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Triple-P Panel (Procalcitonin, Presepsin and Pentraxin3) to Confirm Sepsis

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Abstract

A total of 65 blood samples (25 culture positive sepsis and 40 culture negative sepsis) from patients with sepsis symptoms who resided in the ICU of Hilla city hospitals, were collected, as well as 25 samples as a control (healthy persons) during a period from January to June 2022. Data was documented at the time of admission to the ICU. Regarding PSN and PCT concentration (P value= 0.001), the control group had a significant difference from both the two patients' groups (culture positive and negative groups of sepsis). Whereas the difference was not significant for the PTX3 concentration among patients and control (P value = 0.56). Furthermore, PSN and PCT concentrations did not significantly differ between the culture positive and culture negative groups of sepsis (P value > 0.05). Moreover, there was a significant strong positive correlation between PSN and PCT (r = 0.500; P <0.001).

Keywords: Sepsis, Procalcitonin, Pentraxin 3, Presepsin**,** Immunological parameters.

لوحة پ الثلاثية (بروكالسيتونين، بريسبسين وبنتراكسين 3) لتأكيد تعفن الدم

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الخلاصة

تم جمع ما مجموعه 65 عينة دم (25 تعفن الدم ايجابي الزرع الميكروبي و40 تعفن الدم السلبي الزرع الميكروبي) من المرضى الذين يعانون من أعراض تعفن الدم الذين يقيمون في وحدة العناية المركزة بمستشفيات مدينة الحلة، بالإضافة إلى 25 عينة كمجموعة ضابطة (الأشخاص الأصحاء) خلال الفترة من كانون الثاني إلى حزيران 2022. تم توثيق البيانات في وقت الدخول في وحدة العناية المركزة. كان للمجموعة الضابطة فرق كبير عن مجموعتي المرضى (المجموعات الإيجابية والسلبية للتعفن الدموي) فيما يتعلق بتركيز PSN و PCT (قيمة P = 0.001) في حين أن الفرق لم يكن كبيرا بالنسبة لتركيز PTX3 بين المرضى والمجموعة الضابطة (قيمة P = 0.56). وعلاوة على ذلك، لم تختلف تركيزات PSN و PCT اختلافا كبيرا بين المجموعات الموجبة و السالبة لإختبار زرع تعفن الدم (قيمة P > 0.05). وعلاوة على ذلك، هناك علاقة إيجابية قوية كبيرة بين PSN و PCT (r = 0.500; P <0.001).

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Introduction

Sepsis is an uncontrolled immune response to certain infections by fungi, viruses, or bacteria. The mortality rate of sepsis is still high all over the world and there is confusion in predictive biomarkers for sepsis that may be used in clinical settings. The acquisition of bacteria can lead to bloodstream infections and occasionally induce a fatal body response if bacteria are present long enough and in large enough quantities, especially among elderly patients or those who have a weakened immune system [1]. Since sepsis is a dysregulated immune response and an unusual systemic reaction to infections that causes a life-threatening clinical condition, it must be diagnosed as soon as possible for it to be treated [2]. Although blood cultures are the most frequently used diagnostic method for detecting bacterial sepsis (blood samples from patients suspected of having bacteremia are cultured in artificial media to recover any probable bacteria), this method is slow and insufficiently sensitive when the patient has already received antibiotics or in the presence of fastidious organisms that cannot grow in normal conditions. As a result, other and more specific approaches for detecting bacteria have developed [3]. The acquisition of a particular bacterial infection causes both the innate and adaptive immune systems to be activated in response to pathogen associated molecular patterns (PAMP). In some circumstances, sepsis may develop, and the responsiveness may transfer from a pro-inflammatory to a hyper-inflammatory state, leading to the downregulation of the immune system later. Numerous cytokines, chemokines, and proteins participate in the inflammatory state. Detection of these parameters may provide greater evidence than blood cultures in confirming bacterial infection. Sepsis may be detected and treated early with the assistance of several studies that have been carried out over time to evaluate a variety of potential biomarkers. These markers, which are produced in response to infection and inflammation, include C-reactive protein (CRP), procalcitonin (PCT), pentraxin3 (PTX3) and presepsin (PSN). The assessment of these biomarkers may support the recognition of patients who are developing severe sepsis before organ dysfunction becomes too severe to reduce the mortality rate associated with sepsis [4].

