Evaluation of serum-soluble triggering receptor expressed on myeloid cells-1 as a novel marker in the diagnosis of ventilator-associated pneumonia in adults

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Ventilator-associated pneumonia (VAP) remains the most common nosocomial infection in ICUs. VAP occurs in 10–20% of patients who are mechanically ventilated for more than 48 h. The interval between diagnosis and the availability of microbiological results is the period when clinicians would most benefit from a reliable biomarker that could provide an early indication of poor response. Serum-soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) belongs to the immunoglobin superfamily, and it has the advantage of being increased during infectious processes but not in noninfectious inflammatory conditions. The aim of this study was to assess the value of serum level of sTREM-1 as a diagnostic biomarker for VAP in comparison with commonly used indicators, including procalcitonin (PCT) and C-reactive protein (CRP). This study was carried out on 60 participants. They were divided into two groups: group I included 30 adult patients with clinically suspected VAP, and group II included 30 ICU ventilated patients of the same age group without VAP and free of other infectious diseases who served as the control group. They were selected from the ICUs of Chest and other Departments, Tanta University Hospitals, during the period from January 2014 until September 2014. The present study revealed that serum level of sTREM-1 was significantly higher in patients with VAP in comparison with the control group. It was also concluded that serum level of sTREM-1 was significantly higher in VAP patients with bacterial growth culture results than in VAP patients with no growth culture results. A diagnostic cutoff value greater than 110 pg/ml with a sensitivity of 87.5%, specificity of 83.3%, positive predictive value of 95.5%, and negative predictive value of 62.5% of serum sTREM-1 level could discriminate positive culture results from negative culture results in VAP patients, which were higher than that of serum levels of PCT and CRP. It was concluded that serum level of sTREM-1 was significantly higher in VAP patients in comparison with non-VAP patients and it showed the highest sensitivity and specificity (87.5 and 83.3%, respectively) in differentiating between VAP patients with bacterial growth culture results and VAP patients with no growth culture results compared with PCT and CRP levels, thus rendering serum level of sTREM-1 a novel diagnostic marker for VAP. *Egypt J Broncho* 2015 9:261–268

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Introduction

Ventilator-associated pneumonia (VAP) is a type of nosocomial pneumonia that occurs in patients who receive mechanical ventilation. VAP is usually acquired in the hospital-setting ~48–72 h after mechanical ventilation [1].

It carries a mortality of 10–50%. VAP prolongs patients' mean ICU stay by an estimated 6.1 days and results in high financial costs [2].

The associated organisms and their resistance patterns vary on the basis of the patient group and hospital setting [1]. Most cases of VAP are caused by bacterial pathogens that normally colonize the oropharynx and gut, or that are acquired through transmission from healthcare workers, from environmental surfaces, or from other patients. Common pathogens include *Pseudomonas* spp. and other highly resistant gram-negative Bacilli, Staphylococci, the *Enterobacteriaceae*, Streptococci, and *Haemophilus* spp. [3].

A diagnosis of VAP is suspected when the patient has a new infiltrate on chest radiograph along with fever and raised leukocyte count after 48 h of invasive mechanical ventilation. To diagnose a VAP episode, the presence of clinical signs of pneumonia plus microbiologic confirmation by quantitative cultures is required, and it can be obtained from either tracheal aspirate, bronchoalveolar lavage (BAL) fluid, mini-BAL, or protected brush specimens [4].

Clinical Pulmonary Infection Scoring (CPIS) was introduced to improve the specificity of clinical diagnosis. CPIS combines clinical, radiological, physiological, and microbiological (culture of tracheal

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aspirate) data into a single numerical value. However, recent studies suggest that CPIS has a lower specificity for the diagnosis of VAP compared with quantitative culture of BALF [5].

Quantitative culture of BALF retrieved by means of direct bronchoscopic methods yields the best sensitivity and specificity to diagnose VAP and can differentiate true infection from colonization or inflammation. However, bronchoscopy is an invasive procedure and requires specialized skills [5].

Many biological markers have been studied in an effort to improve the rapidity and performance of current diagnostic procedures in VAP [6].

C-reactive protein (CRP) is used in clinical practice because of its greater availability, but it has limited abilities to distinguish sepsis from other inflammatory conditions [7].

Procalcitonin (PCT), a 116 amino acid propeptide of calcitonin, is a new marker that has been suggested for the diagnosis of invasive bacterial and fungal infections that lead to systemic inflammation. However, the usefulness of this marker in different clinical situations remains uncertain [8].

