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Clinical significance of procalcitonin in critically ill patients with pneumonia receiving bronchoalveolar lavage

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Abstract. *Background:* As a useful tool in intensive care units (ICU), fiberoptic bronchoscopy (FOB) may cause a deterioration of infection. This study is to investigate the clinical significance of procalcitonin (PCT) in critically ill patients with severe pneumonia receiving bronchoalveolar lavage (BAL). *Methods:* A retrospective case-control study was performed in a single respiratory ICU (RICU) with 6-bed. Critically ill patients with severe pneumonia admitted to RICU were consecutively reviewed from March 2017 to October 2019. Chi-square test, Wilcoxon test, Mann Whitney U-test, Kaplan–Meier survival analysis or Cox's proportional hazards regression model was used as appropriate. *Results:* A total of 72 eligible patients were included in the final analysis, 51 of which received BAL performed by FOB. Serum levels of PCT in group received BAL is markedly increased at 24 hours after FOB (p<0.001). Forty-eight hours later, BAL group with decreased serum levels of PCT had less SOFA score and decreased mortality compared with those with increased serum levels of PCT. Furthermore, Kaplan-Meier analysis indicated that patients with decreased serum levels of PCT had improved survival rate during hospital (Breslow test, p=0.041). However, increased PCT after BAL was not an independent risk factor for in-hospital mortality (hazard ratio: 1.689, 95% CI(0.626 ,4.563), p=0.301). *Conclusions:* BAL performed by FOB increased serum levels of PCT. However, PCT levels decreased at 48 hours after BAL predicted a good prognosis of patients with severe pneumonia.

Keywords: Bronchoalveolar Lavage; bronchoscopy; pneumonia; Intensive Care Unit (ICU)

Introduction

Fiberoptic bronchoscopy (FOB) has been widely considered as a safe and useful tool for management of airway problems in intensive care units (ICUs). FOB is routinely used in 83% to 97.7% of ICUs, which is applied for critically ill patients in order to increase high first-pass success rate of intubation, prevent atelectasis, treat hemoptysis, or diagnose ventilator-associated pneumonia (1,2,3). FOB before discontinuation of mechanical ventilation shortens ICUs stays of critically ill patients (5) . However, some side-effects of FOB in critically ill patients should be given more concerns (6,7) . For example, fever following FOB is a common adverse event, which may be attributed to bacterial infection caused by this invasive procedure (7,8). Yigla M et al reported that the bacteremia rate in patients without pulmonary infection undergoing FOB was around 6.5%. FOB may facilitate bacteria to transmit from the upper to the lower airways and damage mucosal integrity leading to penetration of bacteria into the blood stream (9). However, in most cases, bacteremia is transient, which does not need urgently medical intervention (10).

Procalcitonin (PCT) is the prohormone of cal-

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citonin, a promising biomarker for differential diagnosis of bacterial infection. In critically ill patients with pneumonia, an elevated PCT level predicted an increased risk of mortality (11,12). However, PCT might not a reliable biomarker to determine administration or less use of antibiotics in patients with pneumonia (13,14). A previous study indicated that bronchoalveolar lavage under fiberoptic bronchoscopy can effectively relieve the symptoms of patients with severe pulmonary infection, improve clinical efficacy, and reduce PCT levels (15). However, another study reported Bronchoscopy-BAL results in a vast acute phase reaction, such as peripheral neutrophilia and raised values of PCT (16). Considering the different reports of changes in serum PCT levels after bronchoscopy and BAL, it seems that further research is required in studying this effect on the prognosis of patients with severe pneumonia. Hence, in the present study, we investigate the clinical significance of PCT in critically ill patients with pneumonia receiving bronchoalveolar lavage (BAL) performed by FOB.

Methods

Study design and population

A retrospective case-control study was conducted in a single RICU with 6-bed, the study was reviewed and approved by the ethics committee of the Yijishan hospital of Wannan medical college (No. 2016-14 dated December 10, 2016). The clinical data of all critically ill patients admitted in RICU was consecutively reviewed from March 2017 to October 2019.

Critically ill patients with severe pneumonia were included in this study. If patients were admitted to RICU more than once, the data of first RICU admission were collected. Diagnostic criteria for severe pneumonia conformed to the clinical practice guidelines (17). Patients with shock requiring vasopressor support, mechanically ventilated or who have 3 out of 6 minor criteria are considered to have severe pneumonia. The 6 minor criteria include: respiratory rate of 30 breaths per minute or greater; PaO2/FiO2 ratio equal or less than 250; Infiltrates in multiple lung lobes; confusion or disorientation; blood urea nitrogen equal or greater than 20 mg/dL; hypotension requiring aggressive fluid resuscitation. The main reasons of RICU admission for patients including acute exacerbation of chronic obstructive pulmonary disease, acute pulmonary embolism, asthma, and pneumothorax or only received palliative therapy were excluded from this study.

