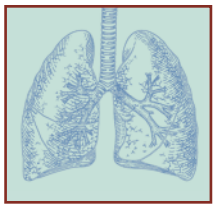

Diagnosing Ventilator-Associated Pneumonia in Critically Ill Patients With Sepsis

By Long-xiang Su, MD, Kun Meng, MD, Xin Zhang, MM, Hui-juan Wang, MD, Peng Yan, BM, Yan-hong Jia, RN, Dan Feng, PhD, and Li-xin Xie, MD

Background Timely diagnosis and prognostic assessment of ventilator-associated pneumonia remain major challenges in critical care.

Objective To explore the value of soluble triggering receptor expressed on myeloid cells 1, procalcitonin, and the Clinical Pulmonary Infection Score in the diagnosis and prognostic assessment of ventilator-associated pneumonia.

Methods For 92 patients, bronchoalveolar lavage fluid was cultured for detection of microorganisms, serum levels of the receptor and procalcitonin and levels of the receptor in exhaled ventilator condensate were measured, and the Clinical Pulmonary Infection Score was calculated.

Results On the day of diagnosis, patients who had pneumonia had higher serum levels of the receptor, procalcitonin, and C-reactive protein; higher white blood cell counts; and higher pulmonary infection and Sequential Organ Failure Assessment scores than did patients without pneumonia. White blood cell count (odds ratio, 1.118; 95% CI, 1.139-1.204) and serum levels of the receptor (odds ratio, 1.002; 95% CI, 1.000-1.005) may be risk factors for VAP. Serum levels of the receptor plus the pulmonary infection score were the most reliable for diagnosis; the area under the receiver operating characteristic curve was 0.972 (95% CI, 0.945-0.999), sensitivity was 0.875, and specificity was 0.95. For 28-day survival, procalcitonin level combined with pulmonary infection score was the most reliable for prognostic assessment (area under the curve, 0.848; 95% CI, 0.672-1.025).

Conclusions In patients with ventilator-associated pneumonia, serum levels of the receptor plus the pulmonary infection score are useful for diagnosis, and procalcitonin levels plus the pulmonary infection score are useful for prognostic assessment.
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Ventilator-associated pneumonia (VAP) is the most severe type of hospital-acquired pneumonia. VAP is difficult to treat, the prognosis is poor, and the cost of treatment is high.[1] New onset of pulmonary infiltrates, fever, and an increase in white blood cell (WBC) count accompanied by purulent tracheal secretions are clinically indicative of VAP. The low specificity of diagnostic tests for VAP, however, tends to result in an extremely high incidence of missed diagnoses[2] and may lead to serious nosocomial infection and high mortality.[3] Quantitative culture of secretions obtained by bronchoscopy of the lower part of the respiratory tract is now regarded as a fairly practicable method for VAP diagnosis.[4] However, bronchoalveolar lavage is an invasive procedure and is often limited in availability because it can easily lead to secondary infection. Moreover, 48 to 72 hours are required for analysis of the lavage fluid. Therefore, rapid and accurate diagnosis of VAP remains a difficult issue for intensive care unit (ICU) physicians.

Triggering receptor expressed on myeloid cells 1 (TREM-1), which is expressed on polymorphonuclear granulocytes and mature monocytes, belongs to an immunoglobulin superfamily of receptors. Bacterial or fungal infection may activate expression of the receptor,[5] and a soluble form of the receptor, sTREM-1, may be released into bodily fluids with the upregulation of TREM-1. Thus, sTREM-1 can be used to distinguish between infectious and noninfectious diseases.[6-12] Recent studies[13,14] have indicated that sTREM-1 in bronchoalveolar lavage fluid (BALF) may be a marker for pulmonary infection and may be of value for VAP diagnosis. Clinically, the procalcitonin test is now widely used as a related biomarker indicative of infection, including the severity and prognosis of the infection.[15-18] The results of some studies[19-21] have suggested that the procalcitonin level might be relevant to the occurrence of VAP. In recent years, the Clinical Pulmonary Infection Score (CPIS) has been used both for the early diagnosis[22] of VAP and as a clinical indicator of the outcome of the infection.[23]

In this study, we measured levels of sTREM-1 and procalcitonin in serum and sTREM-1 levels in exhaled ventilator condensate (EVC) and determined the CPIS. To ascertain the value of sTREM-1 and procalcitonin in the diagnosis of VAP, we compared these indicators with more commonly used indicators, including WBC counts, levels of C-reactive protein, and scores on the Sequential Organ Failure Assessment (SOFA). We also examined the values of all indicators in VAP prognosis.

Low diagnostic specificity may cause an extremely high incidence of missed diagnoses of ventilator-associated pneumonia.