The triggering receptor expressed on myeloid cells (TREM-1) is a member of the immunoglobulin superfamily. Upon invasion of bacteria or fungi, tissues are infiltrated with neutrophils and monocytes that strongly express TREM-1. A soluble form of TREM-1 (sTREM-1) can be measured in various body fluids, possibly reflecting TREM-1 shed from the membranes of activated phagocytes [9].

Patients and methods

The present study was carried out in the Medical Microbiology & Immunology, Chest and Anesthesia Departments, Faculty of Medicine, Tanta University. It was conducted on 60 adult patients during the period from January 2014 until September 2014.

Patients in this study were divided into two groups

Group I included 30 adult ventilated patients with clinically suspected VAP.

Group II included 30 ventilated patients without VAP and free of other infectious diseases who served as the control group.

Demographic variables such as sex, age, together with patient's clinical data, risk factors for pneumonia, and antibiotic regimen were collected from patient's record after getting patient's consent and approval of the ethical committee.

Inclusion criteria

(1) Age more than 18 years.
(2) Evidence of new infiltrates on chest radiographs after 48–72 h of endotracheal intubation.
(3) Presence of at least two of the following:
    (a) Fever.
    (b) Increased white blood cell (WBC) count.
    (c) Purulent respiratory tract secretions.

Exclusion criteria

(1) Patients with pneumonia on admission or within 48 h of mechanical ventilation.
(2) Patients with acquired immunodeficiency syndrome.
(3) Patients with decrease in polymorphonuclear granulocytes (<500/μl).

Material used for bacteriological study

Clinical specimens

Both BALF and serum samples were taken from enrolled patients.

BALF was tested for possible common bacterial pathogens using the following:

(1) Gram-stained smear.
(2) Culture on different bacteriological media.
(3) Biochemical reactions.

Serum samples

They were taken from controls and clinically suspected patients with VAP under complete aseptic technique and centrifuged. Thereafter, the serum samples obtained were stored until processed. Human sTREM-1 and PCT were measured with enzyme-linked immunosorbent assay (ELISA) kit, whereas CRP was measured using the latex agglutination test.

Media used

In this study, the media used were dehydrated oxoid media. They were prepared and sterilized according to the manufacturer's instructions. The following media were used:

(1) Ordinary nutrient agar.
(2) Blood agar.
(3) Chocolate agar.
(4) MacConkey's agar.

Biochemical reaction tests

(1) Optochin sensitivity test (oxoid).
(2) Catalase test.
(3) Coagulase test.
(4) Oxidase test (oxoid).
(5) Citrate utilization test (oxoid).
(6) Urease test (oxoid).
(7) Indole test.
(8) Vogas, Proskauer reaction.
(9) Methyl-Red test.
(10) Bile solubility test.
(11) Sugar fermentation tests.

Detection of serum level of serum-soluble triggering receptor expressed on myeloid cells-1

The CUSABIO Human sTREM-1 ELISA kit is an in-vitro ELISA for the quantitative determination of human sTREM-1.

This assay used the quantitative sandwich enzyme immunoassay technique. Antibody specific for sTREM-1 had been precoated onto a microplate. Standards and samples were pipetted into the wells, and any sTREM-1 present was bound by the immobilized antibody. After removing any unbound substances, a biotin-conjugated antibody specific for sTREM-1 was added to the wells. After washing, avidin-conjugated horseradish peroxidase was added to the wells. Following a wash to remove any unbound avidin-enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of sTREM-1 bound in the initial step. The color development was stopped and the intensity of the color was measured at 450 nm.

All participants in this study were subjected to the following:

(1) Complete medical history with particular emphasis on the age, sex, underlying disease, chief reason for admission, time of onset of pneumonia, and use of mechanical ventilation during the ICU admission.
(2) Clinical examination and recording of the following: body temperature, tracheal secretions, chest radiograph, WBC counts, and CRP.
(3) Group I patients were subjected to bacteriological study of the BALF specimens to determine the causative organism of infection.
(4) Quantitative measurement of human sTREM-1 and PCT in serum using ELISA kits.

Results

This study was conducted on 60 mechanically ventilated patients. They were divided into two groups:

Group I included 30 adult ventilated patients with clinically suspected VAP [18 male (60%) and 12 female (40%)] with a mean age of 38.5 ± 18.8 years.

Group II included 30 ventilated patients without VAP and free of other infectious diseases who served as the control group [15 male (50%) and 15 female (50%)], with a mean age of 45.2 ± 17.6 years.

There were no significant differences between the two groups as regards age and sex distribution.

The most common causes of admission of the studied cases and controls were cerebral hemorrhage (16 cases, 27%) and fracture base (16 cases, 27%), followed by heart failure (eight cases, 13%), cardiogenic shock (eight cases, 13%), renal failure (six cases, 10%), and hemothorax (six cases, 10%) (Table 1).