C-reactive protein represents one of the most acute-phase proteins whose synthesis in the liver, although its low specificity CRP is commonly used in laboratories to diagnose patients with sepsis caused by both viral and bacterial infections [5]. However, unlike CRP serum levels of PCT increase in bacterial infections and have higher diagnostic accuracy than CRP, because CRP is a general screening biomarker that can be elevated in a variety of diseases and inflammations. Whereas PCT is a widely used biomarker to distinguish sepsis from other non-infectious causes [6]. Procalcitonin, a protein of 116 amino-acids with a molecular weight of 13 kDa, was discovered 25 years ago as an intracellular precursor of calcitonin produced by parafollicular (C-cells) of the thyroid gland and by the neuroendocrine cells of the lung and intestine. Intracellular cleavage of PCT by proteolytic enzymes (endopeptidase) produces the active calcitonin hormone which plays an important role in control of the circulating calcium levels. PCT has currently emerged as a potent biomarker for the early detection of bacterial infection [7].

Pentraxin 3 (PTX3) is an acute-phase protein that is structurally similar to CRP. It is most likely generated at the local site of infection by several inflammatory cell types in response to IL-1 and TNF-α. Whereas, CRP is only produced in the liver in response to IL-6. Elevated PTX3 levels, like CRP, have been linked to the severity of sepsis. It is, however, high in non-infectious inflammatory conditions such as autoimmune disease, thus it has no advantage over CRP [8].

Presepsin (PSN), another indicator that represents a new biomarker (sCD14-subtypes), was found and its value was shown in the assessment of sepsis. There are two types of CD14: membrane bound CD14 and soluble CD14. Plasma contains soluble CD14 which is generated by membrane bound CD14. Soluble CD14 is broken down by proteases in plasma and the 13 kDa N-terminal fragments make up the soluble CD14 subtype known as PSN [9]. The Toll-like receptor CD14 subtype can recognize a variety of ligands from both gram-positive and gram-negative pathogens including lipids, peptidoglycans and other surface patterns. In this instance, the presentation of gram-negative bacteria's lipopolysaccharide to Toll-like receptors by CD14 is crucial for the activation of the immune system and the generation of cytokines by effector cells. Recently, PSN appears to have a higher sensitivity and specificity than other inflammatory parameters in the diagnosis of sepsis. This biomarker is not only favorable for the diagnosis of sepsis but also for the evaluation of its severity and prognosis [10].

Materials and Methods

Sample Collection and Processing:

A total of 65 severe sepsis patients, between the ages of 13 and 90 years and all hospitalized to the ICU & RCU of Al-Sadeq hospital and Marjan Medical City from January to June 2022, were enrolled in this study. Each patient's body temperature, complete blood count results (CBC), C-reactive protein (CRP), blood culture findings and the site of infection were documented at the time of admission. In this investigation, the patients were divided into culture positive sepsis group (CPS) and culture negative sepsis group (CNS). A healthy control group which involved 25 participants between the ages of 13 to 80 years were also included. A volume of 3mL of blood was withdrawn from both healthy participants and patients who had a history of an abnormal CBC count and a CRP level above 10 mg/L. The blood culture tests were performed by bacteriologist staff in the microbiology unit using the automated VITEK2 device (bioMérieux) for species identification. The cultivating results revealed that there were 25 culture positive patients and 40 culture negative patients. All bacterial isolates (25 species) were distributed between 15 gram-positive bacteria, such as *S. aureus, S. epidermidis, S. pneumonia, K. kristinae,* and 10 gram-negative bacteria, such as *E. coli, K. pneumonia, P. aeruginosa, S. typhi.*

Biomarkers Diagnosis:

Serum samples were used to determine PCT, PSN and PTX3 levels in 25 culture positive sepsis, 40 culture negative sepsis, and 25 control group. CBC and CRP were measured by Z3 CRP (Zybio/China) and ELISA kits supplied by BT-LAB/China for PCT (Cat. No.: E0977Hu), PSN (Cat. No.: E3754Hu) and PTX3 (Cat. No.: E1938Hu). All of them were read by ELX800 reader (BioTek/USA).

Ethical Approval:

The first step was informed consent in which patients agreed to participate in the study and authorized the collection of information and patient's history without any compulsion. The ethical stance received approval from the Babylon Health Directorate. During sample collection and processing, all health and safety precautions were taken.

Statistical Analysis:

Data analysis was performed by SPSS version 26 and GraphPad Softwares.. The outcomes were presented as mean± SD. Independent T-test was used to compare two groups, while one way ANOVA (Duncan test) was used for multiple comparison groups. Additionally, Pearson's correlation test was used to explain the correlation between pro-inflammatory parameter serum levels. P value < 0.05 was considered to denote statistical significance.