Methods

Patients and Definitions

The study sample was selected from patients hospitalized between March 2010 and March 2011 in the respiratory, surgical, and emergency ICUs of the Chinese PLA General Hospital, Beijing, China. On the basis of the 1991 guidelines[24] of the American College of Chest Physicians and the Society of Critical Care Medicine, the diagnosis criteria advanced by the 2001 International Sepsis Definition Conference,[25] and the 2008 international guidelines[26] for management of severe sepsis and septic shock, patients with sepsis who had undergone tracheotomy or endotracheal intubation or had received mechanical ventilation were selected for the study. In accordance with the 2005 guidelines[27] of the American Thoracic Society and the Infectious Diseases Society of America, the criteria for diagnosis of VAP were evidence of new infiltrates on chest radiographs after 48 to 72 hours of endotracheal intubation and

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presence of at least 2 of the following: fever (temperature >38°C or higher than basal temperature), abnormal WBC count (≥10 000/μL or <4000/μL), and purulent respiratory tract secretions. In addition, the various organizations recommend that lower respiratory tract secretions be collected via bronchoscopy and that BALF samples be cultured for microorganisms (diagnostic threshold, 104 colony-forming units per milliliter). The pulmonary infection identification score was based on the simplified CPIS system advanced by Luna et al.[23]

Newer diagnostic indicators of ventilator-associated pneumonia were compared with more common indicators, including white blood cell counts, C-reactive protein levels, and Sequential Organ Failure Assessment scores.

Accordingly, patients in the study were divided into the VAP group (n = 32) and the non-VAP group (n = 60); the indicator levels and CPIS values of both groups were recorded on the day of admission. On the basis of 28-day survival, the VAP patients were divided into 2 groups: survivors (n = 15) and nonsurvivors (n = 17). Patients were excluded from the study if they were less than 18 years old, had contracted VAP upon ICU admission or within 48 hours after admission, had acquired immunodeficiency syndrome, had a decrease in polymorphonuclear granulocytes (<500/μL), died within 24 hours after ICU admission, refused to participate in the study, or quit treatment during the period of observation. The study was approved by the ethics committee of the hospital and was registered with the US National Institutes of Health Clinical Trials Registry (NCT01406951). The patients and their families were informed of the relevant details, and they signed consent agreements before the study began.

Data and Sample Collection

At ICU admission, the following items were recorded for each patient: age, sex, chief reason for admission, major diagnoses, signs and symptoms, score on the Acute Physiology and Chronic Health Evaluation (APACHE) II, pathogens that caused an infection in the patient at the time of admission, underlying diseases, and use of mechanical ventilation during the ICU admission. Records of the following were also kept: body temperature; oxygenation index (ratio of Pa_{O_2} to fraction of inspired oxygen); tracheal secretions; chest radiographs; BALF culture reports; WBC counts and levels of sTREM-1, procalcitonin, and C-reactive protein upon admission; and VAP occurrence.

Venous blood samples were obtained from patients in the VAP group within 24 hours after admission and on the day that VAP was diagnosed. EVC samples were obtained from the condensate collection bottle attached to the ventilator outlet tubing. BALF samples were collected with sterile disposable suctioning tubes and were washed with sterile saline. Samples of lower respiratory tract secretions were obtained via bronchoscopy on the day that VAP was diagnosed. According to the hospital's medical records, in general, VAP occurred 7 to 8 days after admission. Therefore, specimens were obtained from the non-VAP group on day 7 and within 24 hours after ICU admission. Blood samples were centrifuged at 3000 rpm for 15 minutes at 4°C; the EVC samples, at 10 000 rpm ($5 \times 10^4 g$) for 30 minutes. The supernatant fluids were then transferred to microcentrifuge tubes and stored at -80°C.

Assays

All specimens were renumbered before analysis, and the researchers had no knowledge of each step. The concentration of sTREM-1 was determined in duplicate by using a double-antibody sandwich enzyme-linked immunosorbent assay (Quantikine Human TREM-1 Immunoassay ELISA Kit, DTRM10B, R&D Systems). Levels of C-reactive protein were determined by using scattering turbidimetry (CardioPhase hsCRP, Siemens) and levels of procalcitonin by using enzyme-linked fluorescence analysis (VIDAS BRAHMS PCT Kit; bioMérieux SA). When signs and symptoms of VAP occurred, bronchoalveolar lavage was performed, and the diagnosis of VAP was confirmed by an expert panel. Microbiological assays of the BALF specimens were performed within 1 hour after collection to obtain quantitative cultures and cell counts.[2]

Statistical Analysis

The results for continuous variables with normal distribution, including age, temperature, oxygenation index, WBC counts, APACHE II scores, SOFA scores, and CPIS values, are given as means and standard deviations. Means of the 2 groups of patients (VAP and non-VAP) were compared by using *t* tests. The results for continuous variables with abnormal distribution, including concentrations of sTREM-1 and procalcitonin, are given as medians and interquartile ranges and were compared by using nonparametric tests. The results for qualitative variables, such as sex, type of ICU, sepsis severity, reasons for mechanical ventilation, etiological factors (pathogens causing infection at admission),

