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ORIGINAL ARTICLE

Pentraxin 3 as a Biomarker in Diagnosis of Ventilator Associated Pneumonia

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ABSTRACT

Background: *Timely diagnosis of pneumonia in intubated critically ill patients is challenging because the clinical signs and symptoms lack sensitivity and specificity also microbiological identification of organisms may take 48–72 h. Pentraxin 3 (PTX3) is a marker produced at sites of infection and inflammation which can be measured in few hours.* ***Objective:*** *to assess the role of PTX3 as a biomarker in the diagnosis of Ventilator Associated Pneumonia. (VAP).* ***Methodology:*** *This prospective study was conducted on 60 patients, 30 patients were admitted in the Chest Intensive Care Unit (CICU) of Ain Shams University Hospitals suspected to have VAP by modified Clinical Pulmonary Infection Score (CPIS), Level of PTX 3 was measured in serum and Mini Bronchoalveolar Lavage (MiniBAL) using an ELISA, level of C-Reactive Protein (CRP), Complete Blood Picture (CBC) and bacteriological culture were done to diagnose VAP. In 30 healthy controls we measured the serum level of PTX 3.* ***Results:*** *Bacteriologically confirmed VAP was diagnosed in 24 patients, with most common isolated organism was staphylococcus aureus (23%). The Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the discriminative ability of PTX3 (in serum and MiniBAL) to identify bacteriologically confirmed VAP. For PTX 3 in MiniBAL the Area Under the Curve (AUC) was 0.993 and a cut-off point of ≥3.6 had sensitivity of 95.83% and a specificity of 100.Serum PTX 3 AUC value was 0.826 and cut-off point of 7ng/ml was associated with 62.5% sensitivity, 100% specificity. For CRP, a cut-off level ≥12 mg/dl in serum was associated with 62.5% sensitivity, 83.3% specificity.* ***Conclusion****: PTX3 may serve as a useful biomarker in the detection of bacteriologically confirmed VAP patients.*

INTRODUCTION

Pneumonia represents one of the most widespread infections in intubated ICU patients [1] and is linked with significant morbidity, costs and mortality[2].

Timely and accurate diagnosis of pneumonia is important to starting appropriate treatment and improving patients' recovery and survival. However, to date, it is not possible to diagnose pneumonia rapidly and accurately in intubated critically ill patients[3].

VAP is a pneumonia where the patient is on mechanical ventilation for >2 calendar days on the date of event, with day of ventilator placement being Day 1, and the ventilator was in place on the date of event or the day before[4].

VAP, with frequencies of between 1.2 to 8.5 per 1,0 00 ventilatordays, is the second most prevalent HAI among adult ICU patients[5]. VAP risk is greatest during the first 5 days of mechanical ventilation (3%) with the mean duration between intubation and development of VAP being 3.3 days, this risk declines to 2% day between days 5 to 10 of ventilation, and 1%/day thereafter[6].

The complicated interplay between the endotracheal tube, the nature of risk variables, invading bacterial potency and host immunity mainly affect VAP development, the fact that presence an endotracheal tube is by far the greatest threat factor [1].

VAP is categorized as early-onset or late onset, early onset VAP (<5 d of hospitalization) has better prognosis and bacterial pathogen are more susceptible to antibiotic therapy**,** late-onset VAP presents ≥ 5 days from hospital admission, and is associated with higher morbidity and mortality, and is more often due to resistant organisms[7].

According to the Centers for Disease Control and Prevention guidelines, the clinical diagnosis of pneumonia is made on the basis of the presence of fever, leukocytosis, purulent lung secretions and new infiltrates seen on chest X-rays[8].

The CPIS, was proposed in 1991 as a diagnostic method for VAP, including six criteria: temperature, white blood cell count (cells/mm3), oxygenation paO2: Fio2, chest radiograph findings, tracheal secretions and

culture of tracheal aspirate. Modified CPIS scoring systems only includes data immediately available on patient presentation without culturing of tracheal aspirate [9].

Microbiological culture of Bronchoalveolar Lavage (BAL) fluid is an accepted standard to confirm (or exclude) a clinical diagnosis of pneumonia in intubated ICU patients, but results may take 48hours [10].

Physicians empirically prescribe either broad spectrum antibiotics or probability-based narrow spectrum antibiotics**,** both choices result in giving patients not needed antibiotics till culture results are available [11].