Results

During the study period, the 65 patients (33 males and 32 females) who participated in the study had a mean age of 59.60 ± 18.314 years, with a range of 13-90. In addition to that, the 25 healthy controls (12 males and 13 females) had a mean of 56.08 ± 19.925 years, with a range of 13-80. Statistical analysis revealed no significant differences between the ages of patients and controls (P value = 0.40) and no significant differences between the genders (P value = 0.82). When comparing the patients' group to the healthy control group, significant differences were shown regarding major documented parameters (WBC, GRA, LYM, CRP) at P value <0.001 (Table 1).

Table 1: Parameters comparison between patients and control.

Parameters	Groups	N	Mean	Std. Deviation	P value
WBC	patients	65	16.511	4.6542	<0.001
	control	25	7.740	1.6335	
LYM	patients	65	8.546	8.6089	<0.001
	control	25	26.108	3.6466	
GRA	patients	65	87.128	8.8623	<0.001
	control	25	62.656	4.8527	
CRP	patients	65	13.45	4.748	<0.001
	control	25	4.32	1.520	

Serum samples from 90 participants (25 control, 25 culture positive, and 40 culture negative sepsis) were subjected to ELISA analysis (sandwich method) for the three selected sepsis biomarkers (PTX3, PSN, and PCT) (Figures 1,2 and 3).

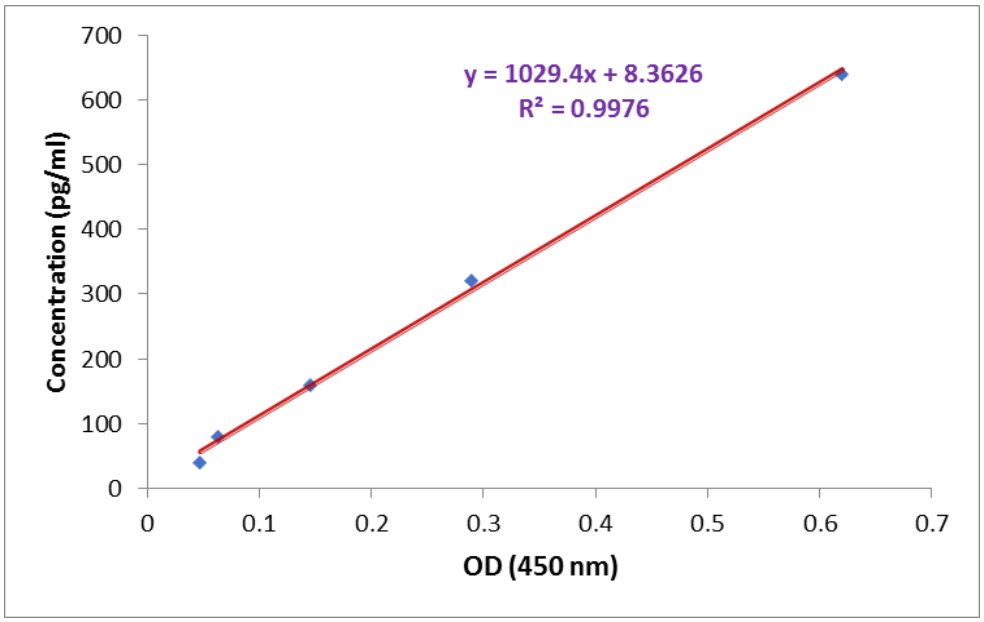

Figure 1: Standard curve for human presepsin in ELISA.