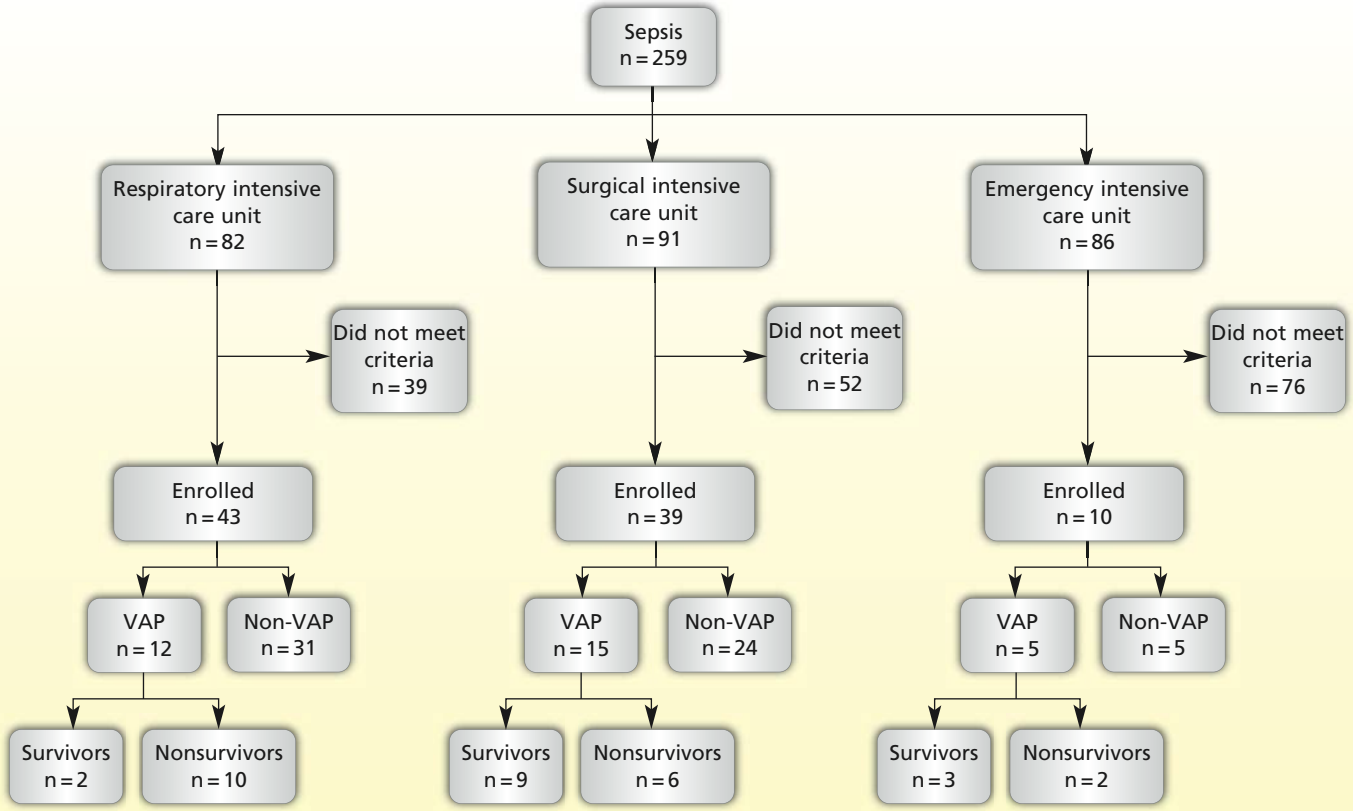


Figure 1 Trial profile for patients with and without ventilator-associated pneumonia (VAP).

underlying diseases, and mortality rate, are expressed as percentages and were compared between the groups by using χ^2 tests. Multivariate logistic regression was used to assess possible risk factors for VAP and to analyze and sort quantitative data related to VAP occurrence and prognostic assessment, and new data containing various combinations of diagnostic indicators (eg, sTREM-1 + WBC count, sTREM-1 + CPIS value, and procalcitonin + CPIS value) were calculated. The value of a number of combinations of indicators for VAP diagnosis and prognostic assessment were further assessed by using receiver operating characteristic (ROC) curves. SPSS 16.0 software (SPSS) was used for all statistical analysis, and a 2-tailed $P < .05$ was considered significant.

Results

Patients

Among the 259 patients with sepsis admitted to the ICUs during the study period, 92 were selected for the study, 32 with VAP and 60 without (Figure 1). Table 1 gives the characteristics of the 92 patients upon admission. Compared with patients in the non-VAP group, patients with VAP had significantly higher levels of C-reactive protein ($P = .02$) and procalcitonin ($P = .009$), and significantly more VAP patients had a history of coronary heart disease ($P = .03$). The 2 groups did not differ significantly in age, sex, temperature, oxygenation index, WBC counts, levels of sTREM-1, APACHE II scores, SOFA scores, CPIS values, sepsis severity, reasons for mechanical ventilation, etiological factors (pathogens), underlying diseases (except coronary disease), or mortality rate.

Patients with a diagnosis of ventilator-associated pneumonia had higher levels of C-reactive protein and procalcitonin.

Value of Serum Levels of sTREM-1 for VAP Diagnosis

Table 2 shows the microbial results of cultures of BALF in the VAP group. Microorganisms were detected in 53 cultures; of these, 36 were gram-negative bacteria (69%), 4 were gram-positive bacteria (8%), and 13 were fungi (25%). A total of 17 cases of infectious complications were traced to more than 2 pathogens, and 11 of these 17 were traced to fungi.

