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Diagnostic efficacy of serum procalcitonin, C-reactive protein concentration and clinical pulmonary infection score in Ventilator-Associated Pneumonia

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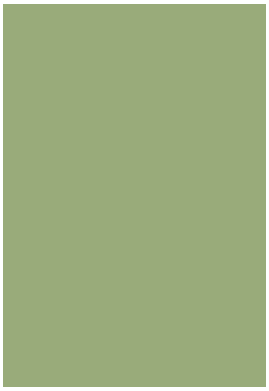

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> Objective: The aim of this study was to evaluate the diagnostic efficacy of serum procalcitonin (PCT), c-reactive protein (CRP) concentration and clinical pulmonary infection score(CPIS) in ventilator-associated pneumonia(VAP). Methods: Forty-nine patients who were admitted to the intensive care unit (ICU) of Zhejiang Hospital with suspected VAP were recruited in this study. The serum level of PCT and CRP of all patients were measured and CPIS was calculated at the time of VAP suspected diagnosis. Of the included 49 patients, 24 were finally confirmed of VAP by microbiology assay. And the other 25 patients were considered as clinical suspected VAP without microbiology confirmation. The diagnostic sensitivity, specificity and area under the receiver operating characteristic (ROC) curve (AUC) were calculated using the serum PCT, CRP concentration and CPIS. The correlation among serum PCT, CRP concentration and CPIS were also evaluated by Spearson correlation test. Results: A total of 100 bronchoscopic aspiration sputum specimen were examined in bacterial culture. 30 samples were found with suspected pathogenic bacteria. Six samples were found with 2 types of suspected pathogenic bacteria. PCT serum concentration and CPIS score were significantly different (P<0.05) between the patient group [1.4 (0.68 ~ 2.24), 6.0 (4.25 ~ 8.00)] and the control group [0.4 (0.17 ~ 1.39), 3.0 (1.00 ~ 5.00)] ; However, the serum CRP [102.8(66.75 ~ 130.90) vs 86.1(66.95 ~ 110.10)] was not statistically different between the two groups (P>0.05). A significant correlation was found between serum PCT and CRP concentrations (r=0.55, P<0.01), but not between PCT vs CPIS and CRP vs CPIS (p>0.05). The diagnostic sensitivity, specificity and AUC were 72.0%, 75.0%, 0.81 (0.69 ~ 0.93) for CPIS; 60.0%, 87.5%, 0.76 (0.62 ~ 0.90) for PCT and 68.0%, 58.3%, 0.59 (0.43 ~ 0.76) for CRP. Conclusion: PCT serum level and CPIS score are elevated in VAP patients and could therefore represent potential biomarkers for VAP early diagnosis. <

Key words: procalcitonin; c-reactive protein; clinical pulmonary infection score; ventilator-associated pneumonia.

Introduction

Ventilator associated pneumonia (VAP) that occurs more than 48 hours after initiation of mechanical ventilation is one of the most diagnosed infectious complication in the department of intensive care unit (ICU) [1, 2]. It has been reported that the morbidity rate ranges from 10% to 20% with a mortality rate of 50% [3-5]. Furthermore, this complication also prolonges the duration of mechanical ventilation, hospital stay and increases the cost of treatment [6-8]. Early diagnosis and effective antibiotic treatment were key methods for improving the prognosis of

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patients with VAP. At present, the most clinical used methods for VAP diagnosis are clinical standards and etiological examination. However, the specificity is low with regard to clinical diagnosis standards because of relative loose criteria. For etiological examination, although its specificity is high, it always needs quantitative or semi-quantitative bacterial culture assays which usually delays the diagnosis process.

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, the latter being involved with calcium homeostasis. C-reactive protein (CRP) is an annular (ring-shaped) pentameric protein found in blood plasma, whose levels rise in response to inflammation. Previous studies have demonstrated that the serum levels of PCT and CRP are elevated in patients with infected lesions and could be potential biomarkers for infection disease diagnosis [9-11]. However, the conclusion about the diagnostic pertinence of serum PCT and CRP for VAP remains controversial [12, 13].

