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Risk Factors for Mortality Due to Ventilator-Associated Pneumonia in a Chinese Hospital: A Retrospective Study

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Background: As a common nosocomial infection, ventilator-associated pneumonia (VAP) often has high mortality. This study aimed to assess the risk factor for mortality owing to VAP.

Material/Methods: This retrospective clinical audit study screened medical records between the period of January 2014 and December 2017. All patients under mechanical ventilation (MV) for ≥ 72 hours were screened against previously reported diagnostic criteria for VAP. The medical records were obtained for cases of documented diagnosis of VAP.

Results: In all, 145 patients (5.0%) diagnosed with VAP were included in the study; the morbidity of VAP was 19.5 episodes per 1000 days of MV. The 30-day mortality rate was 42.8%. Univariate logistic analysis showed that elevated neutrophil-to-lymphocyte ratio (NLR), high blood urea nitrogen/albumin (BUN/ALB) ratio, Multidrug-resistant organism infection, and a higher sequential organ failure assessment (SOFA) score were risk factors for mortality caused by VAP. In the second multivariate analysis, elevated NLR levels ($P=0.038$), high BUN/ALB ratio ($P=0.016$), multidrug-resistant organism infections ($P=0.036$), and a higher SOFA score ($P<0.001$) were still associated with the 30-day mortality rate.

Conclusions: The 30-day mortality rate of VAP was high. Blood NLR and BUN/ALB levels can be used as risk factors to assess the 30-day VAP-related mortality to help clinicians improve the prognosis of VAP.

MeSH Keywords: Mortality • Pneumonia, Ventilator-Associated • Risk Factors

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Background

Ventilator-associated pneumonia (VAP) is a common infection associated with health care. Incidence of VAP results in prolongation of mechanical ventilation (MV), longer hospitalization time, and higher hospitalization costs [1]. In the 2016 guideline by the American Thoracic Society and the Infectious Diseases Society of America, patients with hospital-acquired pneumonia (HAP) and VAP are classified into 2 distinct groups [2]. In addition, VAP incidence has been reported differently in different studies, ranging from 4.5 to 75.5 episodes per 1000 ventilator-days (VD) [3–7]. The incidence of VAP in China was 4.5–55.8 per 1000 VD [8–10]. VAP often has a high mortality rate varying from 19.4% to 53%, particularly in the intensive care unit [9–11]. Although VAP often has characteristics similar to those of HAP, including the appearance of fever, purulent sputum, leukocytosis, decreased oxygenation, and the identification of new infectious pulmonary infiltrates, treatment depends on many factors such as age and the pathogens involved [2,7]. Patients with a higher sequential organ failure assessment (SOFA) score [11] and psychiatric diseases [12] usually have higher attributable mortality. Given that routine blood examination and blood biochemical tests have been commonly used for inpatients, clinicians should be interested in taking full advantage of these tests. Although neutrophil-to-lymphocyte ratio (NLR) and BUN/ALB levels had been considered as prognostic markers for mortality in community-acquired pneumonia [13,14], there has been a lack of evidence to use tests as prognostic markers in cases of VAP, especially in China. Hence, this study planned to assess the risk factors, such as NLR and BUN/ALB levels, for mortality due to VAP, so as to improve outcome.

Material and Methods

Study design

This was a single-center, retrospective, cohort study. The sample was categorized into 2 groups of patients who did and did not die within 30 days due to VAP. In both the subgroups, the frequency of potential risk factors to assess the 30-day mortality was investigated.

Period analyzed and VAP case definition

This study screened medical records between of the time period January 2014 to December 2017 from The Third Affiliated Hospital of Sun Yat-sen University (China). The criteria for a VAP diagnosis [2] included the presence of a new pulmonary infiltrate (appearing 48 to 72 hours post-intubation and initiation of MV) that was associated with more than 2 of the following: temperature $>38.3^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, leukocyte count $>10\times 10^9/\text{L}$ or $<4\times 10^9/\text{L}$, and purulent respiratory secretions.

Data collection

All patients were aged between 18 years old and 90 years old. All cases requiring MV for ≥ 72 hours were screened against previously reported diagnostic criteria for VAP. The medical records were screened to obtain a documented diagnosis of VAP. Data were collected on age and gender, comorbidity, prior therapy, laboratory test results, and death within 30 days. SOFA score was calculated on the day of the diagnosis of VAP. Patients with severe immune disease, patients with records missing key data, and patients with no record of microbial testing were excluded. Lower respiratory tract samples were collected for microbiological diagnosis. Pathogenic bacteria were confirmed using standard microbiological methods [15]. The antimicrobial susceptibility test and interpretation were performed following classic methods and guidelines. Multidrug-resistant (MDR) organism infections were defined as pathogens that were resistant to at least 1 antibiotic from 3 classes tested [16].

Statistical analysis

For the statistical analysis, the sample was categorized into 2 groups of patients who did and did not die within 30 days due to VAP. Differences between groups were assessed using χ^2 test or Fisher exact test for categorical variables and Student's *t*-test or Mann-Whitney test for continuous variables. Univariate and multivariate logistic regression analysis were used to analyze risk factors for mortality owing to VAP. The *P* value and odds ratio (OR) were reported. $P<0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS (Version 20, SPSS Inc., Chicago, IL, USA).