Clinical presentation of the patients included in the study is shown in Table 2.

Clinical parameters of CPIS [4]:

Temperature	1 = ≥38.4≤38.9	2 = ≤36 or ≥39
White blood count	1 = < 4000 or >11 000	2 = Plus band forms ≥500
Secretions	1 = Moderate/large	2 = Purulent
Chest radiograph	1 = Diffuse/patchy infiltrate	2 = Localized infiltrate
PaO_2/FiO_2 ratio	0 = >240 without ARDS	2 = <240 without ARDS
Culture	0 = <10 000 bacteria or no growth	1 = >10 000 bacteria
Gram stain of direct smear 1 = Positive gram stain		

The frequency of different micro-organisms isolated from cases of positive culture (24 patients) with microbiologically confirmed VAP showed that the highest percentage of cases (30%) were infected with *MRSA* (nine cases) followed by *Pseudomonas aeruginosa* (six cases, 20%), whereas three cases (10%) were infected with *Escherchia coli*, three cases were infected

Table 1 Distribution of studied cases and controls based on the cause of admission

Cause of admission	Patient [*N* (%)]	Control [*N* (%)]	Total [*N* (%)]
Cerebral hemorrhage	9 (30)	7 (23)	16 (27)
Fracture base	9 (30)	7 (23)	16 (27)
Renal failure	3 (10)	3 (10)	6 (10)
Hemothorax	3 (10)	3 (10)	6 (10)
Heart failure	3 (10)	5 (17)	8 (13)
Cardiogenic shock 3 (10)		5 (17)	8 (13)
Total	30 (100)	30 (100)	60 (100)

with *Staphylococcus aureus* (10%), and three cases were infected with *Candida* (10%) (Table 3).

Serum level of CRP in VAP patients was 40.66 ± 55.5 and it was 29.22 ± 39.02 in the control group. Serum level of CRP had no significant difference between patients with VAP and controls ($t = 0.922$, $P = 0.360$) (Fig. 1).

Comparison of PCT level in the studied groups is shown in Table 4.

Serum level of PCT was found to be significantly higher in patients with VAP in comparison with the control group ($t = 3.25$, $P < 0.01$).

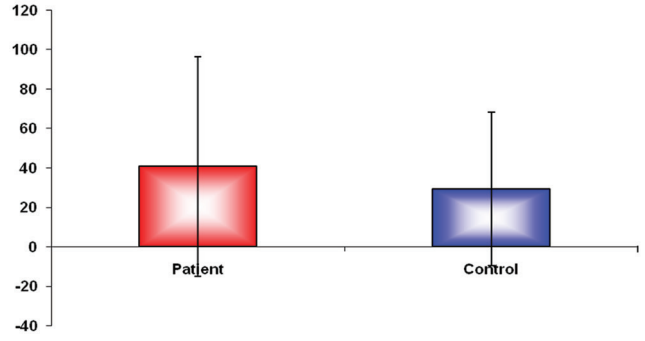
Mean serum level is sTREM-1 in VAP patients was 283.47 ± 187.78 and it was 146.14 ± 177.83 in the control group. Mean serum level is sTREM-1 was found to be significantly higher in patients with VAP in comparison with the control group ($t = 2.9$, $P < 0.01$) (Fig. 2).

There was no significant relation between culture result and serum level of CRP ($P = 0.801$). However, there was a significant relation between culture result and serum level of PCT, with a mean of 55.5 ± 35.5 in no growth result and a mean of 6.66 ± 9.523 in bacterial growth result ($P < 0.001$).

There was also a significant relation between culture result and serum level of sTREM-1, with a mean of 67.532 ± 49.974 in no growth result and a mean of 337.462 ± 169.455 in bacterial growth result ($P < 0.01$) (Table 5).

There was no significant difference between serum level of PCT and the type of causal micro-organism in positive culture results ($P = 0.272$). The highest range of PCT was in *Pseudomonas aeruginosa,* with a mean of 13.002 ± 13.518, and the lowest range of PCT was in *Staphylococcus aureus*, with a mean of 0.980 ± 0.220 (Table 6).

Fig. 1



C-reactive protein (CRP) in the two studied groups.

There was a significant difference between serum level of sTREM-1 and the type of causal micro-organism in culture results ($P < 0.001$). The highest range of sTREM-1 was in *Pseudomonas aeruginosa*, with a mean of 549.677 ± 107.680, and the lowest range of sTREM-1 was in *E. coli*, with a mean of 179.100 ± 6.398 (Table 7).

