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Original Article

# Mortality and ventilator dependence in critically ill patients with ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*

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Ventilator dependence;
VAP onset Time

**Abstract** *Background:* Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a key pathogen associated with ventilator-associated pneumonia (VAP). Research on treatment outcomes, especially ventilator dependence, in patients with VAP caused by CRAB remains limited.
*Methods:* This retrospective multicenter study included ICU-admitted patients with VAP caused by CRAB. The original cohort was included as the mortality evaluation cohort. The ventilator dependence evaluation cohort included cases that survived more than 21 days after VAP and without prolonged ventilation before VAP onset. The mortality rate, ventilator dependence rate, clinical factors associated with treatment outcomes, and treatment outcome differences with various VAP onset times were investigated.
*Results:* In total, 401 patients with VAP caused by CRAB were analyzed. The 21-day all-cause mortality rate was 25.2%, and the 21-day ventilator dependence rate was 48.8%. Clinical factors associated with 21-day mortality included lower body mass index, higher sequential organ failure assessment score, vasopressors usage, CRAB persistence, and VAP onset time $>$ seven days. Clinical factors associated with 21-day ventilator dependence included older age, vasopressors usage, and VAP onset time $>$ seven days.
*Conclusions:* ICU-admitted patients with CRAB-related VAP had high mortality and ventilator dependence rates. Older age, vasopressor usage, and longer VAP onset time were independent factors associated with ventilator dependence.


## Introduction

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 which research and development of new antibiotics is required.[2] As one of the major pathogens in nosocomial infections in intensive care units (ICUs), *A. baumannii* has high carbapenem resistance rate that ranged from 50% in North America to 80% in Asia.[3,4] 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.[7,8] According to the result from a longitudinal prospective cohort study in French, the estimated risk of VAP was 1.5% per day in the first two weeks and decreased to less than 0.5% per day after the 14th day of mechanical ventilation.[9] The risk factors of VAP include advanced age, male sex, smoking, prolonged duration of mechanical ventilation and hospital stay, consciousness-related disorders, burns, comorbidities, prior antibiotic therapy, invasive operations, and gene polymorphisms.[10,11] Mechanical ventilator dependence is a major complication of VAP, which may be as high as 60% in critically ill patients with ventilator support.[12] The mortality rate in patients with weaning failure can be as high as 25—50%.[13,14]

VAP has been classified into subgroups according to the onset time of VAP, although their definitions vary in previous studies.[15—17] The information regarding the impact of VAP onset time on treatment outcomes, such as mortality and ventilator dependence, is very limited. We hypothesized that VAP onset time is an important factor associated with worse outcomes in patients with VAP caused by CRAB. To prove our hypothesis, we enrolled ICU-admitted patients with VAP caused by CRAB and investigated the clinical parameters associated with mortality and mechanical ventilator dependence. The impact of VAP onset time on

treatment outcomes and ventilator dependence was further explored.

## Methods

### Patients and settings

This retrospective cohort study was conducted in five tertiary medical centers in Taiwan. This study was approved by the institutional review boards of all the participating hospitals, and the requirement for informed consent was waived (IRB Numbers: 2018-03-001CC, KMUHIRB-E (1)-20180,141, CE18100A, 1-107-05-054, and CMUH107-REC3-052). All patients admitted to the ICU from January 2016 to December 2016 with documented VAP caused by CRAB were enrolled. The inclusion criteria were: (1) ICU-admitted patients diagnosed with VAP, (2) isolation of CRAB from respiratory specimens. The exclusion criteria were: age $<$20 years, community-acquired pneumonia or health-care associated pneumonia, pneumonia before ICU admission, lung cancer or obstructive pneumonitis, and human immunodeficiency virus infection with CD4 count $<$200. The original cohort was used to investigate all-cause mortality (mortality evaluation cohort). We further excluded patients who were on mechanical ventilation for $\geq$21 days before the occurrence of VAP and patients who died within 21 days of the occurrence of VAP to establish another cohort to evaluate mechanical ventilator dependence (ventilator dependence evaluation cohort).

### Pneumonia diagnosis

The diagnosis of pneumonia was based on new or progressive infiltrates in the chest radiograph, in addition to at least two clinical findings suggestive of pneumonia. The suggestive clinical findings included exacerbated cough, increased production of purulent sputum, fever ($\geq$38 °C) or hypothermia ($<$35 °C), and leukocytosis (white cell count $\geq$10,000/cumm) or leukopenia (white cell count $<$4000/cumm). VAP was defined as pneumonia developing $\geq$48 h after endotracheal intubation with invasive mechanical ventilator.