Biomarkers can assist improve accuracy and speed of VAP diagnosis. PTX3 is a is an acute-phase mediator produced by different kinds of cells at sites of infection and inflammation, in the lungs; leucocytes, endothelial cells and epithelial cells may produce PTX3 when stimulated, and it can be measured in few hours [12].

The accuracy of PTX3 levels in BAL fluid for diagnosing pneumonia might be superior to other current biomarkers with 96.7% *sensitivity*, 100% specificity [13].

The aim of this study was to assess the role of PTX3 as a biomarker in the diagnosis of VAP during the course of six months in the CICU of Ain Shams University hospitals.

METHODOLOGY

This prospective study was performed at the CICU of Ain Shams University Hospitals, Egypt during the period from April 2018 to March 2019. The study was approved by the ethical and moral committee of Faculty of Medicine Ain Shams University (No. FMASU M S 84/2019). 60 persons were included in this study, they were divided into two groups:

Group I:

Patients group: Thirty adult patients intubated and mechanically ventilated were followed up for appearance of any of the following signs of VAP after 48 h (by using the modified CPIS):

1-Fever, 2-Leukocytosis, 3-Abundant tracheal secretions 4-New lung infiltrates 5-paO_2 \FiO_2 < 240 mmHg.

-Electrocardiography was done when needed to diagnose and exclude any cardiac conditions that might cause pulmonary infiltrates.

Exclusion criteria

The patients having pneumonia at the time of admission to the ICU and/or chronic respiratory disease as chronic obstructive pulmonary disease, interstitial lung disease were excluded from the study.

Group II: Control group:

It included thirty apparently healthy persons with matched age and sex.

For patients group data which included temperature measurement, respiratory rate, oxygen saturation, pressure of arterial oxygen to the fraction of inspired oxygen (PaO2/FiO2), plain chest X-ray, CBC and CRP were collected. MiniBAL fluid was collected and analyzed according to Abd- Elfatah et al., [14] and then the sample was divided in to 2 parts.

The first part was used for quantitative bacterial culture by serial dilution technique was done and the growths were expressed as a number of Colony Forming Units (CFU)/ml and according to Papazian et al.,[15] the threshold applied to quantitative cultures for the diagnosis of VAP was 10^4 CFU/ml. Characteristic colonies were identified by Gram stain, and biochemical reactions according to Colle et al [16].

The second part of the sample was centrifuged and then stored with the serum samples at ⁻20 C until analysis by using the Human PTX3 ELISA. And for all participants in the study blood samples were collected then centrifuged and serum samples were stored at ⁻20 C. Serum samples were tested for PTX 3 using human PTX3 ELISA kit (bioassay technology lab, Cat. No: E1938Hu, China), based on double-antibody sandwich ELISA using 96- wells plate which has been pre-coated with human PTX3 monoclonal antibody. It was done according to the manufacturer's instructions. Standards and samples were added to the wells. The wells were washed then PTX3 antibody labeled with biotin was added, and combined with Streptavidin-HRP to form immune complex, and incubated then washed again to remove the uncombined enzyme. Chromogen solution A then solution B were added to each well, the color of the liquid changed into the blue, then the color finally became yellow by the addition of acidic stop solution. The optical density (OD) were measured at 450 nm wavelength by spectrophotometer. Finally, according to standards' concentration and the corresponding OD values, the standard curve linear regression equation was calculated out, and then the OD value of the sample was applied on the regression equation to calculate the corresponding sample's concentration.

Statistical analysis:

Statistical presentation and analysis of the present study were conducted, using the mean, standard deviation and Chi-square test by SPSS V.20. P <0.05 was considered as significant.

ROC curves were constructed for each marker, and AUC for each marker was calculated. optimal cut-off points were determined based on ROC curves. The sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) for the studied parameters in predicting bacteriologically infected ventilated patients were calculated.

Numerical data were reported as Mean, Standard deviation, Frequency and percentage of non-numerical data.

Student T Test was used to assess the statistical significance of the difference between two study group means.

