other hospitals.

## Conclusions

This multicenter retrospective study enrolled patients with VAP caused by CRAB from five referral medical centers. The overall ventilator dependence rate on day 21 was 63.5% and patients with ventilator dependence had poor treatment outcomes. The independent factors associated with ventilator dependence included advanced age, higher APACHE II score, PF ratio <200, and late onset VAP. In addition to the higher ventilator dependence rate, we also found that VAP patients with late onset VAP had higher mortality rates. Our study identified clinical factors associated with ventilator dependence in patients with VAP caused by CRAB. It also indicated that VAP-onset time is an important factor associated with treatment outcomes. Further prospective studies are warranted to verify our findings.

## Abbreviations

VAP: Ventilator-associated pneumonia; ICU: intensive care unit; CRAB: Carbapenem-resistant *Acinetobacter baumannii*; PF ratio: PaO<sub>2</sub>/FIO<sub>2</sub> ratio; HAP: hospital-acquired pneumonia; MDR: multidrug-resistant; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment, ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure

## Declarations

### Ethics approval and consent to participate

This study was approved by the Institutional Review Boards of all the participating hospitals, and the requirement for informed consent was waived (IRB NOS:2018-03-001CC, KMHIRB-E (1)-20180141, CE18100A, 1-107-05-054, and CMUH107-REC3-052).

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

### Funding

This study was financially supported by the Cancer Progression Research Center, National Yang-Ming Chiao-Tung University through The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

### Authors' contribution

H-HK, J-YF, C-KP, C-CS, Y-CL, M-CC, H-SH, and K-YY conceptualized the study. H-HK, J-YF, S-HW, C-MC, Y-CS, and Z-RZ curated the data. H-HK, J-YF, H-SH, and K-YY conducted the formal analysis of data. H-HK, J-YF, C-KP, C-CS, Y-CL, M-CC, H-SH, K-YY, and Y-TL developed the methodology. H-HK, J-YF, C-KP, C-CS, Y-CL, M-CC, H-SH, and K-YY carried out project administration. J-YF, C-KP, C-CS, Y-CL, M-CC, H-SH, and K-YY supervised the research. H-HK, J-YF, H-SH, and K-YY wrote the original draft. H-HK, J-YF, C-KP, S-HW, C-CS, C-MC, Y-CL, Y-CS, M-CC, Z-RZ, H-SH, and K-YY reviewed and edited the manuscript. All authors read and approved the final manuscript.

### Acknowledgements

This study was supported by grants from the Ministry of Science and Technology (Taiwan) (MOST 105-2314-B-010-041-MY3), Taipei Veterans General Hospital (V108C-057, V109C-033). This study was financially supported by the Cancer Progression Research Center, National Yang-Ming Chiao-Tung University through The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

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## Tables

Table 1. Characteristics and disease severities of VAP patients who are dependent and not dependent on ventilators<sup>a</sup>