### Microbiological tests and treatment regimens

CRAB was determined as the causative pathogen if CRAB was the only pathogen isolated from respiratory specimens, including endotracheal aspirates (moderate or heavy growth by semiquantitative method), bronchoalveolar lavage fluid ($\geq 10^4$ colony-forming units (CFU)/mL), and protected specimen brush ($\geq 10^3$ CFU/ml). In respiratory specimens with the growth of mixed pathogens, CRAB was determined as the key pathogen if it had the highest burden in quantitative or semiquantitative analysis. Patients with mixed pathogen and fewer bacterial burdens in CRAB were determined as VAP caused by non-CRAB and were excluded from analysis. Carbapenem-resistance was defined as resistance to at least one carbapenem (imipenem, meropenem, doripenem, or ertapenem) in the antimicrobial susceptibility test results. The results of the susceptibility tests of the cultured isolates to carbapenems were determined according to the Clinical and Laboratory Standards Institute recommendations.[18] The resistance status of colistin and the MICs were determined by broth microdilution as recommended by the joint CLSI-EUCAST Polymyxin Break-points Working Group in all the participating hospitals.[19] The collection date of the index culture study was defined as the pneumonia index date. Intravenous antibiotic administration for $\geq$ two days, within seven days of the VAP index date, were recorded. We defined adequate therapy as at least one in vitro active antimicrobial agent in the antibiotics regimen within seven days of VAP index date.[20]

### Data collection and diseases severities definitions

The 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, the sequential organ failure assessment (SOFA) score on ICU admission day, the pneumonia index date, and 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. The VAP onset time was determined from the date of initiation of mechanical ventilator support to the VAP index date.[21,22]

### Treatment outcomes evaluation

The main treatment outcomes evaluated in the present study included all-cause mortality and ventilator weaning. All-cause mortality at day 21 after the VAP index date was evaluated in the mortality evaluation cohort. Ventilator dependence rates on day 7, day 14, and day 21 were calculated since the VAP index date. The decisions regarding weaning and extubation were made by the physicians in charge based on clinical judgment. 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 non-invasive ventilation within the subsequent three days in the ICU and complete liberation from mechanical ventilation for seven consecutive days.[23] The ventilator weaning status was determined on day 21 after the VAP index date. Ventilator dependence was defined as constituting $\geq$21 consecutive days of mechanical ventilation for $\geq$6 h per day.[23] The other treatment outcomes evaluated in this study included the overall number of days of ventilator use, hospital stays, ICU stays, all-cause mortality at day seven and day 14, and ventilator use at day seven and day 14 after VAP occurrence.

### Statistical analysis

The demographic characteristics and disease severity scores were compared using the Mann–Whitney U-test for non-parametric continuous variables or Student's t-test for parametric continuous variables. The Chi-square test and Fisher's exact test were used for categorical variables. Multivariate Cox regression analysis was used to identify independent factors associated with 21-day mortality (in mortality evaluation cohort) and multivariate logistic regression analysis was used to identify independent factors associated with day 21 mechanical ventilator dependence status (in ventilator dependence evaluation cohort). All variables with P-value $<0.1$ in the univariate analysis were included in the multivariate model. To investigate the clinical impact of VAP onset times, we compared the treatment outcomes between patients with varied VAP onset times (two to seven days, eight to 14 days, and $>14$ days).[21,22] 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, 570 ICU-admitted 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 Fig. 1. Finally, 401 ICU-admitted patients with VAP caused by CRAB were included in the mortality evaluation cohort, and 254 were included in the ventilator dependence evaluation cohort.

The baseline demographic characteristics and disease severities between the enrolled patients with different treatment outcomes are presented in Table 1. Their mean age was 71.6 $\pm$ 14.8 years, and 66.6% were males. More than one-third of them had a smoking history, and 65.8% were admitted to the medical ICU. The median APACHE II score on ICU admission was 23 (interquartile range [IQR] 17–28), and the median SOFA score on the pneumonia index date was eight (IQR 5–10). Nearly half of the patients used vasopressors when VAP was diagnosed, and one-third of them had a PF ratio $<200$. The median number of days with ventilation before VAP occurrence was ten (IQR 6–16), and the overall hospital mortality rate was 44.4%.

In the mortality evaluation cohort, 101 patients (25.2%) died within 21 days of VAP occurrence. When compared to survivors, non-survivors had a lower body mass index (BMI), were more likely to be admitted to medical ICU, to have an autoimmune disease, to have higher APACHE II score and SOFA score, to be under vasopressor, to have PF ratio $<200$, to have CRAB persistence, and to have a longer ICU stay, hospital stay, and ventilator days before VAP onset.

In the ventilator dependence evaluation cohort, 124 (48.8%) remained under mechanical ventilator support on day 21 after VAP occurrence. Compared to patients without ventilator dependence, those with ventilator dependence were older, had higher APACHE II and SOFA scores, were more likely to use vasopressor, to have dialysis, and to have longer ICU stays and ventilation days before the occurrence of VAP (Table 1). Patients with ventilator dependence on day 21 had significantly higher hospital mortality.