Material and methods

Patients

Patients admitted to the ICU department form January 2015 to June 2017 in Zhejiang Hospital for mechanical ventilation were screened as potential cases. Written informed consent was obtained from all the included patients. The study was approved by the Local Ethics Committee of Zhejiang Hospital. The patients inclusion criteria were: ① Age more than 18 years; ② mechanical ventilation more than 48h; ③ With suspected VAP diagnosis: (1) Persistent or new invasive shadows in the lung; (2) At least two below items: temperature more than 38 °C or less than 36 °C; leucocyte count>10×10-9/L or <410×10-9/L; purulent sputum. ④ With confirmed VAP diagnosis: (1) Persistent or new invasive shadows in the lung; (2) At least two below items: temperature more than 38 °C or less than 36 °C; leucocyte count >10×10^9/L or <4×10^9/L; purulent sputum; (3) Any of the item below: bronchoscopic aspiration sputum specimen bacterial culture +++～++++; Pathogenic bacteria were cultured from blood. The patients exclusion criteria were ① confirmed pulmonary or extrapulmonary infection before mechanical ventilation; ② malignant carcinomas; ③ HIV positive patients; ④ confirmed extrapulmonary infection during mechanical ventilation ⑤ potential increase of serum PCT or CRP related to other diseases; ⑥ acute myocardial infarction; ⑦ dead within 48h.

Serum PCT, CRP measurement

On the day of VAP suspected diagnosis or confirmation diagnosis, 6mL of peripheral blood were sampled from each included patient and then centrifuged to separate the serum. The obtained serum was stored at -20 °C for subsequent assays. The serum PCT and CRP concentration were measured by electrochemiluminescence immunoassay and nephelometry assay, respectively. Procedures were performed according to the manufacturer's recommendations.

CPIS score evaluation

Pulmonary infection score (CPIS) was used to make the diagnosis of VAP by predicting which patients will benefit from obtaining pulmonary cultures [14]. Diagnosis of the CPIS results in fewer missed VAP episodes and can also prevent unnecessary antibiotic administration due to treatment of colonized patients. The CPIS score evaluation system is shown in *Table 1*.

Parameter	Score
Temperature (°C)	
≥36.5 and ≤38.4	0
≥38.5 and ≤38.9	1
≥39.0 or ≤36.5	2
leucocyte count(10-9/L)	
≥4 and≤11	0
<4 or 11	1
<4 or >11, AND band forms ≥50%	2
Tracheal Secretions	
None or scant	0
Non-purulent	1
Purulent	2
PaO_2/FiO_2(mmHg)	
>240, ARDS or pulmonary contusion	0
≤240 and no ARDS	2
Chest Radiograph	
No infiltrate	0
Diffuse (or patchy) infiltrate	1
Localized infiltrate	2

Table 1. *CPIS score evaluation system.*

Statistical analysis

Stata 11.0 statistical software was used for all the data analysis. Because of abnormal distribution, the serum concentration of PCT and CRP was expressed as a median value, with a 95% confidence interval and analyzed by non-parametric Mann-Whitney U-test. The CPIS score was expressed as means ± standard deviation (SD) and compared by a student-t test between two groups. A receiver operator characteristic (ROC) curve was used to evaluate the diagnostic performance of CPIS, PCT and CRP for VAP confirmation. Two tails P values <0.05 were considered as statistically significant.

