J Biochem Tech (2019) Special Issue (2): 133-138
ISSN: 0974-2328

Comparison of Serum CRP, PCT and STREM-1 in Ventilator-Associated Pneumonia (VAP) Positive and VAP Negative in ICU Patients

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Received: 11 August 2018 / Received in revised form: 04 March 2018, Accepted: 20 March 2019, Published online: 25 May 2019

Abstract

Objective: The aim of this study is to determine the role of plasma C-reactive protein (CRP), Procalcitonin (PCT), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) levels in diagnosing ventilator-associated pneumonia.Methods: A total 95 patients admitted to Intensive Care unit (ICU) were divided into VAP positive group (N=50) and VAP negative group (n=45) based on CPIS scoring system. Demographic data, causes of admission, underlying disease were recorded. Serum level of biomarkers were measured after admission to ICU.Results: Serum CRP and PCT levels of patients in the VAP positive group were significantly higher than those without VAP group (P value<0.05). Serum level of sTREM-1 didn't have significant differences between two groups. The most common cause of admission in ICU was neurological abnormalities. Age, sex, duration of admission and underlying diseases didn't have relation with biomarker value.Conclusion: This study found that elevated CRP and PCT serum level provide superior markers to sTREM-1 to predict VAP patients in ICUs. Probably more comprehensive designed studies are needed to achieve a better and earlier way to diagnose VAP.

Key words: C-reactive protein (CRP), Procalcitonin (PCT), soluble triggering receptor expressed on myeloid cells-1(STREM-1), Ventilator-Associated Pneumonia (VAP)

Introduction

One of the most common infections causing long term hospitalization and mortality in critically ill patients who admitted in hospital particularly in Intensive Care Unit (ICU) is pneumonia. In fact Ventilator-Associated Pneumonia (VAP) is the most common nosocomial infection cause long term stay in hospital especially in adult ICU of medical centers (Koenig & Truwit, 2006; Gunasekera & Gratrix, 2015). VAP is affected more than 30% of ventilated patients in ICU and also increase antibiotics prescribing for them. VAP also increase ICU admission, patients' ventilators days, healthcare costs and on the other hand cause multidrug resistance infections (Spalding, 2017; Affara et al., 2014). VAP is defined as lung parenchymal inflammation due to a bacterial infection in patients who are under endotracheal ventilation in hospital for more than 48 hours (Affara et al., 2014). According to difficulties in definite diagnosis of VAP in critically ill patients and also absence of specified clinical or radiological or microbiological signs and symptoms in early diagnose of that, Centers for Disease Control and Prevention (CDC) suggested guidelines for faster diagnose and earlier start of treatment for VAP included complex of clinical, radiological and microbiological signs and symptoms (Rewa & Muscedere,2011; Control, 2016). We need a better system for definite diagnose of VAP so Clinical Pulmonary Infection Score (CPIS) was proposed in1991 as a guideline for better diagnoses of VAP patients. In this system some clinical, radiological and microbiological items was used that include body temperature, leukocyte count, volume and character of tracheal secretions, arterial oxygenation, chest X-ray(lung infiltration), Gram stain and culture of tracheal aspirate that each one had points. Patients with CPIS >6, was considered positive for VAP (Safdar et al., 2013). Despite the limitation of sensitization and specification of this scoring system, it still used as a helpful mechanism for VAP diagnosis and its

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outcome (Celik et al., 2014).

In suspicious and definite VAP patients, some biomarkers and cytokines such as soluble triggering receptor expressed on myeloid cells-1(sTREM-1), Procalcitonin (PCT), C-reactive protein (CRP) or Tumor necrosis factor receptor 1 (TNFR1) will change (Martin-Loeches et al., 2015; Bloos et al., 2011; Moreno et al., 2016; Luyt et al., 2011; Afifi et al., 2015; Tanrıverdi et al., 2015). CRP considered as a biomarker of acute phase of the disease that will rise in infections and also any tissue inflammations. It is as a non-specific marker but it has been proven that will helpful in some infections (Melbye & Stocks, 2006). In so many studies, according to patients with suspicious of having VAP in ICU, it used as a supporting inflammation marker, however it doesn't yet have enough sensitivity and Specificity for diagnosis and is more used to evaluate treatment management (Povoa et al., 2005; van der et al., 2005; Coelho et al., 2007). PCT is also an inflammatory marker in sepsis that in sever bacterial infections have increased levels. Many studies have been conducted on the diagnostic value of this marker in diagnosis and prognosis of critically ill patients in ICU. In these studies, PCT is a marker for helping us to stop antibiotics in severe infection of patients in ICU. But the value of this marker in diagnosis is questionable (Shehabi & Seppelt, 2008; Linssen et al., 2008). STREM-1 is an inflammatory marker that secreted in many bacterial infections and inflammatory disease. This marker is measurable in biological fluids and serum (Bucova et al., 2012). In many studies, patients with pneumonia secreted this marker in Broncho alveolar lavage (BAL). In these studies, measurement of that in BAL was as a predictor factor for pneumonia, had higher Specificity for pneumonia. In studies on suspected VAP patients in ICUs, measurement of this factor could help in diagnosis or prediction of outcome of disease (Gibot et al., 2004; Shi et al., 2013; Determann et al., 2005). Despite the usefulness of this factor, mini bronchoscopy of critically ill patients is so difficult and complicated. According to the comments given and the role of inflammatory markers in helping out for earlier diagnose of suspected patients with VAP. In this study we were interested to evaluate the serum level of inflammatory markers (CRP, PCT, and STREM-1) and compare them in two patients groups. We finally discuss the serum value of these markers in VAP patients and also the effect of other variables on these markers.