### Independent factors associated with day 21 mortality

Univariate and multivariate Cox regression analyses were performed to identify clinical factors associated with 21-day mortality in patients with VAP. In the univariate analysis, as shown in Table 2, the clinical factors associated with 21-day mortality included lower BMI, medical ICU admission, higher APACHE II scores, higher SOFA scores, vasopressor usage, PF ratio $<200$, CRAB persistence in respiratory specimens on day seven and longer VAP onset time. In the multivariate analysis, the independent clinical factors associated with 21-day mortality included lower BMI (adjusted hazard ratio [aHR] 0.92, 95% confidence interval [CI] 0.88–0.96; $P < 0.001$), medical ICU admission (aHR 1.66, 95% CI 1.05–2.63, $p = 0.026$), higher SOFA score on pneumonia index date (aHR 1.17, 95% CI, 1.10–1.24; $P < 0.001$), vasopressor usage (aHR 2.01; 95% CI, 1.25–3.25; $P = 0.004$), CRAB persistence on day seven (aHR 2.08; 95% CI, 1.10–3.92; $P = 0.023$), and longer VAP onset times (eight to 14 days: aHR 1.95, 95% CI, 1.17–3.23, $P = 0.009$; $>14$ days: aHR 1.82, 95% CI, 1.09–3.04, $P = 0.021$).

### Independent factors associated with ventilator dependence

Table 3 shows the results of the univariate and multivariate logistic regression analysis of the clinical factors associated with ventilator dependence in patients with VAP. In the univariate analysis, the clinical factors associated with ventilator dependence included older age, higher APACHE II score on ICU admission date, higher SOFA score on pneumonia index date, vasopressor usage, dialysis requirement, intravenous colistin, albumin $\leq 3$ mg/dL, and VAP onset times $>$ seven days. In the multivariate analysis, the independent clinical factors associated with ventilator dependence included older age (adjusted odds ratio [aOR] 1.03, 95% CI, 1.01–1.05; $P = 0.004$), vasopressor usage (aOR 2.05, 95% CI, 1.11–3.78; $P = 0.020$) and longer VAP onset times (eight to 14 days: aOR 2.75, 95% CI, 1.49–5.09, $P = 0.001$; $>14$ days: aOR 3.27, 95% CI, 1.40–7.64, $P = 0.006$).

### Impact of VAP-onset times on treatment outcomes

Considering the association between longer VAP onset times and worse treatment outcomes, we categorized the patients into subgroups according to the VAP onset times (two to seven days, eight to 14 days, $>14$ days) and explored the treatment outcomes between subgroups of patients. The comparisons of demographic characteristics between patients with various VAP onset times are shown in Supplementary Table 1. No significant differences in demographic characteristics and comorbidities were identified between patients with VAP onset times 2–7 days, 8–14 days, and $>14$ days. However, patients with VAP onset time