Patients received bronchoscopies in the RICUs were considered at high risks from complications. Therefore, the principle and procedure of bronchoscopy for critically ill patients in this study closely followed the British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults (2). For the BAL procedure, BAL was mainly performed by Yusheng Cheng and carried out in the radiologically most affected lung lobe. In cases of diffuse infiltrates or involvement of multiple lobes, the middle lobe or the lingula was preferred for BAL. For exclusive microbiological sampling, 200 mL of prewarmed 0.9%

saline were instilled into the lobe of interest and then gently aspirated. In the present study, the main indication of FOB for patients was to acquire bronchoalveolar lavage fluid (BAL) with diagnostic purpose. The results of acute physiology and chronic health evaluation II (APACHEII) score and Sequential Organ Failure Assessment (SOFA) score were collected after admission. Meanwhile, laboratory examinations including serum procalcitonin levels, C-reaction protein (CRP) and the percent of blood neutrophil were serial recorded before BAL, 24 hours after BAL and 48 hours after BAL were collected. Procalcitonin was determined using an immunoluminometric assay (Kingfocus Biomedical, China) based on the company instructions. Serum PCT values above 0.5 ng/ml were defined positive values in the patient.

Statistical analysis

Continuous data are presented as median (interquartile ranges(IQRs)), and categorical data are frequencies (n) or percentages. Chi-square test, Wilcoxon test or Mann–Whitney U-test was used as appropriate. A Kaplan–Meier survival analysis (Breslow test) was used to investigate the effect of procalcitonin

after BAL on in-hospital mortality of patients with severe pneumonia. Cox's proportional hazards regression model was used to assess independent risk factors for in-hospital mortality. The statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY) software. All of the p values less than 0.05 were considered to be statistically significant.

Results

In the present study, a total of 308 patients admitted to RICU were reviewed from March 2017 to October 2019. Seventy-two critically ill patients with pneumonia were eligible in the final analysis, 51 of which were received BAL performed by FOB and 21 were not (Figure. 1).

The baseline clinical characteristics of eligible patients were showed in Table 1, the gender and length of stay in BAL group shared statistical difference with those in Control group (41 vs 11, 15 days vs 9 days, p<0.05 for each). However, age, APACHE-II score, SOFA score, PCT, CRP, Neutrophil Count (G/L), blood neutrophils percentage, change of PCT, CRP and neutrophils, invasive mechanical ventilation (IMV) percentage and in-hospital mortality did not differ significantly between the two groups. In the control group, values of PCT were increased at 48 hours after BAL in comparison to before BAL, but there is no statistical significance. Serum PCT levels were increased significantly at 24 hours after BAL (median 2.42 ng/ml, IQRs: 0.57 ng/ml to 13.14 ng/ml, p<0.001), and then decreased at 48 hours after BAL (median 1.26 ng/ml, IQRs: 0.40 ng/ml to 6.30 ng/ml, p<0.01). No significant differences (p=0.72) were observed in Control group (Figure. 2).

As indicated in Table 2, forty-eight hours later, BAL group with decreased levels of PCT had lower SOFA score (median 5, IQRs: 4 to 6.25) and less mortality (23.3%) than BAL group with increased levels of PCT. Other parameters did not reach statistical difference despite IMV percentage was numerically

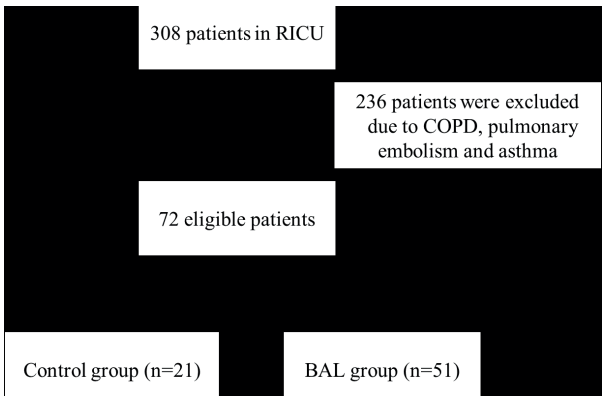

Figure 1. The flow chart of this study.