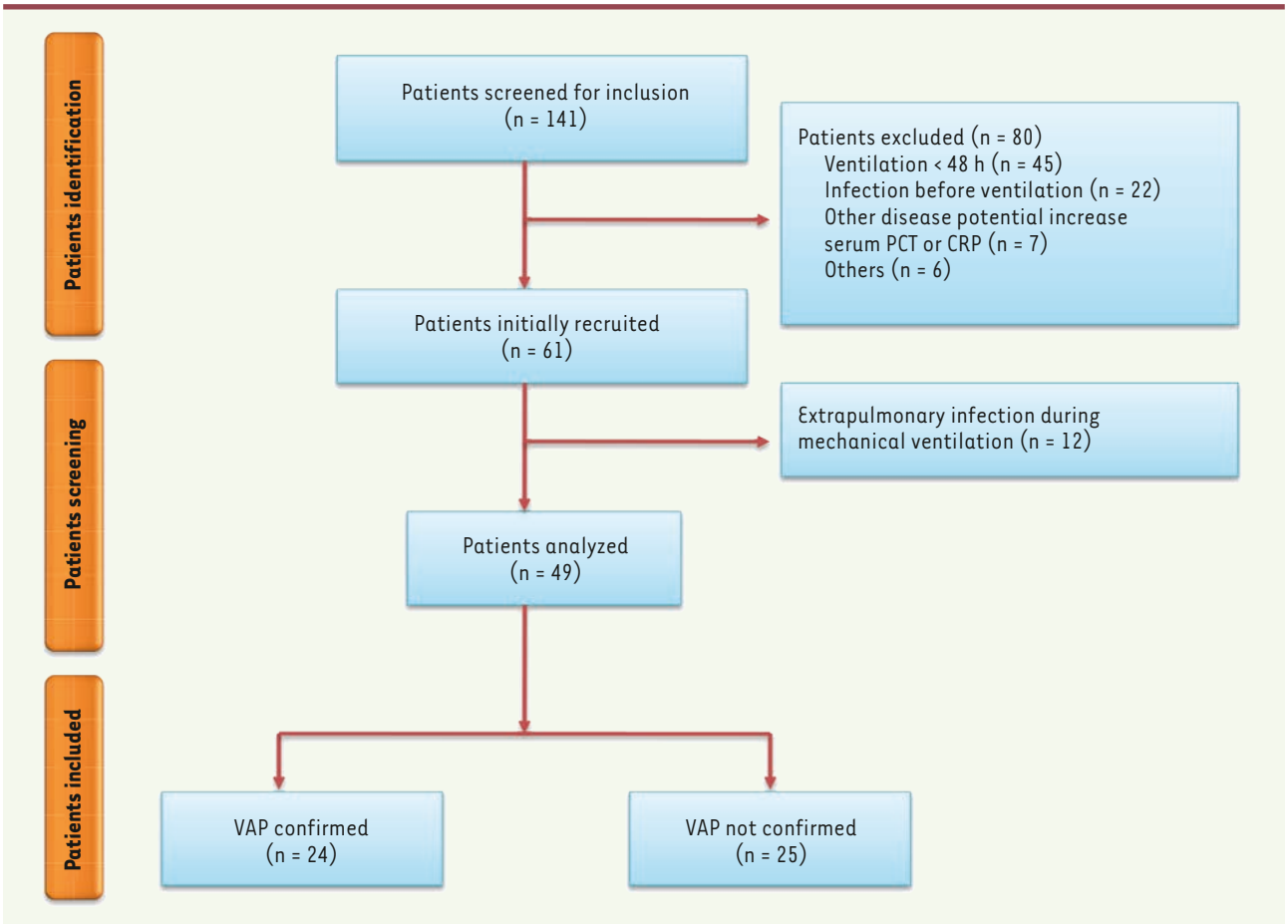

Figure 1. *Patients inclusion and exclusion flow chart.*

Results

Patients inclusion and general characteristics

One hundred and forty-one patients were screened initially. 80 cases were excluded for fail to meet the inclusion critera. Thus, 61 patients were initially recruited in the study. During the treatment process, 12 patients were further excluded because of extrapulmonary infection during the mechanical ventilation. Finally, 49 cases were included for data analysis *(Figure 1)*. Of the included 49 patients, 24 were confirmed with VAP (case group) and 25 subjects were not confirmed (control group) according to bronchoscopic aspiration sputum specimen pathogenic bacteria culture. The general characteristics of the included patients are shown in *Table 2*.

Pathogenic bacteria analysis

A total of 100 bronchoscopic aspiration sputum specimen were examined in bacterial culture. 30 samples were found with suspected pathogenic bacteria. Six samples were found with 2 types of suspected pathogenic bacteria. The suspected pathogenic bacteria distribution is shown in *Figure 2*.

Serum PCT, CRP concentration and CPIS

PCT serum concentration and CPIS score were 1.4 (0.68～2.24), 6.0 (4.25～8.00) in patients group and 0.4 (0.17～1.39), 3.0 (1.00～5.00) in control group, respectively with statistical difference ($P<0.05$); However, the serum CRP [102.8 (66.75～130.90) vs 86.1 (66.95～110.10)] was not statistical different between the two groups ($P>0.05$) *(Table 3)*. A significant correlation was found between serum PCT and CRP concentrations ($r=0.55$, $P<0.01$), but not between PCT vs CPIS and CRP vs CPIS ($p>0.05$) *(Figure 3)*.