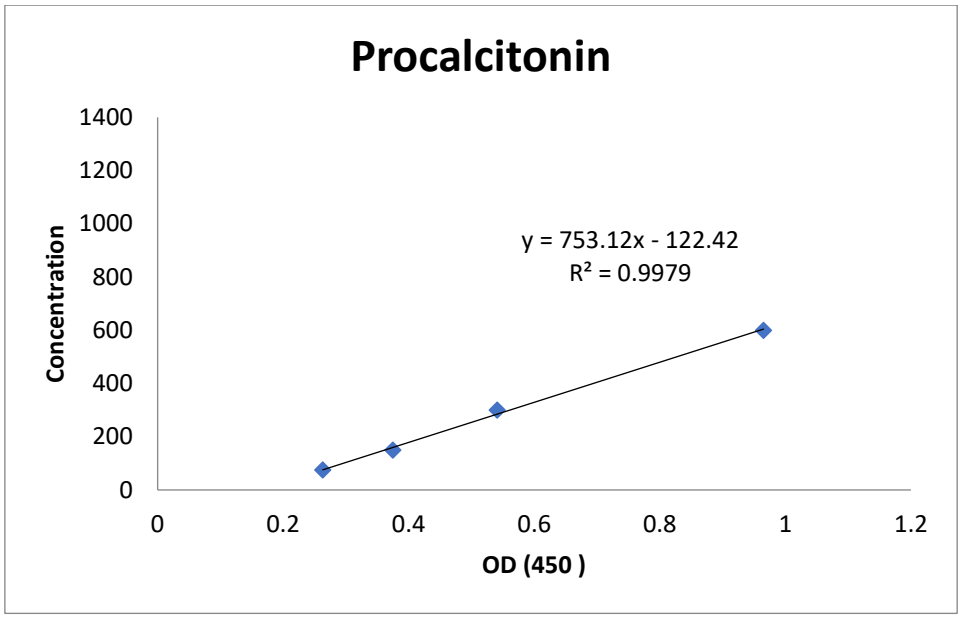

Figure 2: Standard curve for human procalcitonin.

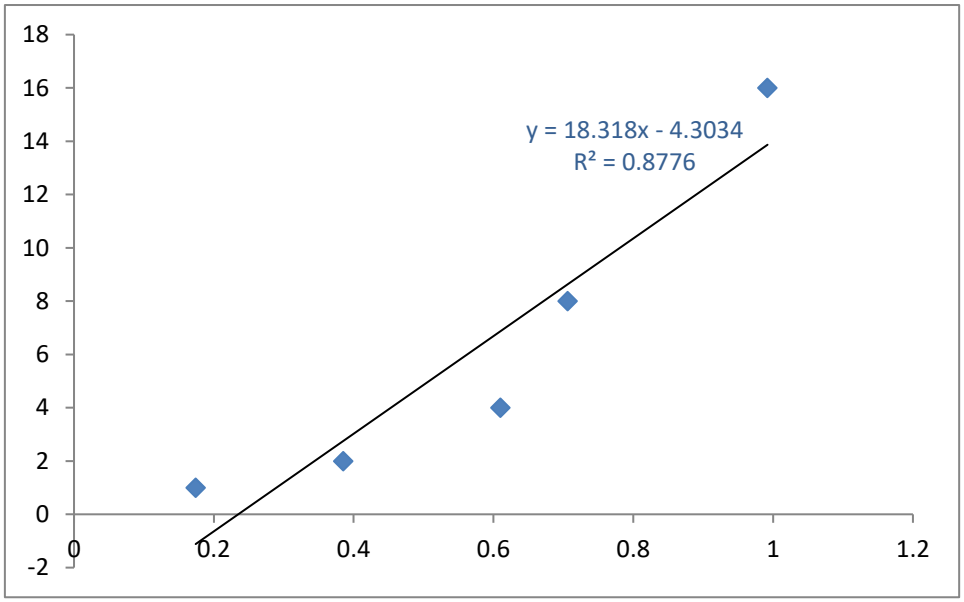

Figure 3: Standard curve for human pentraxin 3.

The control group had a low concentration of PCT 102.07 pg/ml compared to PCT in culture positive sepsis group 134.97 pg/ml and culture negative sepsis group 155.27 pg/ml. Significant differences between control and patients regarding PCT were detected ($P< 0.001$). No significant differences were observed among patients in PCT concentration between culture positive group 134.97 pg/ml and culture negative group 155.27 pg/ml was observed ($P> 0.05$) (Table 2).

Table 2: Comparison of PTX3, PSN, and PCT among different groups (Duncan test)

Parameters	Groups	Mean pg/ml	Duncan test Sig.	P value
Pentraxin	Healthy control	5.93	a	0.56
	Culture positive	5.98	a	
	Culture negative	6.81	a	
Presepsin	Healthy control	199.26	b	<0.001
	Culture positive	274.09	a	
	Culture negative	310.84	a	
Procalcitonin	Healthy control	102.07	b	<0.001
	Culture positive	134.97	a	
	Culture negative	155.27	a	

PSN decreased significantly in control group (199.26 pg/ml) compared to both culture positive sepsis (274.09 pg/ml) and culture negative sepsis (310.84 pg/ml) (P< 0.001). No significant differences were observed between culture positive sepsis and culture negative sepsis among patients (P> 0.05). There were no significant differences in the PTX3 concentration among control (5.93 pg/ml) and both culture positive sepsis (5.98 pg/ml) and culture negative sepsis (6.81 pg/ml) (P= 0.56) (Table 2).