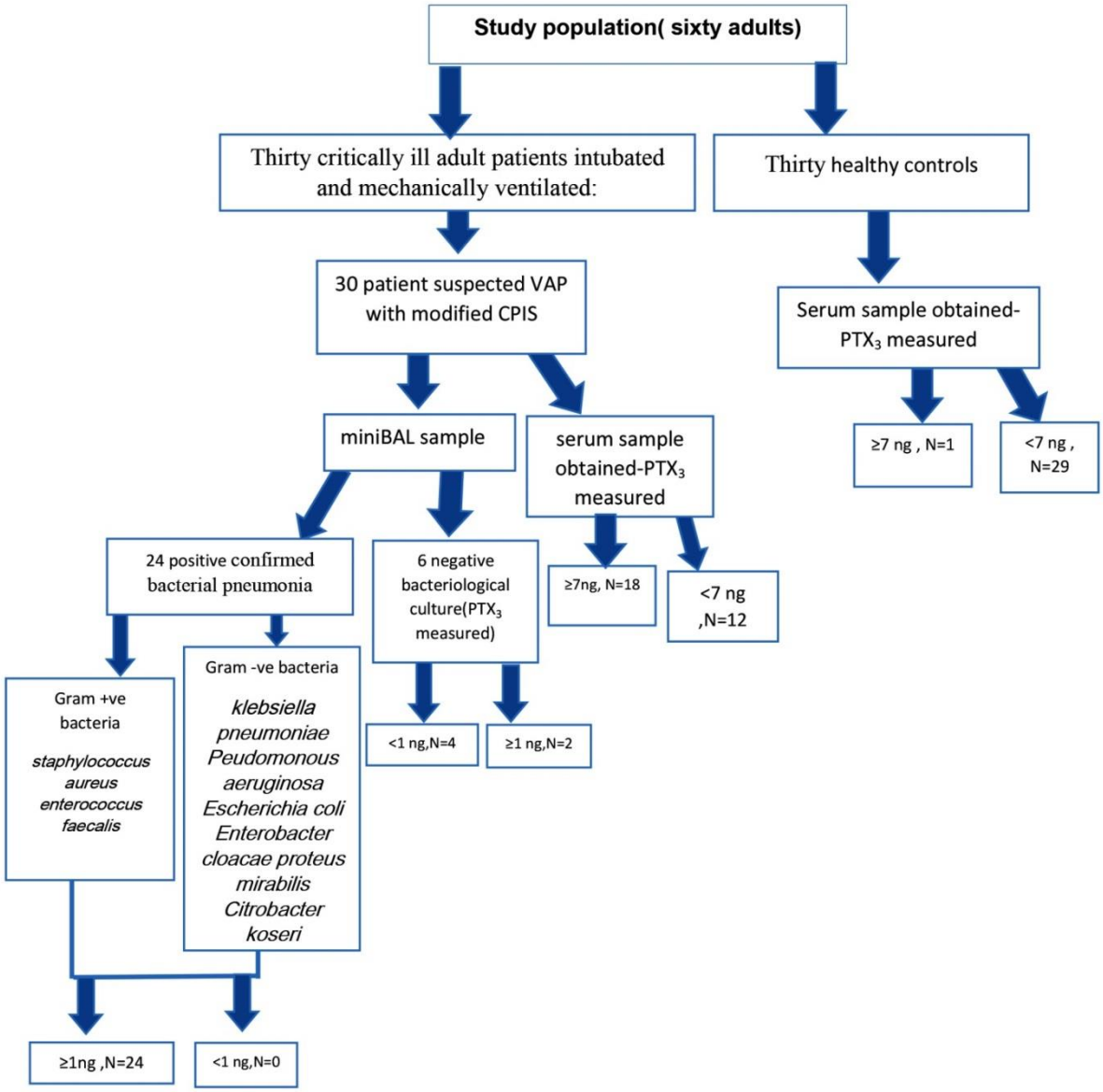
Kaplan-Meier Survival Analysis was used for examining the distribution of time-to-event variables.

Correlation analysis (using Pearson's method) was used to assess the strength of association between two quantitative variables.

RESULTS

Study groups:

The present study included two groups, the first included 30 patients (16 female,14 male, mean age 48±9) with suspected VAP by modified CPIS, and the second included 30 healthy controls (13 female, 17 male, mean age 46±8) (flow diagram 1).



Flow diagram (1): Study population with distribution of PTX3 level among patients and control (cut-off value according to Mauri et al.,[13]).

For CPIS used for diagnosing VAP in patients the mean was 7.77 ± 1.74. Also the mean for onset of VAP in patients was 4.76 (4.14 - 5.38) as illustrated by the survival curve (fig 1, table 1).