Table 1. Baseline clinical characteristics of critically ill patients with pneumonia

	Control group	BAL group	P value
Number, n	21	51	
Male, n	11	41	0.02
Age, years	72 (63-82)	75 (63-82)	0.77
APACHE-II	21 (15.50-26)	22 (18-29)	0.40
SOFA	6 (4-6)	6 (4-7)	0.45
PCT, ng/ml			
pre	0.71 (0.16-4.96)	1.51 (0.32-9.09)	0.15
mid	0.92 (0.40-6.41)	2.42 (0.57-13.14)	0.17
pos	1.01 (0.31-4.05)	1.26 (0.40-6.30)	0.45
CRP, mg/ml			
pre	63.40 (40.27-115.31)	115.70 (45.50-163.80)	0.14
mid	53.86 (36.59-139.75)	93.40 (44.50-155.80)	0.27
pos	57.80 (38.42-120.71)	63.20(26.40-128.40)	0.94
Neutrophil Count (G/L)			
pre	8.4 5.0-10.8	7.8 5.5-10.8	0.77
mid	8.4 5.25-13.35	8.6 5.8-10.9	0.96
pos	8.4 5.5-12.4	7.8 5.5-10.4	0.96
Neutrophils, %			
pre	89.20(83.05-91.55)	89.50 (81.60-92.50)	0.59
mid	89.90 (80.95-91.90)	88.50 (82.70-92.90)	0.73
post	85.60 (76.45-88.05)	85.50 (78.90-91)	0.64
Change of PCT	0.11 (-1.31-1.53)	-2.13 (-4.52-0.26)	0.42
Change of CRP	-2.50 (-12.77-7.77)	-36.68 (-56.55-16.82)	0.11
Change of Neutrophils	-0.28 (-1.55-0.99)	1.31 (-2.01-4.64)	0.94
IMV, %	47.60	66.70	0.18
Length of stay, days	9 (5.50-14)	15 (9-24)	0.003
Mortality, %	19	37.30	0.17

APACHE-II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; PCT: procalcitonin; CRP: C-reaction protein; IMV: Invasive mechanical ventilation; pre: before BAL; mid: 24h after BAL; post: 48h after BAL.

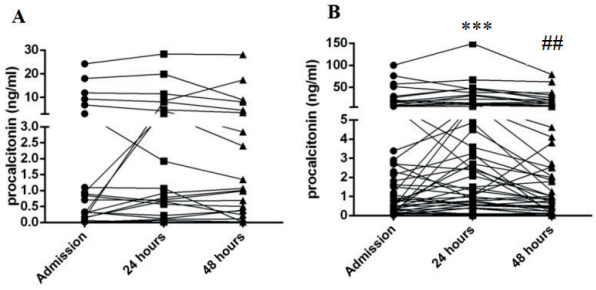

Figure 2. Serial measurements of serum PCT levels in Control group (A) and BAL group (B). Admission: PCT levels was tested at admission to RICU; 24 hours: PCT levels was tested at 24 hours after BAL; 48 hours: PCT levels was tested at 48 hours after BAL. ***p < 0.001 vs Admission, ##p < 0.01 vs 24 hours.

Table 2. Characteristics of patients with pneumonia after BAL performed by FOB

	Decreased group	Increased group	P value
Number, n	21	30	
Male, n	15	26	0.283
Age, years	76 (61.5-83)	72 (63.75-79)	0.301
APACHE-II	24 (18-31)	20 (17-26.5)	0.242
SOFA	5 (4-6.25)	7 (4.5-7)	**0.042**
PCT, ng/ml			
admission	0.51 (0.15-5.99)	2.5 (0.70-11.85)	0.05
24 hours	2.7 (0.785-18.17)	2.41 (0.53-12.30)	0.491
48 hours	2.06 (0.72-12.3)	0.81 (0.21-5.03)	0.157
CRP, mg/ml			
admission	68.27 (32.86-158.7)	129.47 (56.6-167.1)	0.213
24 hours	58.9 (38.6-146.95)	98.49 (49.95-190.28)	0.284
48 hours	60.9 (30.78-110.7)	66.64 (24.65-142.77)	0.592
Neutrophils, %	1		
admission	90.3 (84.25-93)	89.05 (81.18-92.33)	0.235
24 hours	88.5 (80.55-89.25)	88.8 (83.83-93.3)	0.559
48 hours	83.3 (72.75-89.25)	85.85 (79.43-91.25)	0.255
IMV, %	19	43.3	0.081
Length of stay, days	15 (9-24)	9 (5.5-14)	0.737
Mortality, %	23.3	57.1	**0.02**