	All cases	Ventilator		P value
		Not dependent	Dependent	
<b>Case number</b>	274	100	174	
Mean age (Mean, SD)	72.0 (±14.8)	69.4 (±15.6)	73.5(±14.2)	0.032
Men	181 (66.1%)	71 (71.0%)	110 (63.2%)	0.190
Mean BMI (SD)	23.8 (±4.4)	23.9 (±4.3)	23.8 (±4.5)	0.902
Smoking history	103 (38.0%)	39 (39.4%)	64 (37.2%)	0.721
Alcohol consumption	57(21.3%)	21 (21.4%)	36 (21.3%)	0.981
ICU types				0.311
Medical ICU	176 (64.2%)	60 (60.0%)	116(66.7%)	
Surgical ICU	98 (35.8%)	40 (40.0%)	58 (33.3%)	
Comorbidities				
Malignancies	34 (12.4%)	11 (11.0%)	23 (13.2%)	0.592
Renal insufficiency	51 (18.6%)	14 (14.0%)	37 (21.3%)	0.137
Chronic lung diseases	50 (18.2%)	13 (13.0%)	37 (21.3%)	0.088
Diabetes	112 (40.9%)	40 (40.0%)	72 (41.4%)	0.823
Autoimmune disease	10 (3.6%)	3 (3.0%)	7 (4.0%)	0.664
Intravenous antibiotics				
Colistin	85 (31.0%)	22 (22.0%)	63 (36.2%)	0.014
Carbapenem	112 (40.9%)	37 (37.0%)	75 (43.1%)	0.322
Sulbactam	68 (24.8%)	27 (27.0%)	41 (23.6%)	0.526
Tigecycline	77 (28.1%)	25 (25.0%)	52 (29.9%)	0.386
APACHE II scores (Median, IQR) <sup>b</sup>	23.0(17.0–28.0)	21.0 (15.0–25.0)	24.0 (19.0–28.0)	0.002
SOFA scores (Median, IQR)				
ICU admission	8.0 (5.0–10.0)	7.0 (5.0–9.0)	8.0 (6.0–10.0)	0.005
Pneumonia index date	7.0 (5.0–9.0)	6.0 (4.2–8.0)	7.0 (5.0–9.2)	0.093
Presenting features <sup>c</sup>				
Vasopressor	111 (40.5%)	25 (25.0%)	86 (49.4%)	<0.001
PF ratio <200	85 (31.0%)	22 (22.0%)	63 (36.2%)	0.014
Dialysis <sup>d</sup>	70(25.5%)	17 (17.0%)	53 (30.5%)	0.014
MV days before pneumonia (Median, IQR)	8.0(5.0–13.0)	6.0 (4.0–8.0)	10.0 (6.0–14.0)	<0.001
ICU stay before pneumonia (Median, IQR)	8.0(5.0–13.0)	6.0 (5.0–9.0)	10.0 (7.0–14.2)	<0.001
Hospital stay before pneumonia (Median, IQR)	10.5(7.0–18.0)	8.0(5.0–15.0)	12.0(8.0–19.0)	0.001
Laboratory results (Mean, SD)				
Leukocytes (x 10 <sup>9</sup> per L)	12.9 (±8.4)	11.8 (±5.4)	13.5 (±9.7)	0.068
Albumin (g/dL)	2.7(±0.5)	2.8 (±0.6)	2.7 (±0.5)	0.207
CRP (mg/dL)	19.8(±38.4)	14.7 (±24.2)	22.7 (±44.3)	0.065

<sup>a</sup>Data are presented as n (%)

<sup>b</sup>APACHE II score determined on ICU admission

<sup>c</sup>Presence of organ dysfunction on pneumonia index date

<sup>d</sup>Including hemodialysis and continuous venovenous hemofiltration

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; PF ratio, PaO<sub>2</sub>/FiO<sub>2</sub> ratio; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; VAP, ventilator-associated pneumonia; MV, mechanical ventilation

Table 2. Treatment outcomes of VAP patients who are dependent and not dependent on ventilators<sup>a</sup>

	All cases	Ventilator		P value
		Not dependent	Dependent	
<b>Case number</b>	274	100	174	
Total MV days (Median, IQR)	27.5 (15.7–47.0)	12.0 (9.0–17.0)	41.0 (29.0–58.2)	<0001
Hospital stays (days)	50.0 (35.0–73.0)	36.0 (27.0–56.7)	56.0 (43.7–84.0)	<0001
ICU stays (days)	23.0 (16.0–36.0)	16.0 (12.0–21.0)	28.5 (21.0–43.0)	<0.001
<b>All-cause mortality</b>				
Day 28 mortality	35 (12.8%)	5 (5.0%)	30 (17.2%)	0.003
Hospital mortality	79 (28.8%)	12 (12.0%)	67 (38.5%)	<0.001