Table 1: clinical and laboratory data of patients:

Characteristics		Mean , SD,%
onset of VAP(days)		4.37 ± 1.35
TLC		12530 ± 2609.29
Temperature		38.77 ± 0.69
Po2/Fio2	<240	21(70%)
	>240	9(30%)
Tracheal secretions	Abundant	3 (10.0%)
	abundent and purulent	19(63.3%)
	Rare	8(26.7%)
Pulmonary radiography	No infiltrate	1(3.3%)
	Localized infiltrate	12(40.0%)
	Diffuse infiltrate	17(56.7%)
Culture	Negative	6(20%)
	Positive	24(80%)
score		7.77 ± 1.74

Values are given as number with percentage in parentheses or as mean and SD

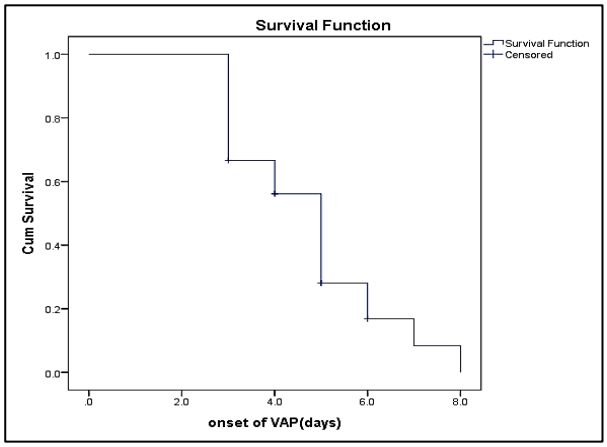


Fig.1: Survival curve of VAP in patient population

29 bacterial pathogens were isolated from 24 patients (80%), the most common isolated organism was *staphylococcus aureus* (8 cases 27.6%), followed by *klebsiella pneumoniae (6 cases* 20.7%), then *Pseudomonas aeruginosa* (4 cases 13.7%), then *enterococcus faecalis(*3 cases *10.3%)*, then *Escherichia coli*(3 cases 10.3%), after it *Enterobacter cloacae*(2 cases 6.9%), *proteus mirabilis*(2 cases 6.9%), and least one was *Citrobacter* (1 case 3.4%),and six patients (20%) were negative for bacteriological culture.

On comparing the levels of serum PTX3 between the patients and healthy control revealed that the patients group had higher levels of PTX3 (2.5±1.8 versus 8.6±5.9, *P* <0.001).Regarding the relationship between CRP, PTX3 and bacteriological diagnosis of VAP, there was a significant correlation between PTX3 Mini BAL level (*P* .001), PTX3 Serum level (*P* <0.001) and CRP (*P* .001) with culture result. (table 2,3).

Table 2: Serum PTX3 level (ng*ml) in patients and control:

PTX3 Serum level		Controls	Patients	Test of sig.	
		Mean±SD	Mean ±SD	p value	sig.
		2.5±1.8	8.6±5.9	<0.001	S
PTX3 Serum level	<7	29	12	<0.001	S
	≥7	1	18		

Table 3: The relationship between CRP, PTX3 and bacteriological diagnosis of VAP

	Culture		t test	
	Negative	Positive		
	Mean ±SD	Mean± SD	p value	sig.
CRP	6.383±3.7717	24.838±22.2024	.001	S
PTX3 MiniBAL level ng*ml	1.217±1.1907	9.158±2.3275	<0.001	S
PTX3 Serum level ng*ml	4.650±1.3910	9.575±6.2091	.001	S

The agreement between CRP, PTX3 and Culture

There was a significant agreement between culture results and CRP level ≥12 mg/dl was 50 %), For PTX3 mini BAL level ≥1 ng/ml was 80 %, And for PTX3 Serum level ≥7 ng/ml was 50 % (table 4,5, 6).