Diagnostic efficacy of Serum PCT, CRP concentration and CPIS

The diagnostic sensitivity, specificity and AUC were 72.0%, 75.0%, 0.81 (0.69～0.93) for CPIS; 60.0%, 87.5%, 0.76 (0.62～0.90) for PCT and 68.0%, 58.3%, 0.59 (0.43～0.76) for CRP *(Table 4)* *(Figure 4)*.

Discussion

Ventilator associated pneumonia(VAP), a common infection disease in the department of intensive care unit (ICU), is one of the main cause of increased mortality, prolonged hospital stay and elevated treatment costs [2, 7]. Accurate and timely diagnosis is the key

Characters	Case(n=24)	Control(n=25)	t/χ^2	P value
Age (y)	55.4±14.5	52.6±16.7	0.63	0.53
Gender [n.(%)]				
Male	15(62.5)	14(56.0)		
Female	9(37.5)	11(44.0)		
Antibiotics[n.(%)]				
Positive	14(58.3)	17(68.0)		
Negative	10(41.7)	8(32.0)		
Ventilation time (day)	8.6±6.2	7.8±6.7	0.43	0.67
Temperature (℃)	38.6±0.7	38.4±0.8	0.93	0.36
PaO2/FiO2 (mmHg)	186.2±86.4	214.5±79.6	1.19	0.24
APACHE Ⅱ	22.4±6.2	16.8±7.1	2.94	0.005
Leukocytes (×10-9/L)	12.3±4.3	11.8±5.1	0.37	0.71
Heart rate (beat/min)	112.3±12.5	106.8±15.6	1.36	0.18
Blood pressure (mmHg)				
Systolic pressure	138.5±22.4	124.5±27.4	1.95	0.06
Diastolic pressure	76.1±14.5	78.1±18.4	0.42	0.68
Basic disease [n.(%)]			2.21	0.97
Type Ⅱ respiratory failure	2(8.3)	2(8.0)		
Type Ⅰ respiratory failure	6(25.0)	7(28.0)		
Heart failure	5(20.8)	6(24.0)		
Cardiopulmonary resuscitation	2(8.3)	2(8.0)		
Post operation	2(8.3)	3(12.0)		
Central respiratory failure	2(8.3)	1(4.0)		
Shock	2(8.3)	1(4.0)		
Stroke	1(4.2)	0(0.0)		
Chest trauma	2(8.3)	3(12.0)		

Table 2. *Characteristics of the patients at the time of VAP suspicion.*

to reduce the risk of death and to decrease the treatment costs [15, 16]. However, major difficulties and controversies still exist in the definition of diagnostic standards for VAP. Most of them focus on: (1) the technique of ideal sampling for routine applications; (2) the evaluation of quantitative culture of respiratory secretions; (3) the advantages and disadvantages of the invasive and non-invasive technologies for VAP diagnosis; (4) whether the diagnosis approach can affect the prognosis or not.

Currently, the most used method for VAP diagnosis is a standardized clinical diagnosis. However, its specificity is low because of relative loose condition. Another drawback for this clinical standard is the high false positive rate which may lead to the abuse of antibiotics and overtreatment. On the basis of this clinical standard, another VAP diagnosis system called clinical pulmonary infection score (CPIS) has been developed. This new system consideres that patients are at high risk of developing VAP when CPIS is greater than 6 points [14, 17]. Pugin[18] and Papazian[19] argued that CPIS is a good approach for VAP diagnosis, exhibiting a relatively high sensitivity and specificity. In the present study, we found that the CPIS in the patient group is significantly higher than in the control group. Further analyses indicated that the diagnosis sensitivity and specificity are 72.0% and 75.0% with the AUC of 0.81 (0.69～0.93) by using the CPIS approach. This demonstrates that CPIS is a good method for VAP diagnosis. Also, thanks to its easy clinical maneuverability, CPIS has been extensively used for clinical practice.