Methods

A retrospective cross-sectional observational study was performed in educational hospital of Isfahan, Iran. All patients who admitted in medical and surgical ICUs of our university hospital between December 2016 till April 2017 who have inclusion criteria were enrolled the study. Regional Ethical committee approved the study protocol. Permission from all patients or their relatives was obtained through an informed consent before enrollment. The study was conducted on all patients 18 years old or older who were under mechanical ventilator for more than 48 hours in ICU. We separated two groups according to CPIS scoring system; patients who had more than 6 points of this system include in case groups and if they had less than 6 points they entered to control groups.

First we recorded the following base-line variables at enrollment: body temperature; leukocyte count; ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2); features of tracheal secretions (volume, color, concentration); semi quantitative tracheal aspirate cultures. We also reviewed the Chest radiography infiltration patterns. Then patients' profiles were reviewed one by one and the following data were retrieved, and two groups were separate according to modified CPIS scoring that we mentioned in table 1.

Table 1: modified CPIS scoring

sign	0	1	2
Temperature(°C)	36.1-38.4	38.5-38.9	≥39or≤ 36
Blood leukocytes($\times 10^9$/l)	4-11	<3.9 or >11.1	>50% band forms
Tracheal secretions	Absence	Presence and non –purulence(white or light yellow)	Presence and purulence (yellow, green or brown)
Oxygenation (PaO_2/FiO_2)	>240 or ARDS		<240 and no ARDS
Semi quantitative tracheal aspirate culture(Cfu/ml)	$<10^3$	$\geq 10^3$ and $\leq 100^3$	$>100^3$
Chest X-ray	No infiltrate	Diffuse or patchy infiltrate	Localized infiltrate

(Safdar et al., 2013)

The following item also recorded for each patients in ICU: age, sex, duration of admission in ICU, reason for admission in ICU and also background illness. After selection of patients we collect 10 cc of whole blood of each patient and transferred to laboratory in a cold chain system. Serum sample were prepared after centrifugation and stored at -40°C.

Quantitative CPR was determined by turbidimetric immunodiagnostic assay with auto analyzer HITACHI -911. The sensitivity of this technique allows the detection of CRP levels as low as 3 mg/lit. PCT and sTREM-1 was determined by enzyme-linked immunosorbent assay (ELISA) with STATFAX 2100 system. Normal range of PCT was under 0.15 ng/ml. The assay range of sTREM-1 was 5-2000 pg/ml.

Results

From December 2016 to April 2017, 95 patients who were hospitalized in our medical and surgical ICU of educational hospital of Isfahan Iran were enrolled in our study. All patients divided to two groups as case who they had CPIS score more than 6 and control groups who they had CPIS score under 6 points as we describe earlier. We also considered some bold and important background illness which we were suspicious that can confuse our result such as hypertension (HTN), Diabetes mellitus (DM), Cancer, End Stage Renal Disease (ESRD). Because there were so many varied reasons cause admission to ICU, we categorized the reasons to some groups for better evaluation; included neurological abnormality (Cerebrovascular accidents, Hydrocephaly, Subarachnoid hemorrhage, guillain barre syndrome, Meningitis, Intracranial hemorrhage), Gastrointestinal(GI) disorders (GI bleeding, GI perforation, Ileus, Bowel obstruction),Cardiovascular disorders (Acute Myocardial infarction, Pulmonary thromboembolism, Deep vein thrombosis) , Cancer(Brain tumor, Mediastinal tumor, Multiple myeloma, Bone cancer) , Multiple trauma and Others. The characteristics of all study groups are summarized in table 2.