Table 4: Agreement between culture and CRP results:

		Culture		Total	Agreement			
		negative	Positive		%	Kappa	p value	Sig.
CRP	<12mg\dl	5 (16.67%)	9 (30%)	14 (46.67%)	66.7%	0.306	0.044	S
	≥12mg\dl	1 (3.33%)	15 (50%)	16 (53.33%)				
Total		6 (20%)	24 (80%)	30 (100%)				

Table 5: Agreement between culture and PTX3 MiniBAL level :

		Culture		Total	Agreement			
		negative	Positive		%	Kappa	p value	Sig.
PTX3 MiniBAL level	<1 ng*ml	4 (13.33%)	0 (0%)	4 (13.33%)	93.3%	0.762	0.000	S
	≥1 ng*ml	2 (6.67%)	24 (80%)	26 (86.67%)				
Total		6 (20%)	24 (80%)	30 (100%)				

Table 6: Agreement between culture and PTX3 serum level:

		Culture		Total	Agreement			
		Negative	Positive		%	Kappa	p value	Sig.
PTX3 Serum level	<7 ng*ml	6 (20%)	9 (30%)	15 (50%)	70.0%	0.400	0.006	S
	≥7 ng*ml	0 (0%)	15 (50%)	15 (50%)				
Total		6 (20%)	24 (80%)	30 (100%)				

Discriminative ability of PTX3 and CRP for bacteriological diagnosis of VAP

ROC curve analyses were performed, MiniBAL PTX3 had excellent diagnostic accuracy in distinguishing bacteriologically infected from uninfected ventilated patients, with an AUC of 0.993 and at a cut-off point of > 3.6 ng/ml; had sensitivity of 95.83% and a specificity of 100%, and at a cut-off level of PTX3 levels ≥1 ng/ml (cut-off level according to Mauri et al.,[13]) was associated with 100.0% sensitivity, 66.7% specificity and total accuracy 93.3%for confirmed bacterial VAP. Serum PTX3 was good predictive of bacteriologically confirmed cases of VAP with an AUC of 0.826 and a cut-off point of ≥7 ng/ml had sensitivity of 62.5% and a specificity of 100% and total accuracy was 70.0%. CRP was significantly discriminative between bacteriologically infected from uninfected ventilated patients with a cut-off level ≥12 mg/dl; had 62.5% sensitivity, 83.3% specificity and total accuracy 66.7% (fig 3,4, table 7,8).

Table 7: Sensitivity, specificity, PPV, NPV of PTX3 and CRP (Cut-off point according to Mauri et al.,[13]).

Biomarker	Cut- off point	Sensitivity	Specificity	PPV	NPV	Accuracy
CRP level mg\dl	≥12	62.5%	83.3%	93.8%	35.7%	66.7%
PTX3 MiniBAL level ng\ml	≥1	100.0%	66.7%	92.3%	100.0%	93.3%
PTX3 Serum level ng\ml	≥7	62.5%	100.0%	100.0%	40.0%	70.0%

Table 8: The discriminative ability of PTX3 (in serum and MiniBal) in predicting bacteriologically confirmed VAP patients.

Biomarker	AUC	95% CI	Cut-off point	Sensitivity	Specificity	PPV	NPV	p value	sig
PTX3 Serum level	0.826	0.645 to 0. 939	≥7	62.5	100	100	40	0.0001	S
PTX3 MiniBAL level	0.993	0.871 to 1. 000	≥3.6	95.83	100	100	85.7	0.0001	S

