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Original Paper

Serum Procalcitonin Level and Mortality Risk in Critically ill Patients with Ventilator-Associated Pneumonia

Bo Li[a] Xin Zhao[b] Shumei Li[c]

[a]Intensive Care Unit, Jining No.1 People's Hospital, Jining, [b]Medical Teaching and Research Office, Jining Health School Of Shandong Province, Jining, [c]Hematology Department, Jining No.1 People's Hospital, Jining, China

Key Words
Critically ill • Procalcitonin • Prognostic biomarker

Abstract
Background/Aims: The prognostic role of serum procalcitonin level in critically ill patients with ventilator-associated pneumonia was unclear. The aim of our study was to investigate the relationship between serum procalcitonin level and mortality risk in critically ill patients with ventilator-associated pneumonia. ***Methods:*** Data of critically ill patients with ventilator-associated pneumonia were retrospectively collected. Demographics, comorbidities, and serum procalcitonin level were extracted from electronic medical records. The primary outcome was mortality within two months after diagnosis. Multivariable Cox regression analyses were performed to assess the prognostic role of serum procalcitonin level in those patients. ***Results:*** A total of 115 critically ill patients with ventilator-associated pneumonia were enrolled in our study. Serum procalcitonin level was not associated with age, gender, or other comorbidities. Univariate Cox regression model showed that high serum procalcitonin level was associated increased risk of morality within 2 months after diagnosis (OR = 2.32, 95% CI 1.25-4.31, P = 0.008). Multivariable Cox regression model showed that high serum procalcitonin level was independently associated increased risk of morality within 2 months after diagnosis (OR = 2.38, 95% CI 1.26-4.50, P = 0.008). ***Conclusion:*** High serum procalcitonin level is an independent prognostic biomarker of mortality risk in critically ill patients with ventilator-associated pneumonia, and it's a promising biomarker of prognosis in critically ill patients.

Introduction

Patients in intensive care units (ICU) are at higher risk of mortality compared with those in general ward environments [1, 2]. Most of these patients in ICU are critically ill with higher severity of sickness and many of them have complications, such as care-associated

Bo Li, MD

Intensive Care Unit, Jining No.1 People's Hospital, NO.6 Jiankang Road, Jining City
Jining, Shandong Province, 272011, (China)
Fax +86-0537-2253431, E-Mail bolisdedu@126.com

infections [3-6]. In hospitals, there are increasing numbers of critically ill patients, but the clinical outcomes for most patients are not obviously improved [1]. A large part of critically ill patients need mechanical ventilation. Ventilator-associated pneumonia is the most common health care-associated complication, which can increase the mortality of critically ill patients [6-9]. It occurs in over 20% of mechanically ventilated patients and accounts for about half of all antibiotics given in the ICU [6-9]. Though many efforts are undertaken to prevent these complications, the ventilator-associated pneumonia is still very common and leads to poor prognosis in critically ill patients [2, 4, 10-12]. Therefore, more studies are needed to develop potential approaches to get better outcomes in critically ill patients with ventilator-associated pneumonia. For patients at high risk of death, early intensive treatments may improve the outcome of patients. There are some biomarkers predicting patients' prognosis in critically ill patients, such as C-reactive protein and osteopontin [13, 14]. However, there is still lack of good biomarkers predicting patients' prognosis, and early detection of patients at high risk of death has proven challenging.

Procalcitonin is a peptide hormone mainly produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells in the lung and the intestine [15, 16]. The level of procalcitonin in the blood stream of healthy individuals is below the limit of detection of clinical assays [17, 18]. The level of procalcitonin rises in response to proinflammatory stimulus, especially to those of bacterial origin. In this case, it is produced mainly by the cells of the lung and the intestine. Measurement of procalcitonin can be used as a marker of severe sepsis caused by bacteria and generally grades well with the degree of sepsis [17, 18]. Currently, procalcitonin assays are widely used in the clinical environment. Previous studies have suggested that patients with infections often have increased levels of serum procalcitonin level [18-20]. However, there was still no conclusive finding on the prognostic role of serum procalcitonin level in critically ill patients with ventilator-associated pneumonia. The aim of our study was to investigate the relationship between serum procalcitonin level and mortality risk in critically ill patients with ventilator-associated pneumonia.