The following items for the 60 patients without VAP who received mechanical ventilation were examined on ICU day 7: temperature, oxygenation index, levels of sTREM-1 and procalcitonin, WBC counts, level of C-reactive protein, CPIS values, and

Table 1
Clinical and biological data upon admission to the intensive care unit of patients with sepsis treated with mechanical ventilation[a]

Characteristics	Ventilator-associated pneumonia: Present (n = 32)	Ventilator-associated pneumonia: Absent (n = 60)	*P*
Age, mean (SD), y	57 (21)	62 (21)	.25
Sex, No. (%)			.64
Male	22 (69)	44 (73)	
Female	10 (31)	16 (27)	
Body temperature, mean (SD), °C	37.8 (1.3)	37.5 (1.1)	.22
Oxygenation index,[b] mean (SD)	213.9 (100.1)	218.9 (103.2)	.82
White blood cell count, mean (SD), cells/μL	13 200 (5000)	12 000 (6300)	.33
C-reactive protein,[c] median (interquartile range), mg/dL	123 (75)	86 (65)	.02
Procalcitonin, median (interquartile range), ng/mL	7.3 (21.4)	1.1 (6.0)	.009
sTREM-1, median (interquartile range), pg/mL	173.4 (208.7)	170.2 (163.4)	.11
APACHE II score, mean (SD)	21.1 (7.8)	17.9 (7.3)	.06
SOFA score, mean (SD)	9.3 (4.0)	7.9 (4.1)	.12
Sepsis severity, No. (%)			.44
Sepsis	7 (21.9)	20 (17.6)	
Severe sepsis	12 (37.5)	22 (22.2)	
Septic shock	13 (40.6)	18 (20.2)	
Reasons for mechanical ventilation, No. (%)			.75
Acute respiratory failure	20 (62)	33 (55)	
AECOPD	1 (3)	5 (8)	
Trauma/postoperative respiratory failure	10 (31)	20 (33)	
Nervous system diseases	1 (3)	2 (3)	
Etiological factors, No. (%)			
Pulmonary infection	29 (91)	52 (87)	.83
Abdominal infection	5 (3)	4 (7)	.31
Urinary tract infection	10 (31)	15 (25)	.31
Trauma/postoperative infection	12 (38)	17 (28)	.37
Bacteremia	5 (16)	17 (28)	.17
Catheter-related infections	4 (12)	9 (15)	.99
Others	3 (9)	2 (3)	.46
Underlying diseases, No. (%)			
Hypertension	14 (44)	20 (33)	.32
Diabetes	10 (31)	11 (18)	.16
Chronic obstructive pulmonary disease	6 (19)	9 (15)	.64
Coronary heart disease	14 (44)	13 (22)	.03
Immunosuppression	1 (3)	6 (10)	.44
Nervous system disease	7 (22)	10 (17)	.54
Chronic kidney disease	2 (6)	5 (8)	.98
Mortality rate, No. (%)	18 (56)	27 (45)	.30

Abbreviations: AECOPD, acute embittering chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; CPIS, Clinical Pulmonary Infection Score; SOFA, Sequential Organ Failure Assessment; sTREM-1, soluble triggering receptor expressed on myeloid cells 1.
[a] Because of rounding, not all percentages total 100.
[b] Ratio of Pao_2 to fraction of inspired oxygen.
[c] To convert to nanomoles per liter, multiply by 9.524.

SOFA scores. The results were compared with the corresponding items for the 32 patients with VAP on the day the pneumonia was detected (Table 3). Compared with the non-VAP group, patients in the VAP group had a significantly lower oxygenation index and significantly higher temperature, serum concentration of procalcitonin, levels of sTREM-1, WBC counts, level of C-reactive protein, CPIS values, and SOFA scores. Figure 2A shows the ROCs of these indicators for VAP diagnosis.

In multivariate logistic regression to assess possible risk factors for VAP, 4 biomarkers were considered: sTREM-1, procalcitonin, WBC count, and C-reactive protein. Values for WBC count were as follows: regression coefficient, 0.112; odds ratio (OR), 1.118; Wald coefficient, 8.821; and 95% CI, 1.039 to 1.204 ($P = .003$). Values for sTREM-1 were regression coefficient, 0.002; OR, 1.002; Wald coefficient, 4.007; and 95% CI, 1.000 to 1.005 ($P = .045$). Meanwhile, quantitative data related to VAP were sorted, and new quantitative data containing indicator combinations were calculated with relevant equations (sTREM-1 + WBC count and sTREM-1 + CPIS). ROC curves were used to determine and assess the value of a number of combinations of indicators for VAP diagnosis (Figure 2B).

Value of sTREM-1 in EVC for VAP Diagnosis

EVC was collected from the 32 patients with VAP on the day the pneumonia was diagnosed and from the 60 patients without VAP on ICU day 7. The concentration of sTREM-1 could be measured in the EVC of 5 patients from the VAP group and 1 patient from the control group; the concentrations of sTREM-1 in the EVC of the other patients were undetectable (data not shown).