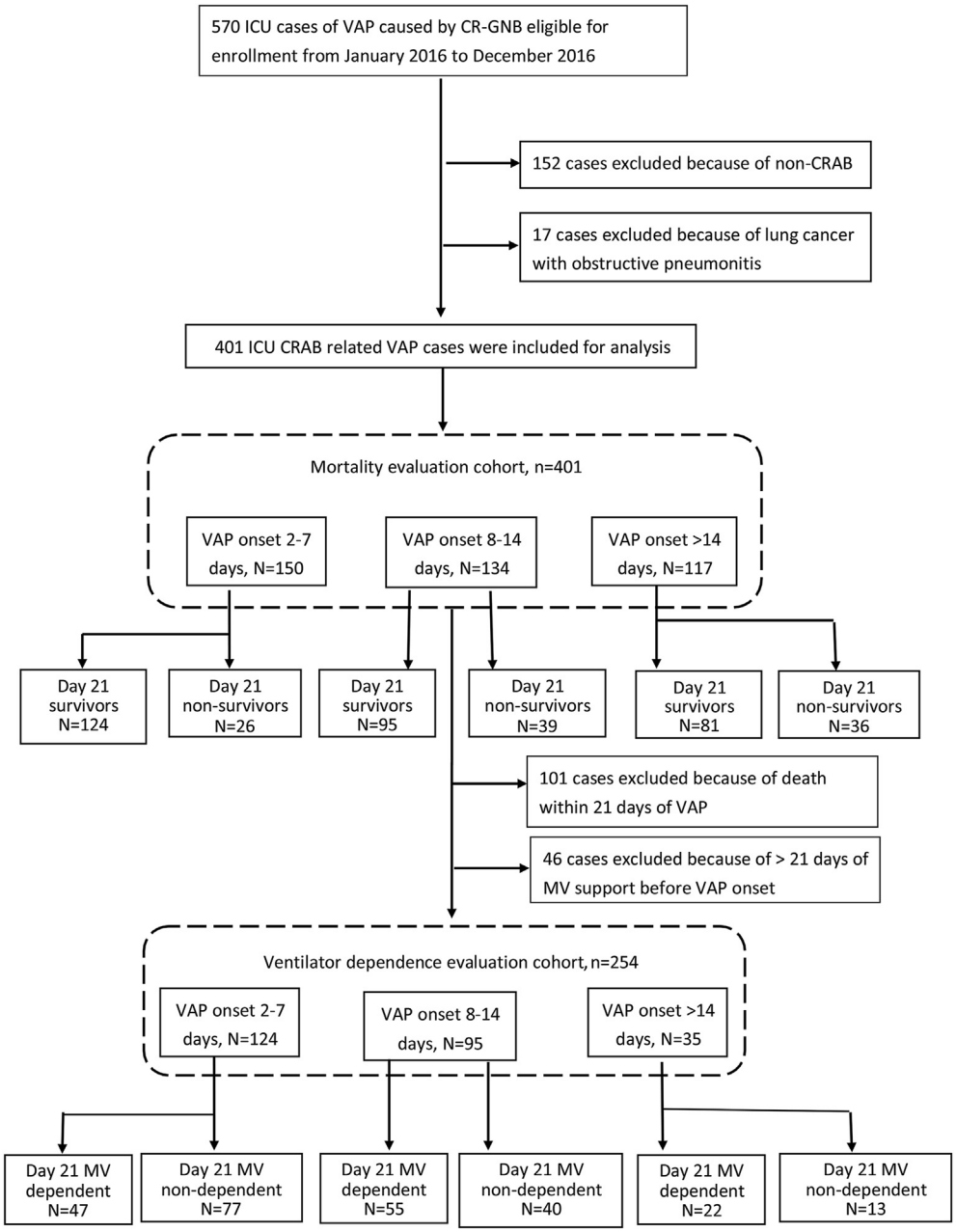


**Figure 1.** Study profile demonstrating the number of cases and reasons for exclusion. Abbreviations: CR-GNB; carbapenem-resistant gram-negative bacteria; CRAB, carbapenem-resistant *Acinetobacter baumannii*; MV, mechanical ventilation; VAP, ventilator-associated pneumonia.

>14 days had more organ dysfunction, lower serum albumin levels and higher serum CRP levels. As shown in Table 4, when compared to patients with a VAP onset time of two to seven days, those with a VAP onset time of eight to 14 days and >14 days had longer ventilation days, and hospital stays after VAP onset, more ventilator dependence, and a higher mortality rate.

The Kaplan-Meier survival analysis of patients with various VAP onset times is shown in Fig. 2A. Patients with a VAP onset time of two to seven days had a significantly lower mortality rate compared to those with a VAP onset time of eight to 14 days (log-rank $p = 0.018$) and >14 days (log-rank $p = 0.014$). Moreover, the curves separated early.

The Kaplan–Meier analysis of the mechanical ventilation-free rate in patients with various VAP onset times is shown in Fig. 2B. Patients with a VAP onset time of two to seven days had a significantly higher ventilator-free rate than those with a VAP onset time of eight to 14 days (log-rank $p = 0.004$) and >14 days (log-rank $p = 0.016$).

## Discussion

Although VAP is a common and important nosocomial infection, studies evaluating the weaning rate in cases of VAP are limited. Tseng et al. reported that the ventilator-