Ethical considerations

This study was approved by the Institutional Review Board of the Hospital and the Ethics Committee of The Third Affiliated Hospital of Sun Yat-sen University (China). Patient consent was obtained, and the information was kept confidential.

Results

Among the 2901 in-patients who underwent MV, VAP occurred in 145 patients (5.0%), with an incidence of 19.5 per 1000 VD (Figure 1). Of these 145 cases, 36 patients (24.8%) were aged >70 years old, 97 patients (66.9%) were male, and 132 patients (91.0%) had received antibiotic therapy within the preceding 90 days. The proportion of VAP pathogens is shown in Figure 2. Of the pathogens found, 82 pathogens (56.6%) were MDR bacteria, with 53 cases of *Acinetobacter baumannii* and 11 cases of *Pseudomonas aeruginosa*. The median value of SOFA score was 3. The 30-day mortality rate was 42.8% (Table 1).

Figure 1. Analysis plan.

Figure 2. The proportion of VAP pathogens (%).

The incidence and mortality rate of annual VAP were almost stable (Figure 3).

The first logistic regression analysis (Table 2) identified the following risk factors for mortality: elevated NLR ratio, high BUN/ALB ratio, multidrug-resistant organism infections, and high SOFA score. In the second multivariate analysis, elevated NLR levels ($P=0.038$; OR: 1.033; 95% confidence interval: 1.002–1.066), high BUN/ALB ratio, multidrug-resistant organism infections, and high SOFA score were still related to the 30-day mortality rate (Table 3).

Table 1. Demographic, laboratory and clinical variables of VAP.

Characteristics	Value
Age >70, y	36 (24.8%)
Gender: Male	97 (66.9%)
Smoke	25 (17.2%)
Diabetes mellitus	18 (12.4%)
Heart failure	21 (14.5%)
Cerebrovascular disease	38 (26.2%)
COPD	11 (7.5%)
Antibiotics therapy in the preceding 90 days	132 (91.0%)
ALB <30 g/l	18 (12.4%)
WBC, $\times 10^9/l$	14.42 $\pm$ 10.57
Lymphocyte count <0.8 $\times 10^9/l$	62 (42.8%)
NLR	18.01 $\pm$ 20.02
BUN/ALB	0.38 $\pm$ 0.27
MDR pathogens	82 (56.6%)
SOFA scores(IQR)	3 (2–10)
30 day mortality	62 (42.8%)

VAP – ventilator-associated pneumonia; COPD – chronic obstructive pulmonary disease; ALB – albumin; WBC – white blood cell; NLR – neutrophil-to-lymphocyte count ratio; BUN/ALB – blood urea nitrogen/blood albumin; MDR – multidrug resistant; SOFA – sequential organ failure assessment; IQR – inter-quartile range.

Figure 3. The incidence and mortality rate of annual VAP.

Discussion

In this study, the incidence of VAP was 19.5 episodes per 1000 VD. We noted that the morbidity was consistent with previous studies [6,8–10]. The majority of pathogens of VAP were MDR

Table 2. Univariate logistic regression analyses of risk factors for 30-day mortality due to VAP.

Characteristics	Non-survivors	Survivors	Univariate		
	n=62 (%)	n=83 (%)	OR	95% CI	P
Age >70, y	19 (30.6%)	17 (20.5%)			0.163
Gender: Male	41 (66.1%)	56 (67.5%)			0.865
Smoke	9 (14.5%)	16 (19.3%)			0.454
Diabetes mellitus	5 (8.1%)	13 (15.7%)			0.177
Heart failure	8 (12.9%)	13 (15.7%)			0.641
Cerebrovascular disease	14 (22.6%)	24 (28.9%)			0.392
COPD	4 (6.5%)	7 (8.4%)			0.657
Antibiotics therapy in the preceding 90 days	60 (96.8%)	72 (86.7%)	4.583	0.978–21.489	0.053
ALB <30 g/l	7 (11.3%)	11 (13.3%)			0.723
WBC, $\times 10^9/l$, mean $\pm$ SD	14.88 $\pm$ 8.86	14.13 $\pm$ 11.73			0.705
Lymphocyte count $<0.8 \times 10^9/l$	30 (48.4%)	32 (38.6%)			0.237
NLR, mean $\pm$ SD	22.33 $\pm$ 24.87	14.57 $\pm$ 14.72	1.023	1.003–1.043	0.026
BUN/ALB, mean $\pm$ SD	0.44 $\pm$ 0.29	0.34 $\pm$ 0.25	4.385	1.161–16.560	0.029
MDR pathogens	43 (69.4%)	39 (47.0%)	2.553	1.280–5.095	0.008
SOFA score, median (IQR)	6 (3–10)	3 (2–7)	2.805	2.037–3.864	<0.001

Data were presented by median (interquartile range), numbers (percentage), or mean $\pm$ standard deviation ($x \pm s$) (continuous). Continuous variables were compared using student's t-test or Mann-Whitney U-test and categorical variables using Pearson's chi-square or Fisher's exact probability test. P-value <0.05 is considered significant. VAP – ventilator-associated pneumonia; COPD – chronic obstructive pulmonary disease; ALB – albumin; WBC – white blood cell; NLR – neutrophil-to-lymphocyte count ratio; BUN/ALB – blood urea nitrogen/blood albumin; MDR – multidrug resistant; SOFA – sequential organ failure assessment; IQR – interquartile range.