Table 2: characteristic of the study population

	Case group(VAP+)	Control group(VAP-)	All patients
	n = 50	n = 45	n = 95
Sex-no (%)			
Male	30(60)	22(49)	52(55)
Female	20(40)	23(51)	43(45)
Age-yr.	61.86±19.81	54.02±19.99	58.15±20.18
Duration of admission-days	17.52±15.51	11.80±14.32	14.81±15.15
Reason of admission-no (%)			
Neurological abnormality	19(38)	18(40)	37(38.9)
GI disorders	6(12)	5(11)	11(11.6)
Cardiovascular disorders	6(12)	3(6.7)	9(9.5)
Cancer	3(6)	2(4.4)	5(5.3)
Multiple trauma	12(24)	13(28.9)	25(26.3)
others	4(8)	4(8.9)	8(8.4)
Underlying disease- no (%)			
HTN	13(26)	14(31)	27(68)
Diabetes	11(22)	6(13)	17(18)
Cancer	3(6)	2(4)	5(5)
ESRD	5(10)	3(7)	8(8)
CRP mg/lit	93.74±44.3	74.89±41.78	84.81±43.93
PCT ng/ml	4.22±4.32	2.11±3.22	3.22±3.96
sTREM-1 pg/ml	776.36±1042.61	557.49±852.23	672.68±958.48

We analyzed the variable between two groups with independent T Test (table 3).

Table 3: T test analysis of biomarkers and background illness

	Variable	Sex$\begin{cases}M\\F\end{cases}$	P-Value	HTN	P-Value	Diabetes	P-Value	Cancer	P-Value	ESRD	P-Value
CRP	Case	93.36±34.89	0.363	96.76±69.01	0.129	82.45±45.51	0.368	89.66±41.10	0.974	75.80±51.41	0.292
		94.3±56.59									
	Control	74.31±41.71	0.924	72.42±41.17	0.966	72.50±38.44	0.413	133.50±40.30	0.555	100.66±30.9	0.230
		75.43±42.76									
	total	85.31±38.72	0.904	84.14±56.56	0.927	78.94±42.19	0.546	107.20±42.74	0.244	85.12±44.15	0.983
		84.21±49.97									
PCT	Case	3.77±4.32	0.815	4.17±4.48	0.777	4.52±4.68	0.380	2.26±3.23	0.113	8.06±4.33	0.507
		4.89±4.33									

	Control	2.03±3.08 2.19±3.41	0.814	1.63±2.84	0.436	2.13±1.44	0.083	1.10±1.27	0.309	0.53±0.49	0.095
	total	3.04±3.91 3.45±4.06	0.620	2.85±3.87	0.576	3.32±4.14	0.904	1.80±2.45	0.412	5.23±5.09	0.134
sTREM-1	case	834.10±1079.70 689.75±1005.42	0.597	787.53±772.43	0.654	467.18±237.87	0.029	662.33±382.96	0.406	780.00±289.38	0.218
	control	354.13±171.58 752.00±1159.13	0.002	779.35±1088.72	0.135	320.66±132.69	0.224	2479.00±2452.24	0.001	295.00±36.38	0.325
	total	631.04±855.77 723.05±1078.00	0.644	783.29±1075.41	0.481	415.47±214.65	0.224	1389.00±1602.12	0.086	598.12±333.52	0.820

As a whole we measured serum level of CRP, PCT and sTREM-1 in two groups. CRP and PCT were higher in patients with ventilator-associated pneumonia than in patients without pneumonia (P Value <0.05), but the levels of sTREM-1 did not differ significantly between the two groups of patients.

As we shown in table 3 there was no correlation between two groups' serum levels of biomarkers and HTN, ESRD. But in patients without pneumonia there was a correlation between sTREM-1 levels and sex. Level of sTREM-1 was higher in patients without VAP who had DM and Cancer. Also PCT level is higher in diabetic patients without VAP.

Levels of all biomarkers showed no correlation with age among two groups. Pearson correlation coefficient analysis showed significant differences between duration of admission in ICU and CRP, PCT among two groups (patients with VAP and without VAP) (P Value < 0.05). But level of sTREM-1 was not different among groups.

Kruskal- Wallis test (One-way ANOVA) was employed to analyze the different reasons of ICU admission and levels of biomarkers in all groups of study. As we shown in table 4 there was no significant differences between reasons of admission and serum levels of CRP, PCT and sTREM-1 among two groups of patients.