**Table 1** Demographic characteristics between patients with good and poor outcomes.[a]

| | All cases | Mortality evaluation cohort, n = 401 | | Ventilator dependence evaluation cohort, n = 254 | |
|---|---|---|---|---|---|
| | | Non-survivors on day 21 | Survivors on day 21 | MV dependence on day 21 | MV independence on day 21 |
| Case number | 401 | 101 | 300 | 124 | 130 |
| Mean age (Mean, SD) | 71.6 (±14.8) | 70.3 (15.9) | 72.0 (14.4) | 74.8 (12.8)** | 69.7 (15.5) |
| Men | 267 (66.6%) | 67 (66.3%) | 200 (66.7%) | 81 (65.3%) | 87 (66.9%) |
| Mean BMI (SD) | 23.6 (±4.7) | 22.3 (5.1) ** | 24.1 (4.5) | 24.0 (4.7) | 24.0 (4.3) |
| Smoking history | 151 (38.0%) | 36 (35.6%) | 115 (38.9%) | 48 (39.3%) | 49 (38.0%) |
| Alcohol consumption | 81 (20.7%) | 21 (21.2%) | 60 (20.5%) | 24 (20.2%) | 26 (20.3%) |
| ICU types | | | | | |
| Medical ICU | 264 (65.8%) | 76 (75.2%)* | 188 (62.7%) | 79 (63.7%) | 82 (63.1%) |
| Surgical ICU | 137 (34.2%) | 25 (24.5%)* | 112 (37.5%) | 45 (36.3%) | 48 (36.9%) |
| Comorbidities | | | | | |
| Malignancies | 47 (11.7%) | 15 (14.9%) | 32 (10.7%) | 17 (13.7%) | 11 (8.5%) |
| Renal insufficiency[b] | 79 (19.7%) | 20 (19.8%) | 59 (19.7%) | 26 (21.0%) | 20 (15.4%) |
| Chronic lung diseases | 67 (16.7%) | 17 (16.8%) | 50 (16.7%) | 25 (20.2%) | 18 (13.8%) |
| Diabetes | 152 (37.9%) | 35 (34.7%) | 117 (39.0%) | 48 (38.7%) | 55 (42.3%) |
| Autoimmune disease | 20 (5.0%) | 9 (8.9%)* | 11 (3.7%) | 6 (4.8%) | 3 (2.3%) |
| Intravenous antibiotics | | | | | |
| Colistin | 119 (29.7%) | 35 (34.7%) | 84 (28.0%) | 46 (37.1%)** | 27 (20.8%) |
| Carbapenem | 178 (44.4%) | 47 (46.5%) | 131 (43.7%) | 57 (46.0%) | 47 (36.2%) |
| Sulbactam | 104 (25.9%) | 21 (20.8%) | 83 (27.7%) | 33 (26.6%) | 41 (31.5%) |
| Tigecycline | 112 (27.9%) | 30 (29.7%) | 82 (27.3%) | 34 (27.4%) | 34 (26.2%) |
| APACHE II scores (Median, IQR)[c] | 23.0 (17.0–28.0) | 24.0 (19.0–29.0)* | 22.7 (18.0–26.0) | 23.0 (19.0–29.0)* | 22.0 (+16.0–25.0) |
| SOFA scores (Median, IQR) | | | | | |
| ICU admission | 8.0 (6.0–10.0) | 8.0 (6.0–11.0) | 8.0 (5.0–10.0) | 8.0 (6.0–10.0)* | 7.0 (5.0–9.0) |
| Pneumonia index date | 8.0 (5.0–10.0) | 10.0 (7.5–13.0)*** | 7.0 (5.0–9.0) | 7.0 (5.0–9.0)* | 6.0 (4.0–8.2) |
| Presenting features[d] | | | | | |
| Vasopressor | 191 (47.6%) | 70 (69.3%)*** | 121 (40.3%) | 59 (47.6%)** | 36 (27.7%) |
| PF ratio <200 | 105 (26.2%) | 34 (33.7%)* | 71 (23.7%) | 30 (24.2%) | 32 (24.6%) |
| Dialysis[e] | 118 (29.4%) | 37 (36.6%) | 81 (27.0%) | 39 (31.5%)* | 25 (19.2%) |
| Laboratory results (Mean, SD) | | | | | |
| Leukocytes (x $10^9$ per L) | 12.9 (±8.4) | 14.2 (±9.6) | 12.4 (±7.9) | 12.5 (±7.5) | 12.6 (±8.7) |
| Albumin (g/dL) | 2.7 (±0.5) | 2.7 (±0.5) | 2.7 (±0.5) | 2.7 (±0.5) | 2.8 (±0.5) |
| CRP (mg/dL) | 21.4 (±45.4) | 29.1 (±64.6) | 19.0 (±37.4) | 22.1 (±44.1) | 15.8 (±27.5) |
| CRAB persistent on day seven | 323 (80.5%) | 90 (89.1%)* | 233 (77.7%) | 88 (71.5%) | 103 (79.2%) |
| ICU stay before VAP (Median, IQR) | 10.0 (6.0–16.0) | 11.0 (7.0–17.0)* | 9.0 (6.0–15.0) | 10.0 (6.0–14.0)*** | 7.0 (5.0–10.2) |
| Hospital stay before VAP (Median, IQR) | 13.0 (7.0–26.0) | 16.0 (9.0–30.2)* | 12.0 (7.0–23.7) | 11.5 (7.0–19.0) | 9.0 (6.0–15.2) |
| Ventilator using days before VAP (Median, IQR) | 10.0 (6.0–16.0) | 11.0 (7.0–18.0)* | 9.0 (5.0–15.0) | 10.0 (6.0–14.0)*** | 6.0 (5.0–10.2) |
| Adequate treatment | 225 (56.1%) | 54 (53.5%) | 171 (57.0%) | 76 (61.3%) | 69 (53.1%) |
| Hospital mortality | 178 (44.4%) | 101 (100%)*** | 77 (25.4%) | 43 (34.7%)*** | 17 (13.1%) |

[a] Data are presented as n (%).
[b] Renal insufficiency was defined as eGFR <60 ml/min/1.73 $m^2$.
[c] APACHE II score determined on ICU admission.
[d] Presence of organ dysfunction on the pneumonia index date.
[e] 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, $PaO_2/FiO_2$ ratio; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; VAP, ventilator-associated pneumonia; MV, mechanical ventilation.