Value of Serum Levels of sTREM-1 for VAP Prognosis

In order to determine their value for VAP prognostic assessment, the following indicators (determined on the day VAP was diagnosed) were compared between the 32 patients with VAP who survived (n = 15) and those who did not (n = 17): temperature, oxygenation index; serum levels of sTREM-1, procalcitonin, and C-reactive protein; WBC count; and values on the CPIS and the SOFA (Table 4). No obvious differences were found in temperature, WBC count, or serum level of C-reactive protein. On the day VAP was diagnosed, the survivors had a higher oxygenation index and a lower serum level of sTREM-1, but the differences were not significant. Compared with the survivors, the nonsurvivors had significantly higher levels of

procalcitonin, CPIS values, and SOFA scores. Logistic regression and an ROC curve (Figure 3) were used to examine the significant indicators: procalcitonin, CPIS, and procalcitonin plus CPIS.

Discussion

We found that upon admission, the only significant differences between patients with sepsis in whom VAP did and did not develop were serum levels of C-reactive protein and procalcitonin and history of chronic heart disease. The higher levels of C-reactive protein and procalcitonin in the VAP group suggest that these patients had more severe infections and a greater likelihood of experiencing VAP than did the non-VAP group. In our study, the mean onset of VAP, mostly delayed VAP,[28] occurred 6.9 days after admission. Delayed VAP is mainly caused by gram-negative bacteria, most commonly *Pseudomonas aeruginosa*.[29,30] In our study, however, *Acinetobacter baumannii* (38%) was the most common causative agent. In addition, the rate of fungal VAP was high. This phenomenon is common in ICUs[31,32] and probably occurs because patients with sepsis who have local or systemic infection or organ dysfunction are usually given broad-spectrum antibiotics or treated with invasive operations and life-support technologies. These therapies are high-risk factors for nosocomial infection.[33]

Recently, much research has been devoted to the value of sTREM-1 levels for diagnosis of VAP. All of these studies focused on the concentration of sTREM-1 in BALF. Gibot et al[7] studied 148 patients with suspected pneumonia who were being treated with mechanical ventilation. Determination of the level of sTREM-1 in BALF was more accurate than clinical observation or other laboratory tests for VAP diagnosis. When sTREM-1 was used to differentiate pulmonary infection from noninfection, the area under the ROC curve was 0.93. In other research, in 28 patients treated with mechanical ventilation, Determann et al[14] determined the concentration of sTREM-1 in BALF collected every other day during the treatment. For patients with VAP, the concentration of sTREM-1 increased considerably 6 days before diagnosis of pneumonia and reached a maximum 4 days after diagnosis. Patients without VAP had no increase in sTREM-1. At an sTREM-1 concentration of 20 ng/mL, the sensitivity for VAP diagnosis was 0.75 and the specificity was 0.84. Huh et al[34] studied 80 patients with suspected infectious pneumonia whose chest radiographs revealed bilateral pulmonary infiltrations. For all patients, irrespective of bacterial or fungal infection, the concentration of sTREM-1 in BALF was statistically significant. For an sTREM concentration of 184 pg/mL, the sensitivity for detection of bacterial or fungal infection was 0.86, and the specificity was 0.90.

We obtained similar results in our study. Compared with the non-VAP group, the VAP group had

Table 2
Relative proportions of common causes of ventilator-associated pneumonia based on 32 bronchoscopically confirmed cases of VAP

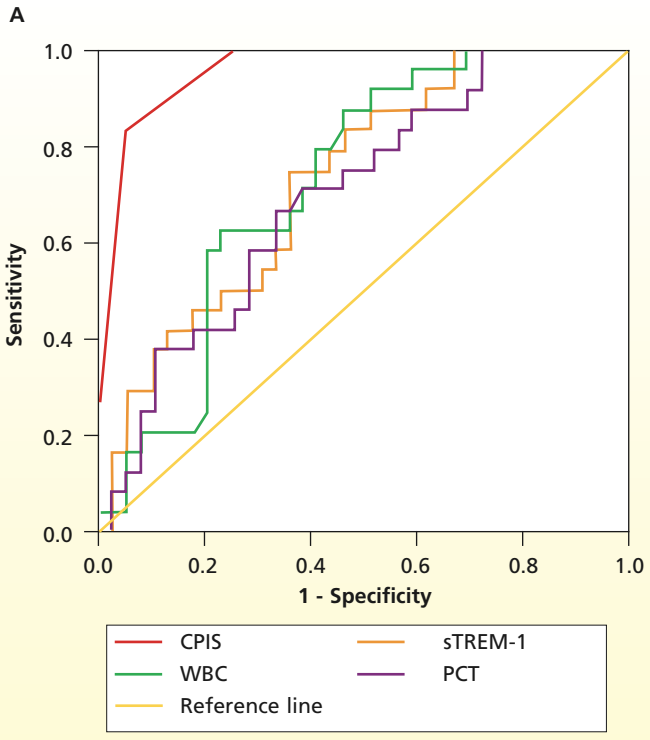
Bacterial species	No. (%)
Gram-negative organisms	
Acinetobacter baumannii	20 (38)
Pseudomonas aeruginosa	5 (9)
Escherichia coli	4 (8)
Klebsiella pneumoniae	2 (4)
Stenotrophomonas maltophilia	2 (4)
Streptococcus pneumoniae	2 (4)
Burkholderia	1 (2)
Gram-positive organisms	
Staphylococcus aureus	2 (4)
Enterococcus	1 (2)
Gram-positive bacilli	1 (2)
Fungi	
Candida albicans	10 (19)
Aspergillus	1 (2)
Other *Candida*	2 (4)
Total	53 (102)[a]