Table 2 Distribution of clinical parameters of clinical pulmonary infection score in the studied cases of ventilator-associated pneumonia

Items	CPIS	*N* (%)
Temperature	1	13 (43.33)
	2	17 (56.67)
White blood count	1	11 (36.7)
	2	19 (63.3)
Secretion	1	9 (30.00)
	2	21 (70.00)
Chest radiograph	1	24 (80.00)
	2	6 (20.00)
PaO_2/FiO_2 ratio	0	6 (20.00)
	2	24 (80.00)
Culture results	0	6 (20.00)
	1	24 (80.00)
Gram stain	0	15 (50.00)
	1	15 (50.00)

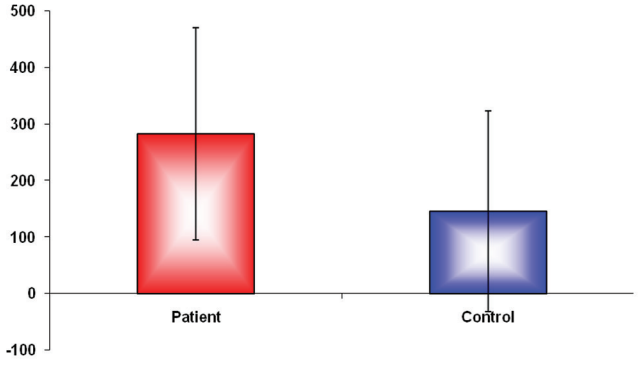
CPIS, clinical pulmonary infection score; PaO_2, arterial oxygen tension, FiO_2, fractional inspired oxygen.

Table 3 Distribution of studied cases based on bacterial culture results

Organism	Culture [*N* (%)]
No growth	6 (20.00)
*MRSA**	9 (30.00)
Pseudomonas aeruginosa	6 (20.00)
*E. coli**	3 (10.00)
Staphylococcus aureus	3 (10.00)
Candida	3 (10.00)
Total	30 (100.00)

*Methicillin resistant staph aureus.

Fig. 2



Serum-soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in the two studied groups.

Table 8 and Figs. 3 and 4 show cutoff point, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of sTREM-1 level to discriminate positive culture result from negative culture result. A diagnostic cutoff value greater than 110 pg/ml was found with a sensitivity of 87.5%, specificity of 83.3%, positive predictive value of 95.5%, and negative predictive value of 62.5%.

Table 9 and Fig. 5 show that sTREM-1 has the highest specificity (83.8%) together with positive predictive value (95.5%), negative predictive value (62.5), and accuracy (0.806) to discriminate positive culture result from negative culture result in cases of VAP.

Table 4 Comparison of serum procalcitonin levels in the studied groups

Groups	PCT		*t*-Test	
	Range	Mean ± SD	*t*	*P*-value
Patients	0.550–100.000	16.433 ± 26.168	3.257	0.002*
Controls	0.020–2.500	0.866 ± 0.759		

PCT, procalcitonin; *Statistically significant, $P < 0.05$.

Table 5 Relationship between culture result and serum levels of the three markers in cases of ventilator-associated pneumonia

Inflammatory marker	Culture (mean ± SD)		*t*-Test	
	No growth	Bacterial growth	*t*	*P*-value
CRP	45.900 ± 47.878	39.352 ± 58.215	0.254	0.801
PCT	55.508 ± 35.556	6.664 ± 9.523	6.176	0.000
sTREM-1	67.532 ± 49.974	337.462 ± 169.455	–3.815	0.001

CRP, C-reactive protein; PCT, procalcitonin; sTREM-1, soluble triggering receptor expressed on myeloid cells-1.

Table 6 Relationship between serum level of procalcitonin and type of causal microorganism in positive culture results in cases of ventilator-associated pneumonia

Culture	PCT		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
Pseudomonas aeruginosa	0.550–26.900	13.002 ± 13.518	1.40	0.272
MRSA	0.680–20.263	7.416 ± 9.332		
E. coli	2.690–2.990	2.827 ± 0.152		
Staphylococcus aureus	0.760–1.200	0.980 ± 0.220		
Candida	1.050–1.600	1.253 ± 0.302		

ANOVA, analysis of variance; PCT, procalcitonin.