Materials and Methods

Patients and outcomes

This was a single-center, retrospective cohort study of critically ill patients with ventilator-associated pneumonia admitted to the ICU department of our hospital. The study was approved by the local ethical committee, and written informed consent was obtained from recruited patients. Patients with SCAP who were hospitalized in our hospital between January 2010 and December 2014 were consecutively recruited in our study. Eligible subjects were those had a clinical or radiologic diagnosis of ventilator-associated pneumonia. Ventilator-associated pneumonia in present study was defined as pneumonia that occurred more than 48 hours after initiation of mechanical ventilation. We excluded patients based on the following criteria: younger than 18 years, discharged from a hospital within the previous 10 days, active pulmonary tuberculosis, an episode of pneumonia within the past 30 days, postsplenectomy, or treatment with other immunosuppressive agents. Demographics, comorbidities, and laboratory variables including procalcitonin were extracted from the electronic medical record. Recorded bedside assessment included temperature, respiratory and heart rates, and blood pressure. The primary outcome was mortality in the following 2 months after diagnosis of ventilator-associated pneumonia.

Measurement of serum procalcitonin levels

Plasma samples and clinical data were prospectively collected. Using standardized phlebotomy procedures, up to 10 ml of peripheral blood was drawn from each of the patients. Blood samples were collected on days 1 of ICU admission in heparinized tubes and centrifuged for 10 minutes at 3,000 g. Then plasma aliquots were stored at -80°C until the time of analysis. Procalcitonin and C-reactive protein (CRP) measurements were performed as part of a pre-operative clinical routine by an immuno-turbidimetric test according to the manufacturer's instructions. Serum procalcitonin level of < 0.5 μg/L was regarded normal both by the manufacturer's instructions and corresponding to our clinical routine practice.

Statistical analysis

The primary endpoint was mortality in the following 2 months after diagnosis of ventilator-associated pneumonia. When investigating the correlation between serum procalcitonin level and the prognosis of critically ill patients with ventilator-associated pneumonia, the serum procalcitonin level were classified into the high procalcitonin level (≥ 1 μg/L) and low procalcitonin level (<1 μg/L). The $\chi 2$ or Fisher's exact test was used to compare the relationships of serum procalcitonin level with demographics, comorbidities, and other key laboratory variables. Both univariate Cox regression model and multivariable Cox regression analyses by adjusting for baseline factors were performed to assess the relationship between serum procalcitonin level and mortality risk in critically ill patients with ventilator-associated pneumonia. A two-tailed P value less than 0.05 was considered statistically significant and was determined using STATA 12.0 software.

Results

Patient characteristics

A total of 115 critically ill patients with ventilator-associated pneumonia were enrolled in our study. The mean age of those 115 patients were 65.5 years (SD, 11.5 years). There were 61 male patients and 54 female patients in the study. 40 of those 115 patients had type 2 diabetes and 43 had cardiovascular diseases. As show in the Table 1, serum procalcitonin level was not associated with age, gender, or other comorbidities. Compared with patients with low serum procalcitonin level, patients with high serum procalcitonin level didn't had higher CRP level (P = 0.87) (Table 1).

Table 1. Difference of demographics and comorbidities by the serum procalcitonin level. (CRP, C-reactive protein; CVD, Cardiovascular disease)

Variables (n)	High level (n=44)	Low level (n=71)	P value
Age(year)			
<60	18	31	0.77
≥60	26	40	
Gender			
Male	22	39	0.61
Female	22	32	
Diabetes mellitus			
No	27	45	0.83
Yes	17	26	
CVD			
No	26	49	0.28
Yes	18	22	
CRP(mg/L)			
<50	23	36	0.87
≥50	21	35	

Procalcitonin and Mortality Risk

Kaplan-Meier curve showed that patients with high level of serum procalcitonin level had higher risk of morality within 2 months after diagnosis ($P_{Log\text{-}Rank}$ <0.001) (Fig. 1). Univariate Cox regression model showed that high serum procalcitonin level was associated increased risk of morality within 2 months after diagnosis (OR = 2.32, 95% CI 1.25-4.31, P = 0.008) (Table 2). Other characteristics were not found to be associated with the prognosis of patients in our study (Table 2).

Multivariable Cox regression model showed that high serum procalcitonin level was independently associated increased risk of morality within 2 months after diagnosis (OR = 2.38, 95% CI 1.26-4.50, P = 0.008) (Table 3).

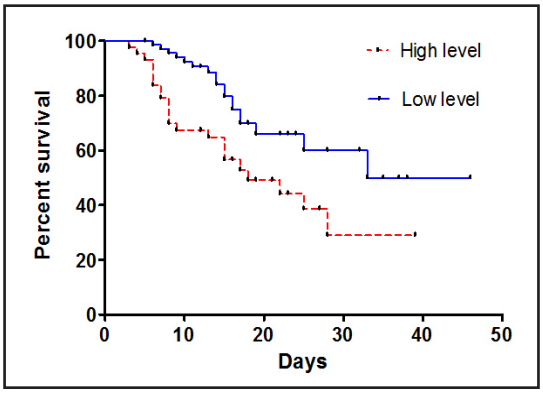

Fig. 1. Kaplan-Meier curve showed that patients with high level of serum procalcitonin level had higher risk of morality within 2 months after diagnosis.