Decreased group: decreased levels of PCT was observed at 48 hours after BAL;Increased group: increased levels of PCT was observed at 48 hours after BAL;APACHE-II: acute physiology and chronic health evaluation II; SOFA: sequential rrgan failure assessment; PCT: procalcitonin; CRP: C-reaction protein; IMV: Invasive mechanical ventilation

Table 3. Comparsion of parameters of survivors and non-Survivors in BAL group

	Survivors	Non-survivors	P value
Number, n	32	19	
Male, n	28	13	0.146
Age, years	71.5 (63.25-76.75)	77 (60-82)	0.219
APACHE-II	20 (17-28.25)	24 (18-30)	0.274
SOFA	5 (4.5-6)	7 (6-8)	**0.002**
PCT (pos/pre 1) %	71.88	36.84	**0.02**
IMV, %	58.8	41.2	0.543
Length of stay, days	16 (10.25-28.5)	14 (7-22)	0.737

APACHE-II: acute physiology and chronic health evaluation II; SOFA: sequential rrgan failure assessment; PCT: procalcitonin;IMV: Invasive mechanical ventilation

increased. Table 3 indicated that survivors had lower SOFA scores (median 5, IQRs: 4.5 to 6, p=0.002) and higher percentage of PCT levels decreased after 48 hours (71.88%, p=0.02) than non-survivors in BAL patients.

Kaplan-Meier method for probability of survival in-hospital stays showed BAL group with decreased levels of PCT observed after 48 hours had improved survival rate during hospital compared with those with increased levels of PCT (Breslow test, p=0.041) (Figure. 3). However, multivariate analysis indicated that increased serum levels of PCT observed at 48 hours after BAL was not an independent risk factor for in-hospital mortality of critically ill patients

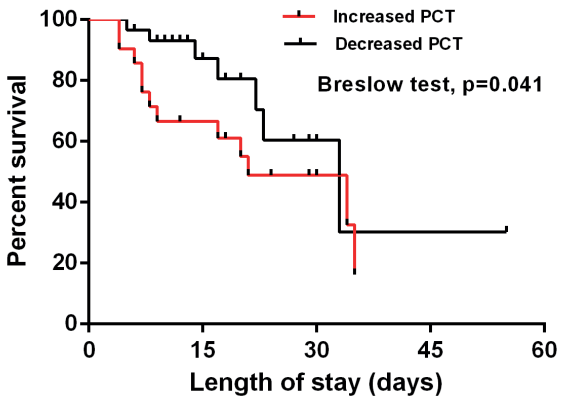

Figure 3. Kaplan-Meier method for probability of survival in hospital stays. Breslow test is used, and p < 0.05 represents as statistic difference. Increased PCT: Serum levels of PCT was increasd at 48 hours after BAL; Decreased PCT: Serum levels of PCT was decreased at 48 hours after BAL.

with pneumonia (hazard ratio: 1.689, 95% CI (0.626, 4.563), p=0.301) (Table 4).

To determine the value of PCT level to predict a prognosis of patients with severe pneumonia after bronchoscopy we performed ROC analysis (Fig. 4) in patients with BAL. The AUC was not statistically significant for PCT levels (AUC, 0.568; 95% CI (0.393, 0.743), p = 0.419).

Discussion

FOB is an indispensable tool and has a great application field in the ICUs setting, which can visualize the airways, guide percutaneous tracheostomy, sample for diagnostic or therapeutic purposes with relatively few complications in critically ill patients (18,19). For example, sticky secretions, hyperaemic mucosa and whitish plaques observed by FOB may be reliable indicators for diagnosing tracheobronchial fungal infection, and early FOB management improves the outcomes of patients with aspiration pneumonia (20,21) . BAL combined with IMV improves the curative effects in critically ill patients with severe pneumonia (22). However, FOB may cause discomfort, and worsen clinical conditions in several critically ill patients (23). In a previous study performed in RICUs indicated that patients requiring repeated FOB had a higher mortality compared with patients did not require FOB (24). Fever is a common phenomenon after FOB, and Hackner et al. indicate that PCT and blood neutrophil counts seem to be useful tools to guide diagnostic and early therapeutic decisions for an underlying bacterial infection when patients develop fever after bronchoscopy (25). FOB is frequently used to sample for diagnostic purpose, such as BAL in critically ill patients, especially in patients with increased or retained airway secretion which is closely related to increased mortality (26). The results of present study were similar to previous study, we also found that in-hospital mortality was higher in patients receiving BAL than that in patient did not require this invasive procedure, though no statistical difference was founded between two groups.