Table 3. The significant risk factors for 30-day mortality due to VAP.

Characteristics	Non-survivors	Survivors	Multivariate		
	n=62 (%)	n=83 (%)	OR	95% CI	P
Antibiotics therapy in the preceding 90 days	60 (96.8%)	72 (86.7%)			0.155
NLR, mean $\pm$ SD	22.33 $\pm$ 24.87	14.57 $\pm$ 14.72	1.033	1.002–1.066	0.038
BUN/ALB, mean $\pm$ SD	0.44 $\pm$ 0.29	0.34 $\pm$ 0.25	7.06	1.443–34.545	0.016
MDR pathogens	43 (69.4%)	39 (47.0%)	2.947	1.072–8.098	0.036
SOFA score, median (IQR)	6 (3–10)	3 (2–7)	3.16	2.134–4.682	<0.001

Data were presented by median (interquartile range), numbers (percentage), or mean $\pm$ standard deviation ($x \pm s$) (continuous). Continuous variables were compared using student's t-test or Mann-Whitney U-test and categorical variables using Pearson's chi-square or Fisher's exact probability test. P-value <0.05 is considered significant. VAP – ventilator-associated pneumonia; NLR – neutrophil-to-lymphocyte count ratio; BUN/ALB – blood urea nitrogen/blood albumin; MDR – multidrug resistant; SOFA – sequential organ failure assessment; IQR – interquartile range.

bacteria, similar to findings reported previously [17,18] suggesting that MDR bacteria were key VAP organisms at our center. This may be attributed to increased prevalence of MDR bacteria in the specific environment [19], and the use of inappropriate initial antibiotics [20]. The mortality was similar to what has been reported in previous studies [9–11] and may be because the patients often had severe infection or morbid state [11]. In addition, we found risk factors which were related to the VAP 30-day mortality, including elevated NLR, high BUN/ALB ratio, multidrug-resistant organism infections, and high SOFA score.

To the best of the authors' knowledge, few studies have evaluated the potential of NLR in adults who had been hospitalized with VAP. Our study demonstrated the favorable performance of elevated NLR as a relative factor of prognosis for 30-day mortality rate in VAP. This finding closely resembled recent evidences on pneumonia patients [13]. Neutrophils and other inflammatory cells can mediate patients' proinflammatory state in the early hyperdynamic phase of infection [21,22]. The augmented innate response with neutrophil-mediated killing can suppress neutrophil apoptosis and is related to systemic inflammatory response [23]. Thus, an increase in neutrophils and a decline in lymphocytes usually is the characteristics of NLR [24]. The NLR may enable clinicians to quickly stratify patients into different prognostic categories, in order to help reduce the VAP-related mortality [13]. A recent study showed that the BUN/ALB ratio is a convenient and important predictor of pneumonia mortality rate and severity of illness [14]. In this study, we also found that the higher the BUN/ALB ratio, the higher the mortality rate. Patients with pneumonia are often dehydrated, and their kidneys usually increase reabsorption of urea, with an elevation of BUN levels [25,26]. Some earlier studies focusing on pneumonia prognosis showed that non-survivors had higher BUN levels and more hypoalbuminemia than survivors. Most of these studies, however,

were on community-acquired pneumonia [22,27,28]. The current study was the first to demonstrate that the BUN/ALB ratio had a negative effect on 30-day VAP mortality. The prognosis in multidrug-resistant organism infections has been reported to be worse, leading to higher VAP mortality rates [29,30]. This finding was the same as our study. This may be because MDR organisms have stronger virulence and MDR infections have limited treatment options [31,32].

In addition to the aforementioned risk factors, it has repeatedly been demonstrated that the impact on mortality is highly dependent on the severity of patients' illness severity [33,34]. In the current study, the non-survivors had higher SOFA scores, indicating they may have more severe sepsis-related organ failure, reinforcing findings previously described in the literature in which patient severity was an important factor in establishing prognosis after infection [11,35,36]. SOFA score of >6 on the day of VAP diagnosis was an independent risk factor for mortality, similarly to the findings of our study [36].

There are several limitations to our study. First, since this was a single-center retrospective study, the sample size was small. Second, all data collected retrospectively would limit the recapitulation of our findings. Further prospective studies are warranted to verify our results, and to monitor patients with these characteristics in order to reduce mortality.

Conclusions

Our results found that the 30-day mortality rate of VAP was high. Some simple and common indicators such as blood NLR and BUN/ALB levels can be used as risk factors to assess the 30-day VAP-related mortality. As routine convention tests, NLR and BUN/ALB should be used to improve the prognosis of VAP.

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