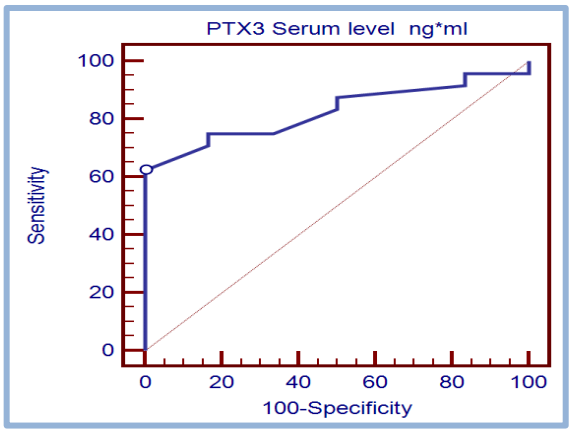


Fig. (2): ROC curve for PTX3 Serum level

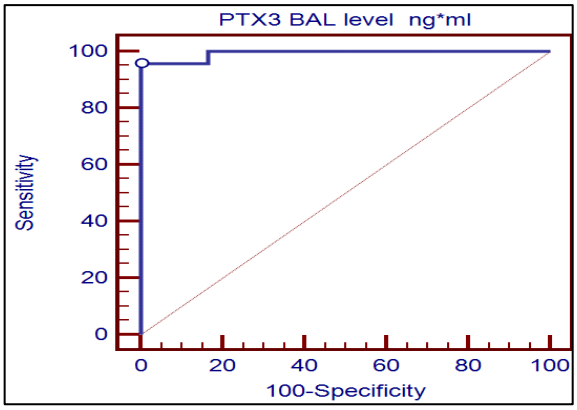


Fig (3): ROC curve for MiniBAL PTX3 level

DISCUSSION

VAP diagnosis remains an important issue to clinicians because of nonspecific clinical criteria standardized for diagnosis, in addition to time consuming bacteriological culture results, that may encourage doctors to start empiric antimicrobial therapy which may cost patient more harm and resistance, thus there is a need for rapid, accurate, and inexpensive diagnostic methods for VAP. [10]

The present study was constructed to assess the role of PTX3 as a biomarker in the diagnosis of VAP during the course of six months in the CICU of Ain Shams University hospitals.

Alveolar fluid sample was taken using MiniBAL technique. This technique is less expensive and more widely available, 29 bacterial pathogens were isolated from 24 patients (80%), the most common isolated organism was *staphylococcus aureus* (8 cases 27.6%) and least one was *citrobacter* (1 case 3.4%) and six patients (20%) were negative for bacteriological culture**,**

For the pathogens detected in bacteriological culture, the present study agreed with Chi et al.,[17] where Bronchoscopic– BAL was obtained and cultured, from which 109 bacterial pathogens were isolated from 91 adult patients with VAP, it revealed that *staphylococcus aureus* (44%) was the most frequently isolated pathogen.

On the other hand, the present study disagreed with Reham et al., [18], who found that the single most common pathogen was *pseudomonas aeruginosa*, accounting for 30 of 48 bacterial isolates.

PTX3 is a is an acute-phase mediator produced by cells of innate immune system. It is produced at sites of infection and inflammation. In the lungs; leucocytes, endothelial cells and epithelial cells may produce PTX3 when stimulated [13]**.**

The present study revealed that MiniBAL PTX3 has excellent ability in detection of bacteriologically confirmed cases of VAP, a cut-off value≥3.6 ng/mL was associated with 95.83 sensitivity, 100% specificity and total accuracy 93.3% ,these results concede with the results of Mauri et al.,[13], who showed that found that BAL PTX3 has a high diagnostic efficiency in the detection of VAP cases at a cut-off value ≥1 ng/ml was associated with 92% sensitivity, 60% specificity and 70% total accuracy for bacteriologically confirmed VAP cases.

Also Bilgin et al., [19]observed that at a cut-off value of 2.56 ng/mL BAL PTX3 was associated with 85% sensitivity, 86% specificity and 86.5% total accuracy in detecting bacteriologically confirmed cases of VAP.

The present study clarified that normal serum PTX 3 levels could be used to rule out VAP, a cut-off value of PTX3 levels ≥7 ng/ml in serum was associated with 62.5% sensitivity, 100.0% specificity, 100% PPV, 40% NPV and 70% total accuracy for bacteriologically confirmed VAP patients.

Our finding agreed to Ibrahim et al., [20], who found that at a cut-off value of ≥ 6 ng/ml for PTX3 in serum was associated with 87% sensitivity, 88.8% specificity, for culture positive VAP.

In contrast to our results Lin et al., [21]found that serum PTX3 threshold of ≥16.43 ng/ml provided a moderate diagnostic efficiency in the detection of VAP with specificity of 74.0% and a sensitivity of 68.6%.

C-reactive protein (CRP) is an acute-phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells [22].

Our results showed that CRP at a cut-off value of ≥ 12 mg/dl in serum was associated with 62.5% sensitivity, 83.3% specificity, 35.7% NPV and 93.8% PPV in detection of bacteriologically confirmed VAP patients.

These results were compatible with Ramirez P et al.,[23], who assessed the level of CRP in patients with suspected VAP and found that at a cut-off value of

19.69 mg/dl; CRP had a 56% sensitivity and 91% specificity for VAP cases.

CONCLUSION

The present study revealed that PTX3 may serve as a useful biomarker in the detection of bacteriologically confirmed VAP patients. Cut- off level 3.6 ng/ml in MiniBAL fluid was associated with elevated sensitivity and NPV. In serum, PTX3 was less sensitive than MiniBAL in diagnosis of VAP.

Conflicts of interest:

The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.

- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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