Discussion

Considering the rising levels of serum procalcitonin in those associated diseases, the measurement of procalcitonin can be used as a diagnostic or prognostic marker of diseases [21, 22]. In present study, we performed a

retrospective cohort study of 115 critically ill patients with ventilator-associated pneumonia. The findings from our study suggest that high serum procalcitonin level is an independent prognostic biomarker of mortality risk in critically ill patients with ventilator-associated pneumonia, and it's a promising biomarker of prognosis in critically ill patients. The finding above has important role in the early detection of patients at high risk of death.

Ventilator-associated pneumonia is the most common health care-associated complication in critically ill patients and it can result in increased risk of early mortality [6-9]. To improve the prognosis of patients' survival, early intensive treatment is important for those at high risk of poorer prognosis. The finding in our study suggested that ventilator-associated pneumonia patients with high level of serum procalcitonin are at high risk of mortality. To improve the prognosis of those patients with high level of serum procalcitonin, early and appropriate antibiotic administration may be added to change the clinical outcomes [2, 10, 20, 23]. However, there is still lack of effective treatment of ventilator-associated pneumonia which can effectively treat critically ill patients [8, 9, 23, 24]. More effective treatments are needed in critically ill patients and more attentions should be focused on that in the future [1, 8, 23].

Table 2. Univariate Cox regression analysis in the retrospective cohort study. (CRP, C-reactive protein; CVD, Cardiovascular disease)

Factors	HR	95%CI	P values
Age (≥60 years)	1.01	0.54-1.88	0.97
Gender (Female)	1.07	0.58-1.98	0.82
Diabetes mellitus	0.83	0.43-1.57	0.56
CVD	1.32	0.70-2.48	0.38
CRP ≥50mg/L	1.36	0.73-2.53	0.33
Procalcitonin ≥ 1 μg /L	2.32	1.25-4.31	0.008

Table 3. Multivariable Cox regression analysis in the retrospective cohort study. (CRP, C-reactive protein; CVD, Cardiovascular disease)

Factors	Adjusted estimates		P values
	HR	95%CI	
CVD	1.07	0.56-2.05	0.83
CRP ≥60mg/L	1.48	0.79-2.77	0.21
Procalcitonin ≥ 1 μg /L	2.38	1.26-4.50	0.008

There are possible explanations on the prognostic role of procalcitonin in critically ill patients. Procalcitonin is an important peptide hormone involved in many types of diseases, especially in those with infection-related diseases [25-29]. The level of procalcitonin rises in a response to a proinflammatory stimulus, especially of bacterial origin. The level of procalcitonin in the blood stream of healthy individuals is below the limit of detection of clinical assays, while in those with diseases, it usually increases obviously. The increased level of procalcitonin can reflect the severity of infection, and patients with higher levels of procalcitonin usually have more severe disease, and thus have poorer prognosis.

Despite of the significant role of serum procalcitonin level identified in our study, several limitations in the study need to be considered. Firstly, the sample size in our study was limited, which could impair the robustness and credibility of the conclusion in our study. Therefore, more studies with large number of recruited patients are needed to validate the finding in our study. Secondly, our study only investigated the association between serum procalcitonin level and mortality risk in the following 2 months after diagnosis of ventilator-associated pneumonia. The outcome used in our study may not be enough to provide a correct evaluation on the prognostic role of procalcitonin in patients with ventilator-associated pneumonia. To provide a more correct evaluation, more types of outcomes may be used in future studies. Finally, there is still lack of good biomarkers predicting patients' prognosis, and early detection of patients at high risk of death has proved challenging. To get a more correct prediction of patients' survival, a prognostic score based on the combination of several biomarkers together may be more useful. Owing to the retrospective design of our study, we were unable to develop such promising score. To get a better prediction on the prognosis of critically ill patients, prospective cohort studies which measure several biomarkers together are necessary.

In conclusion, serum procalcitonin level is an independent prognostic biomarker of mortality risk in critically ill patients with ventilator-associated pneumonia, and it's a

promising biomarker of prognosis in critically ill patients. However, more studies with large number of recruited patients are needed to validate the finding in our study.

Disclosure Statement

The authors declare that they have no competing interests.

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