Discussion

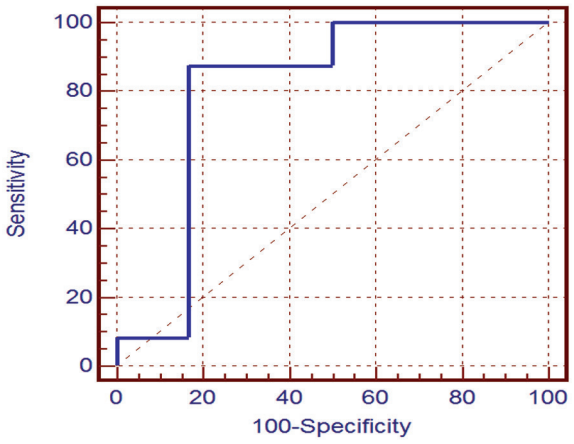
Biomarkers may facilitate clinical confirmation and aid differentiation of pulmonary from nonpulmonary sepsis. This would allow earlier, targeted antibiotic intervention, direct clinicians' decision-making for 'antibiotic use reduction' regimens, and potentially reduce selective pressure for multiresistant bacteria [6].

Some of the biomarkers that are used as an adjunct in the diagnosis of pneumonia include CRP, leukocyte count, immunoglobulins, and proinflammatory cytokines. There are other biomarkers whose importance is growing in the medical field. They are PCT and TREM-1 [10].

CRP is a protein produced in response to infection and/or inflammation and it is widely used in clinical tests to diagnose and manage patients with sepsis. Because the levels of CRP rise significantly during acute inflammation, this biomarker has been used for decades to indicate the presence of significant inflammatory or infectious disease, especially in pediatrics [11].

However, low specificity and inability to differentiate bacterial infections from noninfectious causes of inflammation makes CRP of limited diagnostic value [12].

Fig. 3



Receiver operating characteristic curve (ROC curve) of serum level of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in positive and negative culture results.

Table 7 Relationship between serum level of soluble triggering receptor expressed on myeloid cells-1 and type of causal microorganism in positive culture results in cases of ventilator-associated pneumonia

Culture	sTREM-1		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
Pseudomonas aeruginosa	456.000–728.060	549.677 ± 107.680	13.44	<0.001*
MRSA	57.120–310.000	217.551 ± 119.439		
E. coli	172.300–185.000	179.100 ± 6.398		
Staphylococcus aureus	376.130–390.000	383.710 ± 7.024		
Candida	375.000–390.000	384.880 ± 8.558		

ANOVA, analysis of variance; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; *Statistically significant, $P < 0.05$

PCT is synthesized by a large number of tissues and organs in response to invasion by pathogenic bacteria, fungi, and some parasites. At present, PCT levels have been used to guide empirical antibacterial therapy in patients with acute exacerbations of chronic bronchitis, community-acquired pneumonia, and sepsis. Moreover, PCT levels, along with standard clinical parameters, can assist in determining whether the patient's empirical antibacterial therapy is effective [11].

PCT can increase after trauma or surgery, particularly major abdominal surgery, cardiogenic shock, heat shock, immunotherapy such as granulocyte transfusion, and pancreatitis. PCT can also be elevated in renal impairment in the absence of infection. Given that PCT can be elevated in certain noninfective conditions, it is probably better used to rule out than rule in systemic bacterial infection [13].

Table 8 Receiver operating characteristic curve of serum level of soluble triggering receptor expressed on myeloid cells-1 in positive and negative culture results

ROC curve					
Accuracy	NPV	PPV	Specificity	Sensitivity	Cutoff
0.806	62.5	95.5	83.3	87.5	>110

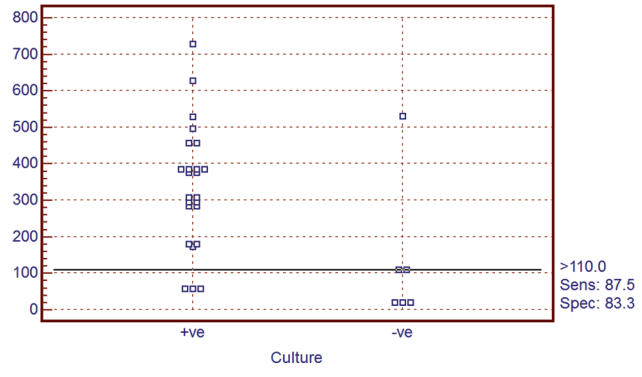
NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

Table 9 Comparison between the serum levels of the three markers in positive and negative culture results by receiver operating characteristic curve

ROC curve						
Inflammatory marker	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
sTREM-1	>110*	87.5	83.3	95.5	62.5	0.806
CRP	≤17.6*	75.0	50.0	85.7	33.3	0.486
PCT	≤20.26*	87.5	66.7	91.3	57.1	0.764

CRP, C-reactive value; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value; ROC, receiver operating characteristic; sTREM-1, soluble triggering receptor expressed on myeloid cells-1.