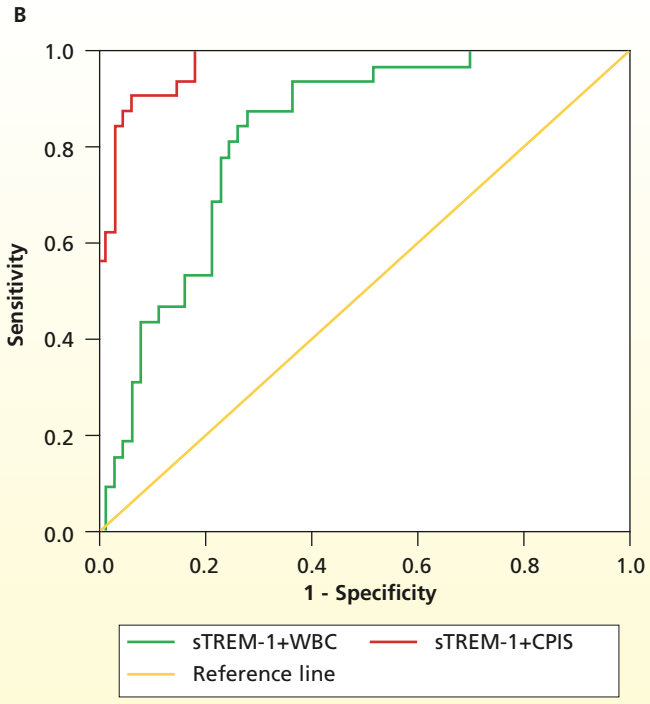
[a]Because of rounding, percentages do not total 100.

Table 3
Comparisons of clinical data of patients with ventilator-associated pneumonia (VAP) on day of confirmation and patients without VAP on day 7 in the intensive care unit

Parameter	Ventilator-associated pneumonia		*P*
	Present (n = 32)	Absent (n = 60)	
Temperature, mean (SD), °C	38.2 (1.2)	37.3 (1.1)	.001
Oxygenation index,[a] mean (SD)	179.6 (102.6)	241.8 (101.1)	.007
sTREM-1, median (interquartile range), pg/mL	295.6 (346.2)	143.5 (209.1)	<.001
White blood cell count, mean (SD), cells/μL	16 700 (7400)	10 900 (6500)	<.001
C-reactive protein,[b] median (interquartile range), mg/L	115 (73)	77 (65)	.01
Procalcitonin, median (interquartile range), ng/mL	4.5 (19.0)	1.4 (5.2)	.008
CPIS, mean (SD)	6.0 (1.5)	1.9 (1.6)	<.001
SOFA score, mean (SD)	10 (4.6)	7.5 (4.7)	.02

Abbreviations: CPIS, Clinical Pulmonary infection Score; SOFA, Sequential Organ Failure Assessment; sTREM-1, soluble trigger receptor expressed on myeloid cells 1.
[a]Ratio of Pao_2 to fraction of inspired oxygen.
[b]To convert to nanomoles per liter, multiply by 9.524.





Variable	AUC	SE	*P*	Asymptotic 95% Confidence interval		Cutpoint	sen	spe	PPV	NPV	YI
				Lower limit	Upper limit						
CPIS	0.958	0.023	<.001	0.914	1.003	4.5	0.833	0.949	0.909	0.883	0.782
sTREM-1	0.732	0.063	.002	0.609	0.855	189.45	0.75	0.641	0.56	0.773	0.391
WBC	0.726	0.063	.003	0.603	0.850	11.1	0.875	0.538	0.536	0.851	0.413
CRP	0.590	0.076	.23	0.440	0.740	–	–	–	–	–	–
PCT	0.699	0.066	.008	0.570	0.829	3.62	0.677	0.677	0.55	0.73	0.344

Variable	AUC	SE	*P*	Asymptotic 95% Confidence interval		Cutpoint	sen	spe	PPV	NPV	YI
				Lower limit	Upper limit						
sTREM-1+WBC	0.820	0.044	<.001	0.735	0.906	0.298	0.875	0.717	0.654	0.884	0.592
sTREM-1+CPIS	0.972	0.014	<.001	0.945	0.999	0.313	0.875	0.95	0.914	0.91	0.825

Figure 2 Receiver operating characteristic curves and comprehensive evaluation of the value of (**A**) Clinical Pulmonary Infection Score (CPIS), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), white blood cell count (WBC), C-reactive protein (CRP), and procalcitonin (PCT) and (**B**) combinations of sTREM-1 + WBC counts and sTREM-1 + CPIS value in the diagnosis of ventilator-associated pneumonia. AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; SE, standard error; sen, sensitivity; spe, specificity; YI, Youden index.

significant changes in temperature, oxygenation index, levels of sTREM-1, levels of procalcitonin, WBC counts, concentration of C-reactive protein, CPIS values, and SOFA scores. When sTREM-1 concentration and WBC count were entered as variables in the regression equation, the ORs were 1.118 (95% CI, 1.039-1.204) and 1.002 (95% CI, 1.000-1.005), respectively, indicating that sTREM-1 concentration and WBC count were the sole risk factors. Analysis of the area under the ROC curve indicated that the combination of sTREM-1 concentration plus CPIS was the most reliable for diagnosis of VAP. With 0.313 as the cutoff point, sensitivity was 0.875, specificity was 0.95, and the Youden index was 0.825 (Figure 2).