<sup>a</sup>Data are presented as n (%) and median (25th–75th percentiles)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; VAP, ventilator-associated pneumonia;

MV, mechanical ventilation

Table 3. Univariate and multivariate analysis of clinical factors associated with ventilator dependence in CRAB-related VAP patients

	Univariate analysis <sup>a</sup>		Multivariate analysis <sup>b</sup>	
	OR (95% CI)	P value	aOR (95% CI)	P value
Age	1.01 (1.00–1.03)	0.029	1.02 (1.00–1.04)	0.021
Male	0.70 (0.41–1.19)	0.191		
BMI	0.99 (0.94–1.05)	0.902		
Medical ICU	1.33 (0.80–2.21)	0.268		
Malignancies	1.23 (0.57–2.64)	0.592		
Renal insufficiency	1.65 (0.84–3.24)	0.140		
Diabetes	1.05 (0.64–1.74)	0.823		
APACHE II score <sup>c</sup>	1.05 (1.01–1.09)	0.003	1.04 (1.00–1.08)	0.017
SOFA score <sup>d</sup>	1.07 (0.99–1.16)	0.068		
PF ratio <200 <sup>e</sup>	2.01 (1.14–3.54)	0.015	2.19 (1.20–3.99)	0.010
Dialysis <sup>e</sup>	2.13 (1.15–3.95)	0.015		
Albumin ≤3 mg/dL	1.88 (1.08–3.27)	0.025		
Intravenous colistin	2.01 (1.14–3.54)	0.015		
Carbapenem	1.29 (0.77–2.13)	0.323		
Sulbactam	0.83 (0.47–1.46)	0.526		
Tigecycline	1.27 (0.73–2.23)	0.387		
<b>VAP-onset times<sup>f</sup></b>				
2 to 5 days	1	-	1	
6 to 10 days	2.16 (1.17–4.00)	0.013	2.28 (1.04–4.99)	0.039
>10 days	6.58 (3.34–12.95)	<0.001	3.92 (1.86–8.29)	<0.001

<sup>a</sup>Odds ratio (OR) and 95% confidence interval (CI) were derived from univariate logistic regression analysis

<sup>b</sup>Adjusted odds ratio (aOR) and 95%CI were derived from multivariate logistic regression analysis