*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$, comparisons between non-survivors and survivors in mortality evaluation cohort; comparisons between MV dependence and MV independence in ventilator dependence evaluation cohort.

**Table 2** Univariate and multivariate analysis of the clinical factors associated with 21-day mortality in CRAB-related VAP patients.

| | Univariate analysis[a] | | Multivariate analysis[b] | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | aHR (95% CI) | *P*-value |
| Age | 0.99 (0.98–1.00) | 0.386 | | |
| Male | 0.99 (0.65–1.50) | 0.982 | | |
| BMI | 0.93 (0.89–0.97) | 0.001 | 0.92 (0.88–0.96) | <0.001 |
| Medical ICU | 1.69 (1.07–2.65) | 0.023 | 1.66 (1.05–2.63) | 0.026 |
| Malignancies | 1.36 (0.78–2.36) | 0.268 | | |
| Renal insufficiency[c] | 0.99 (0.61–1.62) | 0.991 | | |
| Diabetes | 0.84 (0.55–1.26) | 0.410 | | |
| APACHE II score[d] | 1.03 (1.00–1.06) | 0.012 | 1.02 (0.99–1.04) | 0.113 |
| SOFA score[e] | 1.21 (1.15–1.27) | <0.001 | 1.17 (1.10–1.24) | <0.001 |
| PF ratio <200[e] | 1.55 (1.03–2.35) | 0.035 | 1.13 (0.73–1.73) | 0.571 |
| Dialysis[f] | 1.47 (0.98–2.21) | 0.059 | 0.76 (0.48–1.20) | 0.251 |
| Vasopressor | 2.79 (1.83–4.26) | <0.001 | 2.01 (1.25–3.25) | 0.004 |
| Albumin ≤3 mg/dL | 0.98 (0.69–1.38) | 0.908 | | |
| Intravenous colistin | 1.25 (0.78–1.99) | 0.345 | | |
| Carbapenem | 1.10 (0.74–1.62) | 0.633 | | |
| Sulbactam | 0.74 (0.45–1.22) | 0.238 | | |
| Tigecycline | 1.06 (0.69–1.62) | 0.784 | | |
| Day seven CRAB persistence | 2.22 (1.18–4.16) | 0.011 | 2.08 (1.10–3.92) | 0.023 |
| No adequate treatment | 1.23 (0.83–1.83) | 0.282 | | |
| VAP onset times[g] | | | | |
| Two to seven days | 1.00 | – | 1.00 | – |
| Eight to 14 days | 1.82 (1.10–2.99) | 0.018 | 1.95 (1.17–3.23) | 0.009 |
| >14 days | 1.87 (1.13–3.10) | 0.014 | 1.82 (1.09–3.04) | 0.021 |

[a] Hazard ratio (HR) and 95% confidence interval (CI) were derived from the Cox proportional hazard regression analysis.
[b] Adjusted hazard ratio (aHR) and 95% CI were derived from the multivariate Cox proportional hazard regression analysis.
[c] Renal insufficiency was defined as eGFR <60 ml/min/1.73 $m^2$.
[d] APACHE II score on ICU admission date.
[e] SOFA score on the pneumonia index date.
[f] Presence of organ dysfunction on the pneumonia index date.
[g] VAP onset time was determined from the intubation date to the VAP index date.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; PF ratio, $PaO_2/FiO_2$ ratio; SOFA, Sequential Organ Failure Assessment; VAP, ventilator-associated pneumonia.

dependence rate among VAP patients at the time of discharge from hospital was 60%.[12] In our study, the ventilator dependence rate was 48.8% on day 21 after the occurrence of VAP. Although the ventilator dependence rate reported in the present study was lower than the previous report, it still demonstrated that a significant proportion of patients with VAP suffered from difficult weaning and ventilator dependence. Meanwhile, we found that patients with ventilator dependence had higher hospital mortality rates, which suggests that delayed weaning in VAP patients served as an important indicator of poor prognosis.

The mortality rate of VAP is high and previous studies reported a hospital mortality rate that ranges from 24% to 76%, depending on specific settings or specific pathogens.[24–26] Ciginskiene A et al. reported a hospital mortality rate of 63.3% in patients with VAP caused by drug-resistant *A. baumannii*.[27] In addition to disease severities, several studies reported late-onset HAP/VAP as an important factor associated with increased mortality rate.[25,26,28] A recent multicenter, prospective observational study report that the 30-day mortality rate was 19.2% for early-onset HAP and 31.4% for late-onset HAP.[26] In our study, the independent factors associated with 21-day mortality included BMI, disease severities, CRAB persistence, and longer VAP onset time. Administration of various antibiotics against CRAB was not an independent factor associated with mortality in multivariate analysis. However, the prescription of antibiotics is correlated with disease severity and susceptibility profiles. Further stringent data collection and analysis would be needed to reach a firm conclusion.