Fig. 4



Level of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) serum level, cutoff point, sensitivity, and specificity in positive and negative culture result.

The TREM-1 is a member of the immunoglobulin superfamily. Its expression on phagocytes is upregulated by exposure to bacteria and fungi. A soluble form of TREM-1 (sTREM-1) can be found in body fluids, such as plasma, pleural fluid, BALF, urine, and cerebrospinal fluid, which can be assayed by means of ELISA using commercial immunoassay kits. It has the advantage of being increased during infectious processes but not in noninfectious inflammatory conditions [11].

As regards positive culture results in VAP patients, this study showed that *MRSA* and *Pseudomonas aeruginosa* were the major isolates that were responsible for 30 and 20% of VAP cases, respectively, followed by *Escherichia coli*, *Staphylococcus aureus,* and *Candida albicans* each 10% of VAP cases.

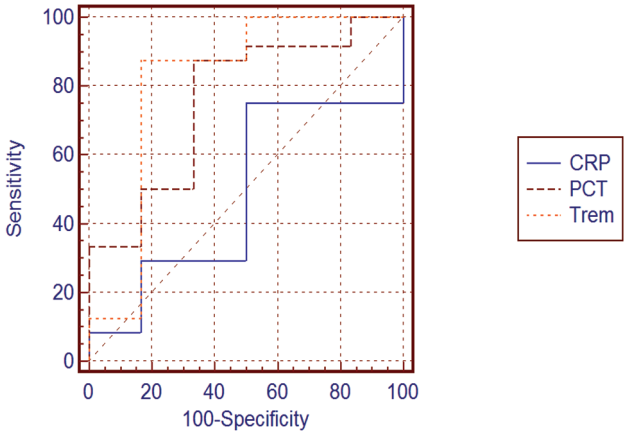
The results of Charles *et al.* [14] were compatible with our results, as they had found that *Pseudomonas aeruginosa* was the most common Gram-negative bacteria associated with VAP, followed by *Staphylococcus aureus*. In addition, Lee *et al.* [15] reported that methicillin-resistant Staphylococcus aureus (*MRSA*) was the most common gram-positive bacteria associated with VAP.

In contrast with our study, Harde *et al.* [4] reported that the most common organism was *Acinetobactor baumanni*.

This study showed that serum level of CRP has no significant difference between patients with VAP and controls ($P = 0.360$).

In agreement with our study, Oppert *et al.* [8] reported that CRP was not useful for VAP diagnosis. In addition, Linssen *et al.* [16] stated that CRP was not able to differentiate VAP patients from non-VAP patients.

Fig. 5



Comparison between the serum levels of the three markers in positive and negative culture results by receiver operating characteristic curve (ROC curve).

The findings of Povoa *et al.* [17] is in disagreement with the findings of our study; they showed that CRP has a good accuracy in the diagnosis of VAP in a population of ICU patients. However, the CRP concentrations included in the study for the nonseptic group were the values measured after 2 days of ICU stay and were compared with the leukocyte count and temperature on the day of ICU admission.

This study also showed that serum level of PCT is significantly higher in patients with VAP than in controls ($P = 0.002$).

This is in agreement with the findings of Duflo *et al.* [18], who reported that serum PCT was significantly increased in the VAP group compared with the non-VAP group. In contrast, Gilbert [19] said that there were no significant differences in the levels of PCT between patients with pulmonary infections and those without pulmonary infections. However, they could not exclude the possibility that some patients with true VAP were misclassified as not having pneumonia and recovered spontaneously.

As regards serum level of sTREM-1, this study showed that it is significantly higher in patients with VAP than in controls ($P < 0.001$).

In agreement with our study, Phua *et al.* [20] said that serum sTREM-1 levels were significantly higher in pneumonia and asthma patients than in controls. Moreover, Rivera-Chavez and Minei [21] said that measurements of sTREM-1 in plasma from patients in the surgical ICU may be a valuable tool for early distinction between infected and noninfected patients.

In contrast, Determann *et al.* [9] found that there was no relationship with development of VAP and serum sTREM-1. However, microbiological confirmation was carried out using nondirected bronchial lavage technique 'blind sampling'; thus, it is possible that some patients were misdiagnosed as having no pneumonia.

As regards the relation between culture result (bacterial growth and no growth) and serum levels of the three markers in cases of VAP, this study showed that, there was no significant relation between culture result and serum level of CRP ($P = 0.801$). There was a significant relation between culture result and serum level of PCT, with a mean of 55.508 ± 35.556 in no growth result and a mean of 6.664 ± 9.523 in bacterial growth result ($P = 0.000$). There was also a significant relation between culture result and serum level of sTREM-1, with a mean of 67.532 ± 49.974 in no growth result and a mean of 337.462 ± 169.455 in bacterial growth result ($P = 0.001$).