<sup>c</sup>APACHE II score on ICU admission date

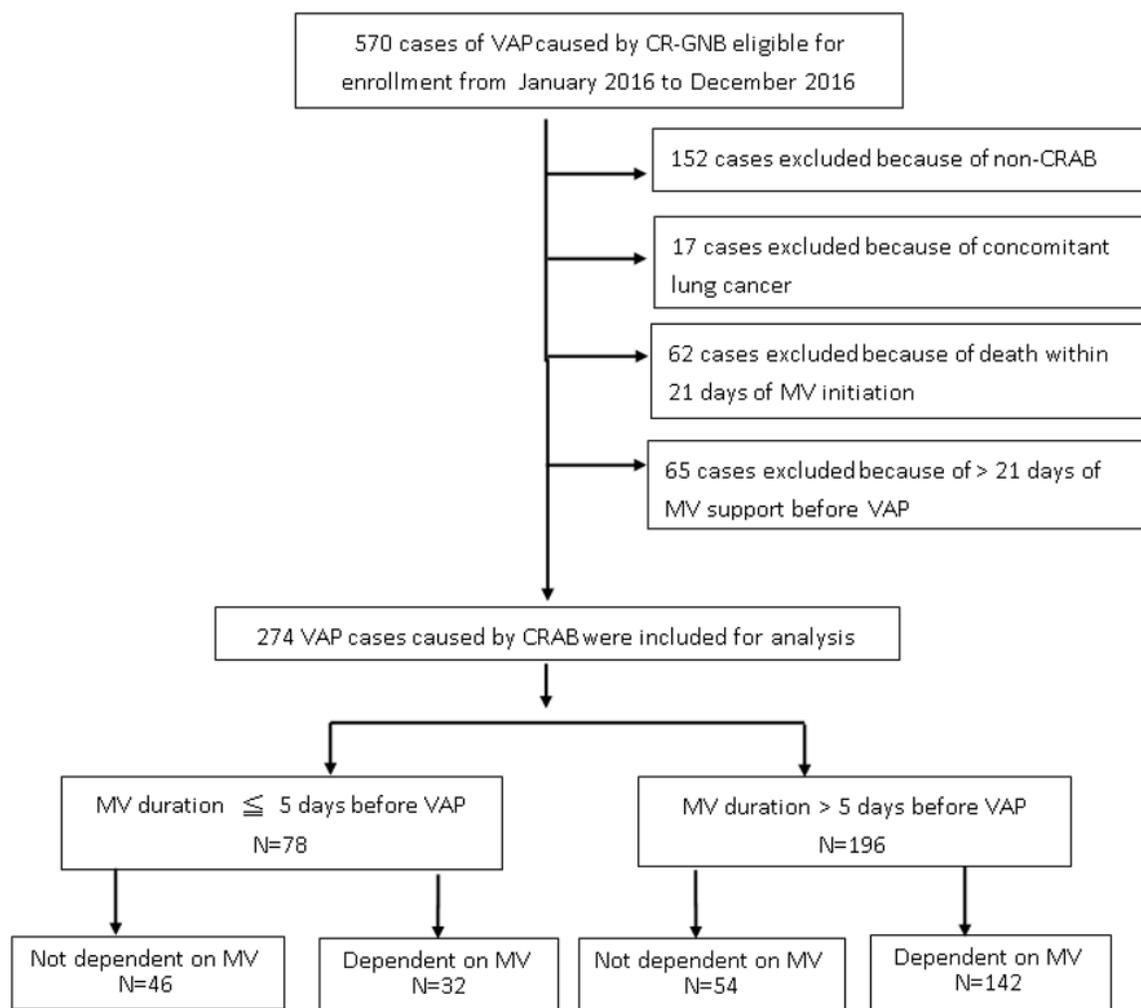
<sup>d</sup>SOFA score on pneumonia index date

<sup>e</sup>Presence of organ dysfunction on the pneumonia index date

<sup>f</sup>VAP onset time was determined from admission date to VAP index date

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; PF ratio, PaO<sub>2</sub>/FiO<sub>2</sub> ratio; SOFA, Sequential Organ Failure Assessment

## Figures



**Figure 1**  
Study profile demonstrating the number of cases and reasons for exclusion. CR-GNB; carbapenem-resistant gram-negative bacteria; CRAB, carbapenem-resistant *Acinetobacter baumannii*; MV, mechanical ventilation; VAP, ventilator-associated pneumonia