It is widely accepted that PCT is a valuable and useful biomarker for detecting bacterial infection. High PCT concentrations were found in bacterial infection compared to lower levels in viral infection or patients without infection. Meanwhile, serum level of PCT was positively correlated with the severity of pulmonary infection (27,28). In a previous study, FOB including BAL could increase the bacteraemia rate in patients with or without pulmonary infection (9,29). Meanwhile, FOB increases the risk of incidence of cross-transmission in critically ill patients (30). It was reported that PCT was a useful to distinguish a bacterial infection due to FOB, but CRP was not (31). In a retrospective study, Kronberger et al. found that ICU patients with pneumonia undergoing invasive respiratory sampling by BAL, relevant bacteria could be cultivated in 24.4% of samples, but no correlations of markers of infection, including PCT, CRP and WBC counts, with the microbiological result of BAL were identified in the

Table 4. Independent risk factors for in-hospital mortality (Cox multivariate regression analysis)

	HR (95% CI)	P value
SOFA	1.361 (1.05-1.763)	0.02
Increased PCT	1.689 (0.626-4.563)	0.301
APACHE-II	0.96 (0.89-1.036)	0.291
Age	0.996 (0.964-1.029)	0.804

Increased PCT: increased levels of PCT was observed at 48 hours after BAL
SOFA: sequential rrgan failure assessment; APACHE-II: acute physiology and chronic health evaluation II; procalcitonin: PCT

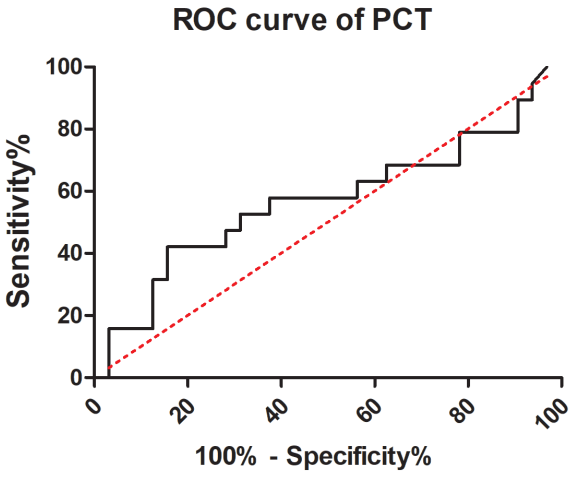

Figure 4. ROC analysis for prediction of a prognosis of patients with severe pneumonia after bronchoscopy: Procalcitonin level (AUC, 0.568; 95% CI (0.393, 0.743), p = 0.419).

whole collective of ICU patients (32). In this study, we found serum levels of PCT was significantly increased at 24 hours after BAL performed by FOB, and then decreased after 48 hours, implicating that a transient deterioration of pulmonary infections associated with this invasive procedure.

Mortality in patients with severe pulmonary infection ranges from 17 to 48 % (33,34). In patients developing septic shock, the mortality could reach up to the 50% in ICUs (35). Consistent with previous reports, the hospital mortality of patients in this study ranged 19% to 37.3%. APACHE II and SOFA are two scoring models to predict mortality in critically ill patients in ICUs. High score of APACHE- II or SOFA is positively associated with mortality (36). In this study, the average of APACHE- II score as well as the median of SOFA score was higher in non-survivors than survivors in BAL group. The decline rate of logarithm PCT over the first 72 hours independently predicted hospital and 90-day mortality of patients with undifferentiated infection or suspected sepsis (37). In critically ill patients with ventilator-associated pneumonia, PCT is an independent prognostic biomarker of mortality (38). In the present study, we found decreased PCT observed at 48 hours after BAL predicted a better prognosis of patients in hospital stay. However, multivariate analysis found that changes of PCT levels after BAL was not an independent risk factor for mortality in critically ill patients with severe pneumonia.

This study has explored the clinical significance of PCT level in critically ill patient with pneumonia received BAL. However, it has several limitations that may have influenced its results. First, the sample size of this retrospective study was small. Multicenter prospective studies are further needed to validate the findings of this study. Second, the majority of bacteria cultures from sputum specimen are positive, however, no direct evidence is presented for infections deterioration caused by BAL. For example, we did not perform immediate blood culture after BAL. Finally, despite high serum levels of procalcitonin after BAL performed by FOB were observed, adequate antimicrobial therapy before FOB may complicate the associations between procalcitonin and outcomes of patients.

Conclusions

BAL performed by FOB increased serum levels of PCT. However, PCT levels decreased at 48 hours after BAL may suggest a good prognosis of patients with severe pneumonia. Changes of PCT after BAL was not an independent risk factor for hospital mortality of critically ill patients with pneumonia.

Data Availability

The data sets used during the present study are available from the corresponding author upon reasonable request.

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