The combination of procalcitonin plus Clinical Pulmonary Infection Score was the most reliable for prognostic assessment.

Collecting BALF via a bronchoscope is an invasive, expensive procedure and is inconvenient for clinical studies. To overcome this limitation, Horonenko et al[35] searched for alternatives and compared the concentration of sTREM in BALF with the concentration in EVC. Among 23 patients treated with mechanical ventilation, VAP was diagnosed in 14. EVC samples from the 11 of the 14 had an obvious increase in the level of sTREM-1, suggesting that the concentration of sTREM in EVC may be of value in VAP diagnosis and exclusion. In our study, only 5 of the patients with VAP had detectable levels of sTREM-1 in EVC samples on the day that VAP occurred and was clinically confirmed. In the course of EVC collection, we discovered that all 5 patients had large amounts of secretions discharged from the respiratory tract that had entered the ventilator tubing. In other words, in patients with large quantities

of sputum, inflammatory cytokines might be detected in the patients' EVC. Therefore, VAP diagnosis based solely on the detection of inflammatory cytokines in EVC samples might lead to a high rate of misdiagnosis. Thus, this technique should be applied with caution in clinical practice.

In 96 patients with VAP, Duflo et al[36] found an obvious difference in serum levels of procalcitonin between survivors and nonsurvivors. The authors suggested that the ideal cutoff point for serum procalcitonin for a poor prognosis should be 2.6 ng/mL. At that concentration, sensitivity and specificity for not surviving VAP were 0.74 and 0.75, respectively. Luyt et al[19] measured procalcitonin levels on days 1, 3, and 7 after VAP occurrence and found that serum levels of procalcitonin were significantly higher in VAP patients who survived than in VAP patients who died. These authors identified the 7-day concentration (>0.5 ng/mL) as the cutoff point and stated that procalcitonin was an ideal independent indicator, with a more ideal sensitivity and specificity than those of WBC count and serum levels of C-reactive protein. We found that with 28-day survival as the demarcation line, nonsurvivors had higher serum levels of procalcitonin, CPIS values, and SOFA scores on the day of VAP occurrence and diagnosis than did survivors, whereas differences between nonsurvivors and survivors for other indicators were not significant. After logistic regression, areas under ROC curves were determined for the statistically significant parameters procalcitonin level, CPIS, and procalcitonin plus CPIS. The combination of procalcitonin plus CPIS was the most reliable for prognostic assessment. With 0.516 as the cutoff point, sensitivity was 0.867, specificity was 0.818, and the Youden index was 0.685.

Our study did have limitations. First, the sample size was rather small; only 32 patients with VAP were included. Second, among the 53 pathogenic isolates cultured from BALF samples, 13 were fungi (25%). In terms of limitations of quantitative cultures,[37,38] the detection of fungal pathogens is not certain because of possible contaminating organisms. However, we cannot rule out the possibility of colonizing organisms. Our findings are just the objective results of cultures to detect microorganisms. Third, the method used to measure serum levels of sTREM-1 for VAP diagnosis might not be as direct and effective as the method used to measure levels of the receptor in BALF samples. For EVC specimens, the rate of detection of sTREM-1 was not high. Because of the types of EVC collectors commonly used in Europe and North America, such as the EcoScreen (Erich JaegerR Co),[39] we cannot exclude the possibility that the method we used to collect EVC could lead to false-negative results. Although ventilator condensate has potential detection value, standardization of the collection and testing methods is needed. Fourth, considering the near-optimum value of sTREM-1 in prognostic assessment of sepsis,[40,41] sTREM-1 might be important in assessing VAP prognosis. We did not do any assessment of changes in the value of sTREM-1 over time for VAP therapy and prognosis. Thus, we cannot exclude the possibility that the dynamic changes in the concentration of sTREM-1 have an effect on the value of the marker in assessing the results of therapy and prognosis in patients with VAP.