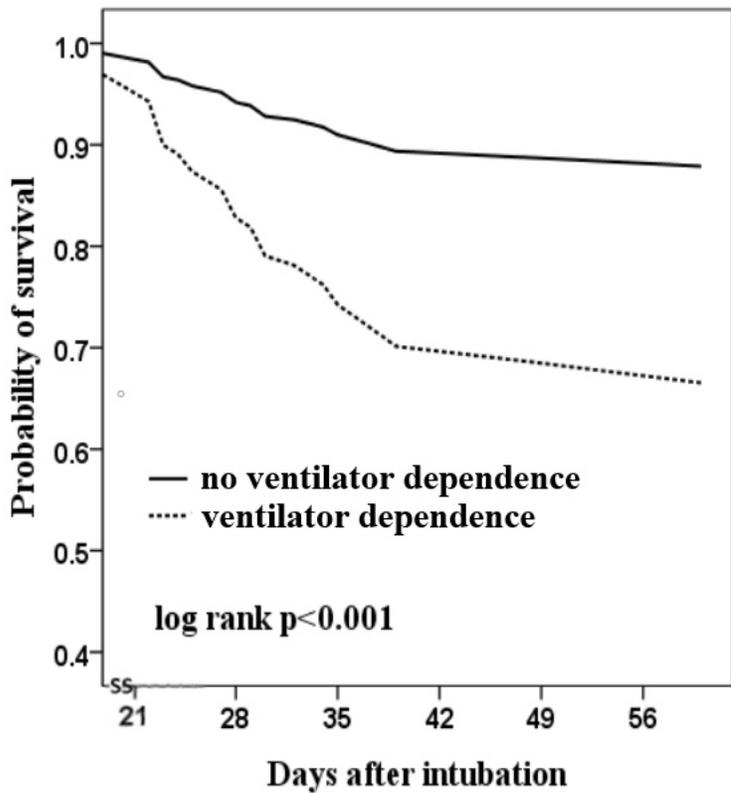
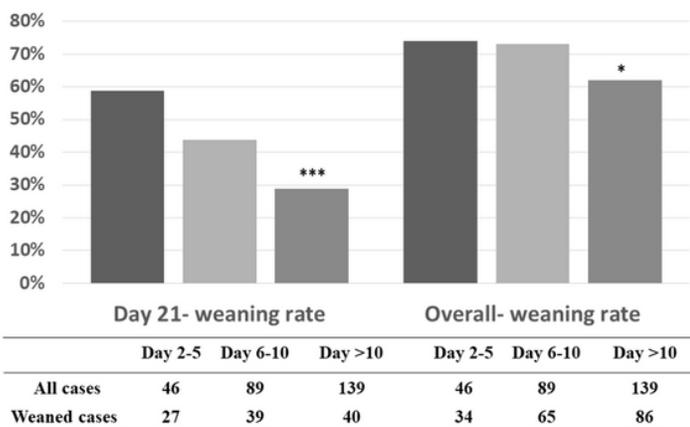


Figure 2

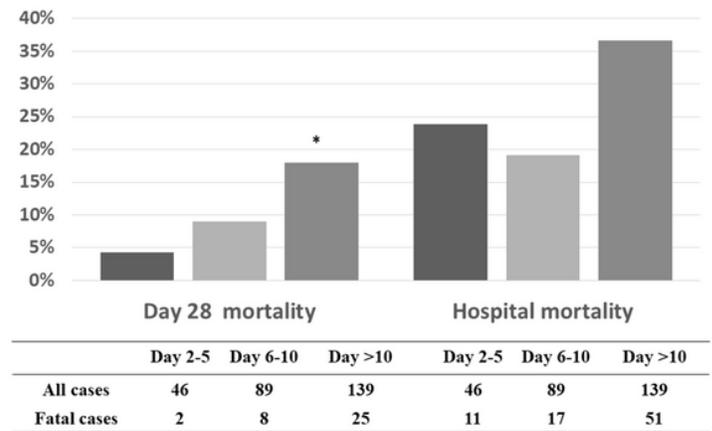
Kaplan–Meier curves of patient survival with ventilator dependence and no ventilator dependence. VAP, ventilator-associated pneumonia

**A.**



\* p < 0.05 \*\*p < 0.01 \*\*\*p < 0.001

**B.**



\* p < 0.05 \*\*p < 0.01 \*\*\*p < 0.001

Figure 3

Treatment outcomes in patients with various VAP-onset times. (A) Day 21- and overall- ventilator-weaning rates. (B) Day 28 and hospital mortality rates. Patients are categorized based on VAP-onset times (time between admission date and VAP index date) into the following groups: 2–5 days, 6–10 days, and >10 days. VAP, ventilator-associated pneumonia