Procalcitonin (PCT), a peptide precursor of the hormone calcitonin, and C-reactive protein (CRP) an annular (ring-shaped) pentameric protein, were always elevated in the serum of patients with infected lesions. They have been therefore extensively applied as biomarkers of infection disease. However, serum concentration of PCT and CRP as biomarkers for VAP diagnosis have been seldomly reported.

In the present study, we included 49 patients with suspect or confirmed VAP and evaluated the clinical efficacy of serum PCT and CRP as biomarkers for VAP confirmation diagnosis. We found that serum level of PCT and CPIS score are elevated in VAP patients, and,

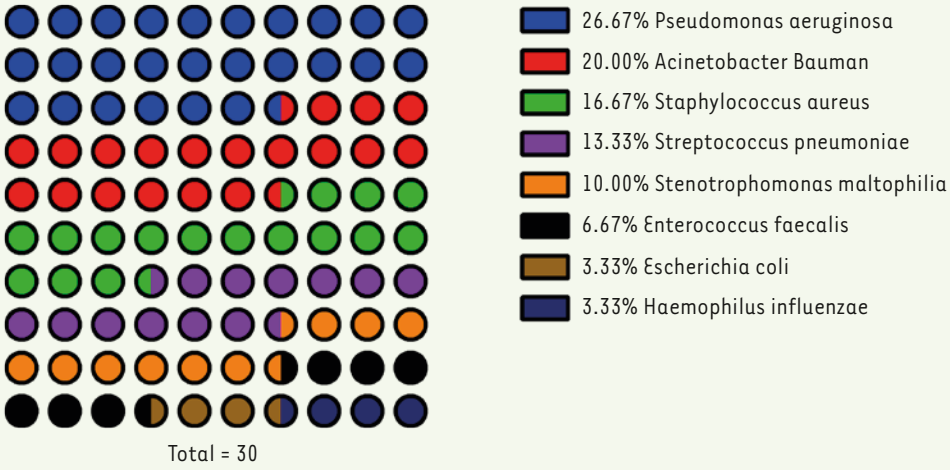

Figure 2. *Suspected pathogenic bacteria of 30 bronchoscopic aspiration sputum specimen.*

Serum markers	Case(n=24)	Control(n=25)	P value
CPIS	6.0(4.25～8.00)	3.0(1.00～5.00)	<0.05
CRP(ng/mL)	102.8(66.75～130.90)	86.1(66.95～110.10)	>0.05
PCT(mg/L)	1.4(0.68～2.24)	0.4(0.17～1.39)	<0.05