Table 4:kruskal-wallis analysis the variable biomarker in groups with different reasons of admission

	neurological abnormality	GI disorders	Cardiovascular disorders	Cancer	Multiple trauma	others
CRP						
Case	79.63±41.81	99.83± 18.08	82.33±40.18	141.00±136.39	108.50±14.39	89.00±20.94
Control	56.27± 43.03	90.80±56.94	113.33±11.54	81.00±50.91	87.76±31.59	65.00±31.37
Total	68.27±43.46	95.72±38.50	92.66±35.81	117.00±105.02	97.72±26.56	77.00±27.83
PCT						
Case	4.19±4.45	6.00±3.80	5.11±5.17	0.90±0.95	3.90±4.62	3.80±4.29
Control	2.02±3.05	3.52±3.87	0.36±0.05	0.95±0.21	2.09±3.45	2.70±4.86
Total	3.13±3.94	4.87±3.86	3.53±4.72	0.92±0.68	2.96±4.07	3.25±4.28
sTREM						
case	800.68± 1117.82	1013.33±889.27	1156.33±1616.94	571.33±244.03	608.08±1006.82	394.00±265.36
control	330.61± 171.19	1203.60±1691.46	1555.66±2313.70	268.00±66.46	443.92±450.97	536.00±417.65
total	572.00±833.87	1099.81±1244.87	1289.44±1735.58	450.00±241.83	522.72±757.16	465.00±332.71

Discussion

VAP is one of the most common and usual nosocomial infection in critically ill adult patients in ICU. VAP is defined as lung parenchymal inflammation due to a bacterial infection in patients who are under endotracheal ventilation in hospital for more than 48 hours (Affara et al., 2014). Definite diagnosis of VAP is unclear.it is based on clinical suspicious of VAP and also some radiological and microbiological parameters that can help us in early diagnose of VAP.

In this study we evaluated the role of some inflammatory biomarker in serum of patients who had VAP criteria and compare with patients with same condition but without VAP criteria. CRP is a sensitive biomarker of inflammation and infections but it isn't a specific data for infection (Tanrıverdi et al., 2015). Povoa P and et al studied about the CRP level in critically ill patients especially in patients with VAP and they also suggested that monitoring of CRP is a useful data for VAP prediction (Póvoa et al., 2017). Afifi MH and his colleagues was also study about the CRP level in VAP patients and they found that CRP is useful as diagnostic marker but not as a prognostic one in VAP (Afifi et al., 2015). Some underlying disease can effect on the serum level of CRP for example in several studies showed that there are a relationship between CRP levels and cardiovascular disorder such as HTN (Hage, 2014), DM (Wang et al.,

2013), cancer (Guo et al., 2013) and ESRD (Babaei et al., 2014). In our study we also found that in VAP patients mean level of CRP is higher and had a significant difference between two groups (P value <0.05). In spite of evaluation of some underlying disease there was no correlation between HTN, DM, Cancer and ESRD and CRP level in all and each groups of study. We also recognized that there was no difference between varied reasons of admission.

PCT is also known as a specific biomarker for infection and sepsis. This marker is used in ICU patients for predicted association of bacterial infection, but its diagnostic accuracy remain inadequate because of multiple reasons such as remaining elevation of PCT for several weeks after resolution of disease, several bacterial infection during ICU staying and may be some other conditions that can cause PCT elevation such as surgery, trauma, circulation factors, etc. so PCT is not a specific biomarker (Tanrıverdi et al., 2015). AA El Halim et al compare serum PCT level between two groups with VAP positive and without VAP and they found significant higher PCT level in VAP group (El Halim et al., 2013). Snjezana Mehanic concluded that the increase in the serum level of PCT can be a diagnostic marker in predicting VAP outcome (Mehanic & Baljic, 2013). JC Sotillo-Díaz explained in a systematic review and metaanalysis the same data that PCT can provide additional information for VAP (Sotillo-Díaz et al., 2014). In our study PCT serum levels were significantly different between two group (P value< 0. 05). But there was no correlation between underlying disease and reason of admission with PCT levels. The mean of PCT levels, are higher in VAP group compared to control group.

STREM-1 is a putative biomarker for diagnosis of VAP, this marker secrete from monocyte and neutrophils (Grover et al., 2015). Many studies bring up data about the effect and level of this biomarker in BAL fluids (Shi et al., 2013; Determann et al., 2005). Sébastien Gibot and his colleagues worked on this marker and found that level of sTREM-1 in BAL fluids in VAP patients was higher than patients without pneumonia and this marker had a sensitivity of 98% (Gibot et al., 2004). This test need mini bronchoscopy to achieve the BAL and fluids to measure the sTREM-1 level on them. But it was so aggressive work in critically ill patients with low oxygenation and mechanical ventilation so we think about a more comfortable and accessible data that we can trust to improve the ability of physician to differentiate patients with VAP better. So we detected this marker in serum of patients. But our results weren't significantly different between two groups of patients. However some studies, have suggested that sTREM-1 isn't a high value predictor for VAP (Palazzo et al., 2012).

Conclusion

In conclusion, serum levels of many inflammatory biomarkers may vary in VAP patients such as CRP, PCT. Although sTREM-1 is detectable in serum of ill patient but cannot differentiate VAP positive or VAP negative patients. Owing to the limitations of our retrospective design, collecting data and sample size, some clinical studies are needed to provide further proof for the clinical diagnostic of serum sTREM-1 in VAP.

Interest of conflict: there is not any interest of conflict.

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