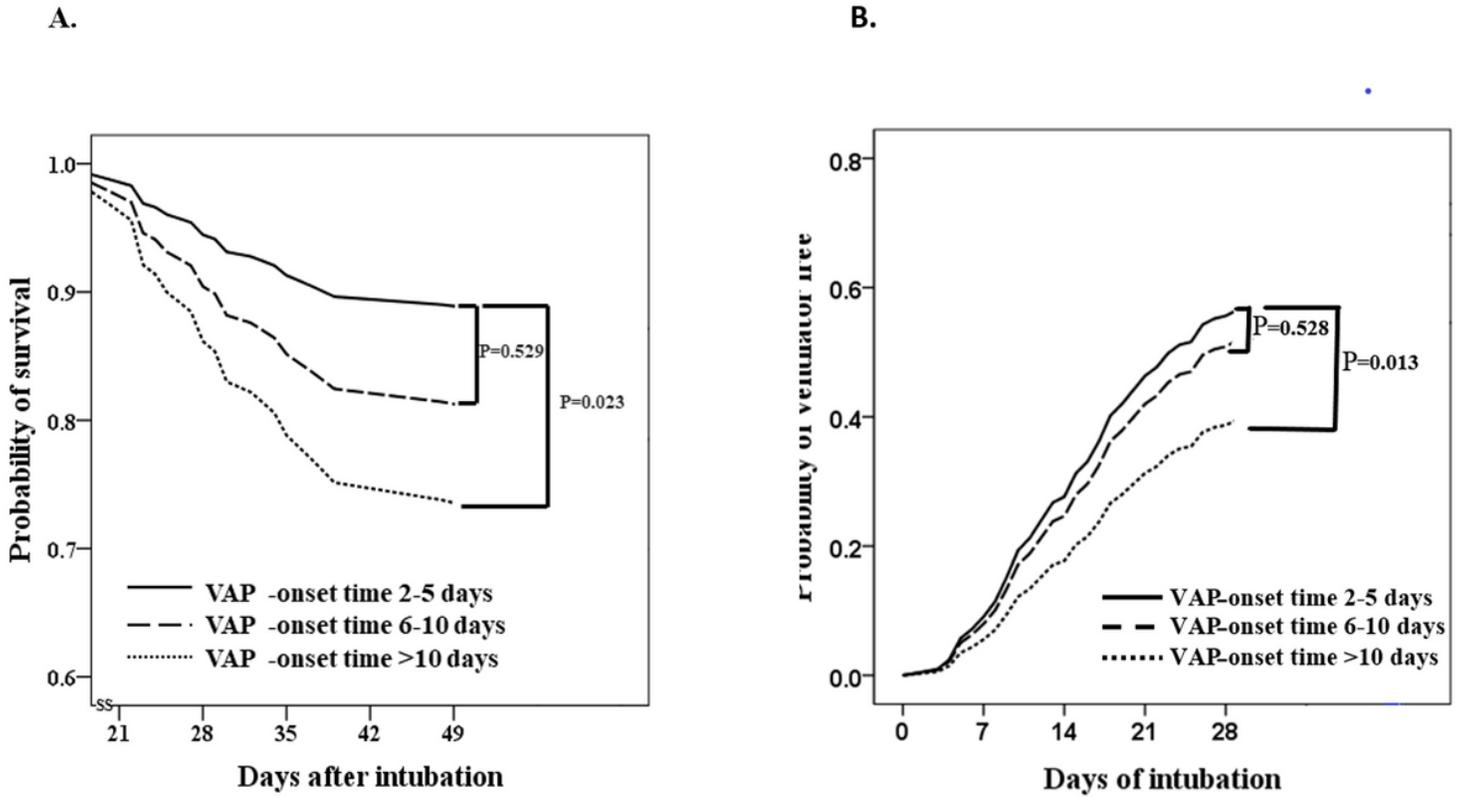


Figure 4

Kaplan–Meier curves of (A) survival and (B) ventilator weaning in patients with VAP-onset times of 2–5 days, 6–10 days, and >10 days. VAP-onset time was time between admission date and VAP index date. VAP, ventilator-associated pneumonia.

## Supplementary Files

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