Table 4
Comparisons of parameters between surviving and nonsurviving patients with ventilator-associated pneumonia

Parameter	Survivors (n = 15)	Nonsurvivors (n = 17)	*P*
Body temperature, mean (SD), °C	38.2 (0.6)	38.2 (1.6)	.63
Oxygenation index,[a] mean (SD)	205.8 (100.3)	156.4 (101.8)	.10
sTREM-1, median (interquartile range), pg/mL	295.0 (307.7)	320.7 (455.5)	.77
White blood cell count, mean (SD), cells/μL	17 300 (8800)	16 100 (6200)	.82
C-reactive protein,[b] median (interquartile range), mg/L	120 (79)	111 (70)	.68
Procalcitonin, median (interquartile range), ng/mL	3.0 (3.9)	15.3 (22.9)	.03
CPIS, mean (SD)	5.4 (1.2)	6.6 (1.5)	.03
SOFA score, mean (SD)	8.1 (5.0)	11.7 (3.6)	.05

Abbreviations: CPIS, Clinical Pulmonary Infection Score; SOFA score, Sequential Organ Failure Assessment score; sTREM-1, soluble triggering receptor expressed on myeloid cells 1.
[a]Ratio of Pao_2 to fraction of inspired oxygen.
[b]To convert to nanomoles per liter, multiply by 9.524.

Conclusions

The combination of CPIS plus sTREM-1 helps improve diagnosis of VAP, and the combination of procalcitonin plus CPIS may be useful for VAP prognosis. Measurement of these indicators (CPIS, sTREM-1, and procalcitonin) is conducive to timely diagnosis and relevant medical intervention to enhance cure rates and reduce mortality. However, large-sample studies are necessary to replicate our findings.

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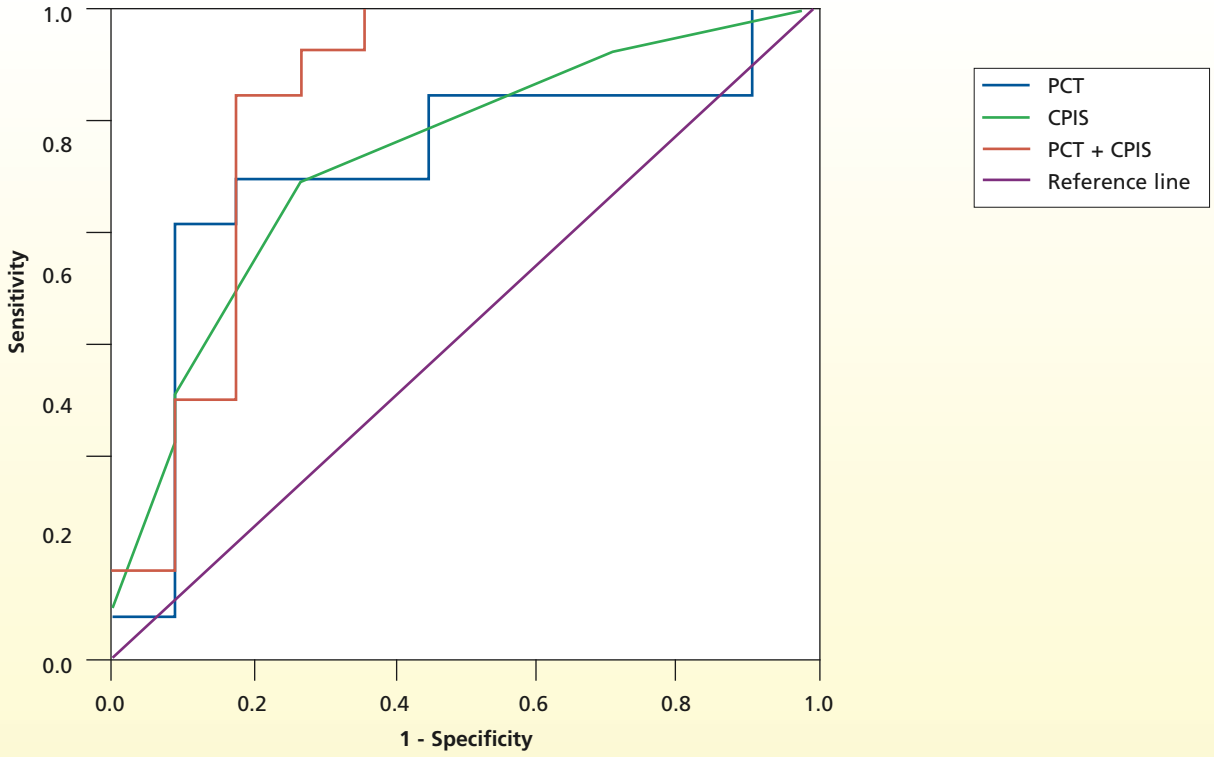

Variable	AUC	SE	*P*	Asymptotic 95% Confidence interval		Cutpoint	sen	spe	PPV	NPV	YI
				Lower limit	Upper limit						
PCT	0.752	0.104	.03	0.547	0.956	9.47	0.667	0.909	0.89	0.56	0.576
CPIS	0.764	0.096	.02	0.575	0.953	5.5	0.733	0.727	0.75	0.58	0.46
PCT + CPIS	0.848	0.09	.003	0.672	1.025	0.52	0.867	0.818	0.84	0.75	0.685

Figure 3 Receiver operating characteristic curves and comprehensive evaluation of prognostic value of procalcitonin (PCT), Clinical Pulmonary Infection Score (CPIS), and PCT + CPIS for diagnosis of ventilator-associated pneumonia. AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; SE, standard error; sen, sensitivity; spe, specificity; YI, Youden index.

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