Table 3. *Serum PCT and CRP concentrations and CPIS.*

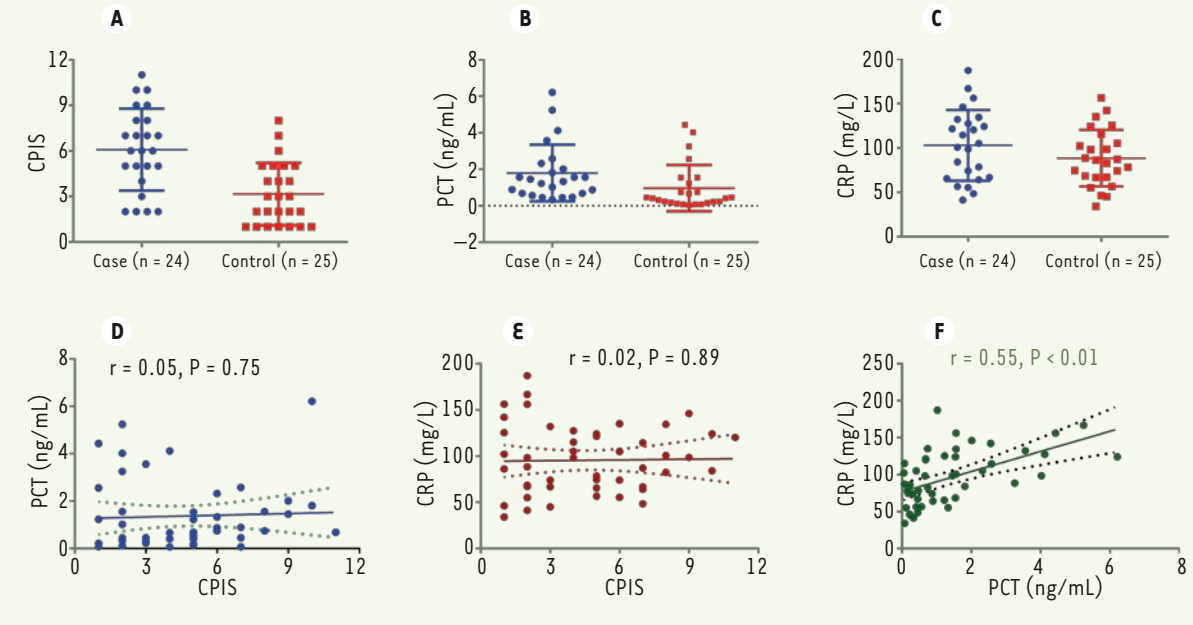

Figure 3. ***Serum PCT, CRP concentration and CPIS score of the two groups.*** ***(A)*** Scatter plot of CPIS score of the two groups. ***(B)*** Scatter plot of serum concentration of PCT. ***(C)*** Scatter plot of serum concentration of CRP. ***(D)*** Pearson correlation for serum PCT concentration and CPIS score. ***(E)*** Pearson correlation for serum CRP concentration and CPIS score. ***(F)*** Pearson correlation for serum PCT and CRP concentration.

hence, that they could represent useful potential biomarkers for VAP early diagnosis. However, the serum CRP was not found to be statistically different between the two groups. It indicates that its diagnostic value is limited.

Parameter	CPIS	PCT	CRP
Sensitivity	72.0%	60.0%	68.0%
Specificity	75.0%	87.5%	58.3%
Likelihood ratio	2.88	4.8	1.63
AUC (95%CI)	0.81 (0.69～0.93)	0.76 (0.62～0.90)	0.59 (0.43～0.76)
P value	<0.001	<0.001	0.27
Cut-off	4.50	0.46	98.45

Table 4. *Diagnostic value of serum PCT, CRP concentration and CPIS.*

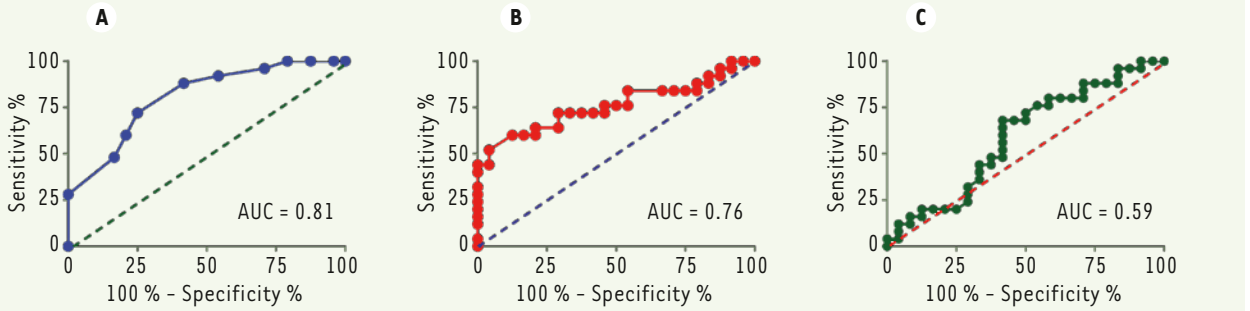

Figure 4. *ROC curve of serum PCT, CRP concentration and CPIS for confirmation diagnosis of VAP.* ***(A)*** ROC curve of CPIS. ***(B)*** ROC curve of PCT. ***(C)*** ROC curve of CRP.

Besides the positive findings of this work, this study also had several limitations. Firstly, only 49 patients were included in this study. Thus, the statistical power is limited due to the relative small samples size. Secondly, all the patients were recruited from a single hospital, which may lead to a sample selection bias. Thirdly, more than half of the patients received antibiotic drugs before mechanical ventilation treatment. The antibiotic drug used may decrease the positive rate of bacterial culture. In view of these above limitations, well-designed large multicenter prospective cohort studies are needed for further evaluate this VAP early diagnosis method. Such studies should provide more and relevant clinical evidence of the interest of using this method. ◊

DISCLOSURE OF CONFLICT OF INTEREST

None.

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