Several clinical factors have been reported to be associated with delayed weaning in ICU patients with respiratory failure.[29–34] However, investigations of the clinical factors associated with ventilator dependence in patients with VAP are scarce. Tseng et al. reported that impaired cardiac function, high oxygenation index, higher APACHE II and SOFA scores were independent factors in predicting ventilator dependence of patients with VAP.[12] Our findings identified that older age and vasopressor were independent factors associated with ventilator dependence. These factors are also clinical factors associated with treatment responses of VAP.[35,36] It suggested that the treatment of VAP plays a pivotal role in ventilator weaning. Ventilator weaning is feasible only when VAP is well-controlled.

**Table 3** Univariate and multivariate analysis of the clinical factors associated with 21-day ventilator dependence in patients with CRAB-related VAP.

| | Univariate analysis[a] | | Multivariate analysis[b] | |
|---|---|---|---|---|
| | OR (95% CI) | *P*-value | aOR (95% CI) | *P*-value |
| Age | 1.02 (1.00–1.04) | 0.007 | 1.03 (1.01–1.05) | 0.004 |
| Male | 0.93 (0.55–1.56) | 0.788 | | |
| BMI | 0.99 (0.94–1.05) | 0.980 | | |
| Medical ICU | 1.02 (0.61–1.71) | 0.917 | | |
| Malignancies | 1.71 (0.77–3.83) | 0.186 | | |
| Renal insufficiency[c] | 1.45 (0.76–2.77) | 0.250 | | |
| Diabetes | 0.86 (0.52–1.42) | 0.559 | | |
| APACHE II score[d] | 1.04 (1.00–1.08) | 0.017 | 1.02 (0.98–1.06) | 0.185 |
| SOFA score[e] | 1.08 (1.00–1.17) | 0.034 | 1.03 (0.93–1.14) | 0.490 |
| PF ratio <200[e] | 0.97 (0.55–1.73) | 0.938 | | |
| Dialysis[f] | 1.92 (1.08–3.43) | 0.026 | 1.35 (0.67–2.72) | 0.398 |
| Vasopressor | 2.37 (1.40–3.99) | 0.001 | 2.05 (1.11–3.78) | 0.020 |
| Albumin ≤3 mg/dL | 2.09 (1.18–3.70) | 0.011 | 1.67 (0.90–3.12) | 0.103 |
| Intravenous colistin | 2.14 (1.23–3.74) | 0.007 | 1.84 (0.99–3.39) | 0.051 |
| Carbapenem | 1.50 (0.90–2.48) | 0.113 | | |
| Sulbactam | 0.45 (0.15–1.34) | 0.155 | | |
| Tigecycline | 1.06 (0.61–1.85) | 0.820 | | |
| Day seven CRAB persistence | 0.66 (0.37–1.18) | 0.168 | | |
| VAP onset times[g] | | | | |
| No adequate treatment | 0.714 (0.43–1.17) | 0.187 | | |
| Two to seven days | 1 | – | | |
| Eight to 14 days | 2.25 (1.30–3.88) | 0.004 | 2.75 (1.49–5.09) | 0.001 |
| >14 days | 2.77 (1.27–6.02) | 0.010 | 3.27 (1.40–7.64) | 0.006 |

[a] Odds ratio (OR) and 95% confidence interval (CI) were derived from univariate logistic regression analysis.
[b] Adjusted odds ratio (aOR) and 95% CI were derived from the multivariate logistic regression analysis.
[c] Renal insufficiency was defined as eGFR <60 ml/min/1.73 $m^2$.
[d] APACHE II score on ICU admission date.
[e] SOFA score on the pneumonia index date.
[f] Presence of organ dysfunction on the pneumonia index date.
[g] VAP onset time was determined from the intubation date to the VAP index date.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; PF ratio, $PaO_2/FiO_2$ ratio; SOFA, Sequential Organ Failure Assessment; VAP, ventilator-associated pneumonia.

**Table 4** Treatment outcomes of the patients with various VAP onset times.

| | Case number | All cases | VAP onset times | | |
|---|---|---|---|---|---|
| | | | 2–7 days | 8–14 days | >14 days |
| MV days after VAP onset | 401 | 24.6 (±33.3) | 19.9 (±23.7) | 27.3 (±42.6) | 27.7 (±31.5)* |
| ICU stays after VAP onset | 401 | 17.0 (±17.9) | 16.5 (±16.4) | 16.5 (±19.3) | 18.3 (±18.0) |
| Hospital stays after VAP onset | 401 | 49.3 (±40.3) | 41.6 (±26.8) | 43.0 (±46.7) | 66.3 (±42.1)*** |
| MV dependence after VAP onset | | | | | |
| Day seven | 254 | 202 (79.5%) | 93 (75.0%) | 79 (83.2%) | 30 (85.7%) |
| Day 14 | 254 | 159 (62.6%) | 63 (50.8%) | 68 (71.6%)** | 28 (80.0%)** |
| Day 21 | 254 | 124 (48.8%) | 47 (37.9%) | 55 (57.9%)** | 22 (62.9%)** |
| Mortality after VAP onset | | | | | |
| Day seven | 401 | 50 (12.5%) | 11 (7.3%) | 24 (17.9%)** | 15 (12.8%) |
| Day 14 | 401 | 81 (20.2%) | 22 (14.7%) | 33 (24.6%)* | 26 (22.2%) |
| Day 21 | 401 | 101 (25.4%) | 26 (17.3%) | 39 (29.1%)* | 36 (30.8%)** |