Delévaux *et al.* [22] reported that PCT values were more discriminative than WBC and CRP in distinguishing a bacterial infection from another inflammatory process.

Moreover, Ramirez *et al.* [23] found that, when comparing patients with VAP and nonconfirmed VAP, only PCT levels were significantly higher in patients with VAP, whereas CRP levels were not significantly different.

Porfyridis *et al.* [24] found that sTREM-1 levels were significantly higher in the pneumonia group than in the nonbacterial pulmonary disease group.

This study revealed a diagnostic cutoff value of 17.6 mg/l or less with a sensitivity of 75%, specificity of 50%, positive predictive value of 85.7%, and negative predictive value of 33.3% of CRP level to discriminate positive culture result from negative culture result.

Refaat *et al.* [25] analyzed the ability of CRP to discriminate between infection of bacterial origin and no infection. The optimal cutoff was 59 mg/l, with a sensitivity of 80%, specificity of 60%, positive predictive value of 86%, and negative predictive value of 71%.

This study also revealed a diagnostic cutoff value of 20.26 ng/ml or less with a sensitivity of 87.5%, specificity of 66.7%, positive predictive value of 91.3%, and a negative predictive value of 57.1% of PCT level to discriminate positive culture result from negative culture result.

Menéndez *et al.* [26] concluded that a cutoff value of 0.36 mg/dl for PCT to predict positive blood cultures showed a sensitivity of 85%, specificity of 42%, and negative predictive value of 98%.

Schuetz *et al.* [27] revealed that, when using the microbiological definition, at a cutoff value of 180 mg/dl, CRP had a high specificity of 86 and 100%, with a low sensitivity of 54 and 67% and concluded that high initial values of PCT and high peak levels of CRP do not *per se* point to underlying infection as the high increase in PCT and CRP rather reflects the nonspecific systemic inflammatory response due to the underlying disease and hypothermia than true bacterial infection.

The present study revealed a diagnostic cutoff value of more than 110 pg/ml with a sensitivity of 87.5%, a specificity of 83.3%, a positive predictive value of 95.5% ,and a negative predictive value of 62.5% of sTREM-1 level to discriminate positive culture result from negative culture result.

Huh *et al.* [28] obtained similar results as they studied 80 patients with suspected infectious pneumonia

whose chest radiographs revealed bilateral pulmonary infiltrations. The sTREM-1 concentration was significantly increased in patients with bacterial or fungal pneumonia compared with that in patients with viral pneumonia, atypical pneumonia, tuberculosis, or noninfectious inflammatory disease. The concentration of sTREM-1 was an independent predictor of bacterial or fungal pneumonia, and a cutoff value of more than 184 pg/ml yielded a diagnostic sensitivity of 86% and a specificity of 90%.

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Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Charles MVP, Kali A, Easow JM, Joseph NM, *et al.* Ventilator-associated pneumonia. *AMJ* 2014; **7**:334–344.

2 Zielińska-Borkowska U, Skirecki T, Złotorowicz M, *et al.* Procalcitonin in early onset ventilator-associated pneumonia. *J Hosp Infect* 2012; **3**:92–97.

3 Park DR, Park DR, Park DR. Antimicrobial treatment of ventilator-associated pneumonia. *Respir Care* 2005; **50**:932–932952; discussion 952–955.

4 Harde Y, Rao SM, Sahoo JN, *et al.* Detection of ventilator associated pneumonia, using clinical pulmonary infection score (CPIS) in critically ill neurological patients. *JOACP* 2013; **2**:20.

5 Palazzo SJ, Simpson T, Schnapp L. Biomarkers for ventilator-associated pneumonia: review of the literature. *Heart Lung* 2011; **40**:293–298.

6 Rea-Neto A, Youssef NC, Tuche F, Brunkhorst F, Ranieri VM, Reinhart K, Sakr Y. Diagnosis of ventilator-associated pneumonia: a systematic review of the literature. *Crit Care* 2008; **12**:R56.

7 Pierrakos C, Vincent JL. Sepsis biomarkers: a review. Critical Care 2010; **14**:R15.

8 Oppert M, Reinicke A, Müller C, *et al.* Elevations in procal-citonin but not C-reactive protein are associated with pneumonia after cardiopulmonary resuscitation. *Resuscitation* 2002; **53**:167–170.

9 Determann RM, Millo JL, Gibot S, Korevaar JC, Vroom MB, van der Poll T, *et al.* Serial changes in soluble triggering receptor expressed on myeloid cells in the lung during development of ventilator-associated pneumonia. *Intensive Care Med* 2005; **31**:1495–1500.

10 Summah H, Qu JM. Biomarkers: a definitive plus in pneumonia. *Mediators Inflamm* 2009; **67**:53-57.

11 Henriquez-Camacho C, Losa J. Biomarkers for sepsis. *Bio Med Res Int* 2014; **2014**:1-6.

12 Cho SY, Choi JH. Biomarkers of sepsis. *Infect Chemother* 2014; **46**:1–12.

13 Kibe S, Adams K, Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. *J Antimicrob Chemother* 2011; **66**: Suppl 2:ii33–ii33ii40.

14 Charles MVP, JM Easow, Joseph NM, *et al.* Incidence and risk factors of ventilator associated pneumonia in a tertiary care hospital. *AMJ* 2013; **6**:178–182.

15 Lee MS, Walker V, Chen LF, Sexton DJ, Anderson DJ. The epidemiology of ventilator-associated pneumonia in a network of community hospitals: a prospective multicenter study. *Infect Control Hosp Epidemiol* 2013; **34**:657–662.

16 Linssen CF, Bekers O, Drent M, Jacobs JA. C-reactive protein and procalcitonin concentrations in bronchoalveolar lavage fluid as a predictor of ventilator-associated pneumonia. *Ann Clin Biochem* 2008; **45(Pt 3)**: 293–298.

17 Povoa P, Coelho L, Almeida E, Fernandes A, Mealha R, Moreira P, Sabino H. C-reactive protein as a marker of ventilator-associated pneumonia resolution: a pilot study. *Eur Respir J* 2005; **25**:804–812.

18 Duflo F, Debon R, Monneret G, Bienvenu J, Chassard D, Allaouchiche B Alveolar and serum procalcitonin: diagnostic and prognostic value in ventilator-associated pneumonia. *Anesthesiology* 2002; **96**:74–79.

19 Gilbert DN. Procalcitonin as a biomarker in respiratory tract infection. Clin Infect Dis 2011; **52**: Suppl 4:S346–S346S350.

20 Phua J, Koay ES, Zhang D, Tai LK, Boo XL, Lim KC, Lim TK Soluble triggering receptor expressed on myeloid cells-1 in acute respiratory infections. *Eur Respir J* 2006; **28**:695–702.

21 Rivera-Chavez FA, Minei JP. Soluble triggering receptor expressed on myeloid cells-1 is an early marker of infection in the surgical intensive care unit. *Surg Infect (Larchmt)* 2009; **10**:435–439.

22 Delèvaux I, André M, Colombier M, Albuisson E, Meylheuc F, Bègue RJ, *et al.* Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes? *Ann Rheum Dis* 2003; **62**:337–340.

23 Ramirez P, Garcia MA, Ferrer M, Aznar J, Valencia M, Sahuquillo JM, *et al.* Sequential measurements of procalcitonin levels in diagnosing ventilator-associated pneumonia. *Eur Respir J* 2008; **31**:356–362.

24 Porfyridis I, Plachouras D, Karagianni V, Kotanidou A, Papiris SA, Giamarellou H, Giamarellos-Bourboulis EJ. Diagnostic value of triggering receptor expressed on myeloid cells-1 and C-reactive protein for patients with lung infiltrates: an observational study. *BMC Infect Dis* 2010; **10**:286.

25 Refaat A, Affara N, Abdel-fatah W, *et al.* Diagnostic accuracy of inflammatory biomarkers in bronchoalveolar lavage from patients with ventilator-associated pneumonia. *EJCDT* 2014; **63**:723–730.

26 Menéndez R, Sahuquillo-Arce JM, Reyes S, Martinez R, Polverino E, Cillóniz C, *et al.* Cytokine activation patterns and biomarkers are influenced by microorganisms in community-acquired pneumonia. *Chest* 2012; **141**:1537–1545.

27 Schuetz P, Affolter B, Hunziker S, Winterhalder C, Fischer M, Balestra GM, *et al.* Serum procalcitonin, C-reactive protein and white blood cell levels following hypothermia after cardiac arrest: a retrospective cohort study. *Eur J Clin Invest* 2010; **40**:376–381.

28 Huh JW, Lim CM, Koh Y, Oh YM, Shim TS, Lee SD, *et al.* Diagnostic utility of the soluble triggering receptor expressed on myeloid cells-1 in bronchoalveolar lavage fluid from patients with bilateral lung infiltrates. *Crit Care* 2008; **12**:R6.