Data are presented as the mean ± standard deviation or n (%).
Abbreviations: VAP, ventilator-associated pneumonia; MV, mechanical ventilation; ICU, intensive care unit.
*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$, compared with the VAP onset times in the two to seven-day group.

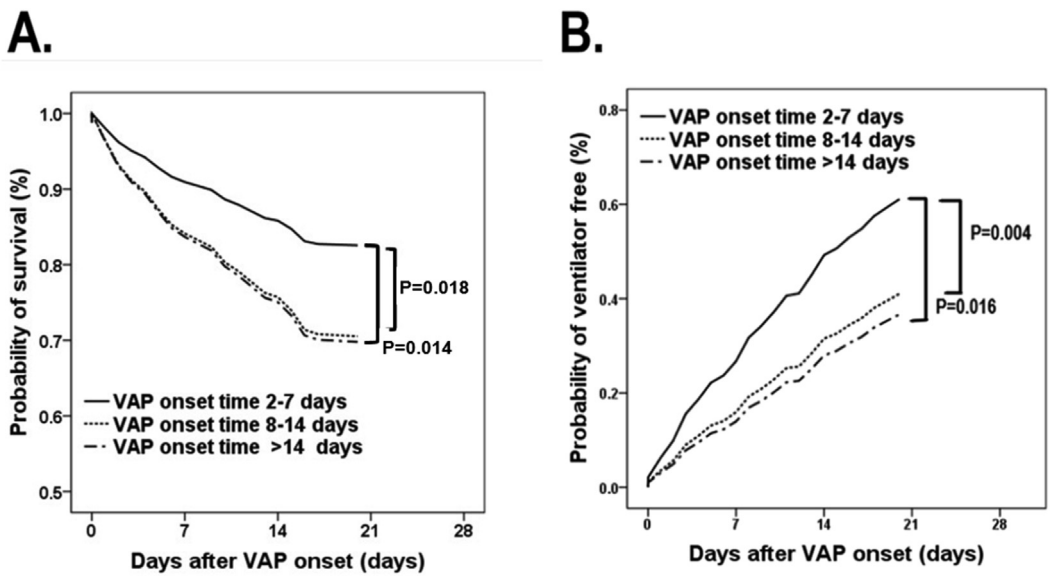


**Figure 2.** Kaplan—Meier curves of (A) survival and (B) ventilator weaning in patients with VAP onset times of two to seven days, eight to 14 days, and >14 days. The VAP onset time was defined using the prior duration of mechanical ventilation. VAP, ventilator-associated pneumonia.

The present study demonstrated that patients with longer VAP onset time had higher all-cause mortality rate and ventilator dependence rate. We also found that longer VAP onset time was an independent factor associated with worse outcomes in multivariate analysis after adjusting comorbidities, disease severities, and antibiotics usage. Meanwhile, previous studies reported that protocolized weaning, active rehabilitation, avoidance of oversedation, and application of the pneumonia bundle are all important approaches to reduce delayed weaning and prevent late-onset VAP.[37] Although not been evaluated in this study, these factors should never be neglected.

This study has several limitations. First, as a retrospective study, some important parameters were not collected, such as the application of lung protective strategy and setting of positive end-expiratory pressure in patients with acute respiratory distress syndrome. Therefore, these factors could not be adjusted for in our analysis. Second, the time to start weaning and the weaning protocols were not unified in the participating hospitals and depended on the doctor in charge. Finally, this study included patients from referral medical centers that specialized in the management of critically ill patients. Therefore, it may not be possible to apply our study findings to other hospitals.

In conclusion, this multicenter retrospective study reported a high mortality rate and ventilator dependence rate in patients with VAP caused by CRAB. Longer VAP onset time was an independent factor associated with mortality and ventilator dependence. VAP patients with longer VAP onset times also had longer hospital stays after the occurrence of VAP. Our study demonstrated poor treatment outcomes in patients with VAP caused by CRAB and suggested that the VAP onset time is an important indicator for mortality and ventilator dependence. Clinicians should be aware of the correlation between longer VAP onset time and worse treatment outcomes in patients with VAP associated with CRAB. Efforts to facilitate early weaning from ventilator support deserve further investigation to understand their roles in improving mortality and ventilator dependence.

## Declaration of competing interest

The authors declare that they have no competing interests.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.04.004.