The results of the correlation test revealed significant strong positive correlation between PSN and PCT (r = 0.500; P <0.001) that means when PSN is increased, the PCT also increases significantly. PTX3 showed positive correlation with both PCN (r= 0.24; P= 0.03) and PCL (r= 0.26; P= 0.012) (Table 3).

Table 3: Correlation between Pentraxin 3, Presepsin, and Procalcitonin.

Parameters		Pentraxin	Presepsin	Procalcitonin
Pentraxin	Correlation Coefficient		0.246*	.265*
	Sig. (2-tailed)		0.03	0.012
Presepsin	Correlation Coefficient	0.246*		.500**
	Sig. (2-tailed)	0.03		0.001
Procalcitonin	Correlation Coefficient	.265*	.500**	
	Sig. (2-tailed)	0.012	0.001	

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

The current study showed no significant differences between gender and each age, pentraxin, presepsin, and procalcitonin. The P value for these parameters were 0.43, 0.31, 0.70, and 0.33 respectively. (Table 4)

Table 4: Distribution of variables among genders

Variables	Gender	N	Mean	Std. D	P value
Ages (years)	Female	32	60.06	20.26	0.43
	Male	33	56.27	18.30	
Pentraxin	Female	32	7.21	7.52	0.31
	Male	33	5.79	2.91	
Presepsin	Female	32	307.28	273.59	0.70
	Male	33	286.44	153.90	
Procalcitonin	Female	32	166.44	217.82	0.33
	Male	33	129.05	41.87	

In this study, different age groups showed no significant differences among pentraxin (0.26), presepsin (P= 0.28) and procalcitonin (P= 0.63) (Table 5).

Table 5: Distribution of investigated parameters among age groups

Variables	Age Groups (Years)	N	Mean	Std. Deviation	P value
Pentraxin	13- 38	12	5.80	3.46	0.26
	39- 64	22	5.19	1.48	
	65- 90	31	7.67	7.73	
Presepsin	13- 38	12	304.28	218.20	0.28
	39- 64	22	245.12	47.83	
	65- 90	31	330.37	283.98	
Procalcitonin	13- 38	12	141.80	43.17	0.63
	39- 64	22	124.33	34.33	
	65- 90	31	166.07	222.22	

Discussion

Sepsis is a complicated inflammatory response that is a major cause of morbidity and mortality worldwide [11]. Despite the fact that it is generally under-recognized. One person dies from sepsis infection every three to four seconds since there are an estimated 19 million cases in the world each year [12, 13]. Mortality rates for septic patients have decreased from about 37% to 30% in many clinics that have started to implement the Surviving Sepsis Campaign's recommendations. Nevertheless, this is still an unacceptable level [14]. Hence, to reduce death rates, it is essential to identify patients who are more likely to die from sepsis to allow for earlier and more suitable therapies. Although several risk factors are implicated in sepsis manifestations, the main causative agent is an infectious pathogen such as bacterial infections (*S. aureus* and *K. pneumonia*)

The laboratory identification of septic patients using blood cultures is one of the easiest and most often used investigation to identify the source of bloodstream infections. Blood cultures may give false negative results, particularly when the patients have already taken antibacterial drugs. Moreover, the most difficult part of the interpretation is determining whether the isolating organism from a blood culture is a contaminant (false positive) or a pathogenic bacterium that causes infections [15].

Another routine screening test includes the complete blood count (CBC). Among all the sepsis parameters under investigation, CBC values might be extremely useful since it is simple to carry out, accessible in all healthcare facilities, and the first-line laboratory test that is most frequently ordered in all clinical settings [16]. The WBCs count and their types (Lymphocyte and Granulocytes) are included in the CBC result and can be reported either as an absolute value or as a percentage. The abnormal WBC value indicates the presence of acute inflammation caused by unidentified causative agents. While the relative value is useful for determining which WBC population is primarily involved in the inflammatory process, thus providing an etiological diagnosis. Lymphocytes and granulocytes respond to microbial infection and their responsiveness is characterized by an increase in granulocytes and a decrease lymphocytes percentage. Hohlstein *et al*. [17] suggested that the decreased lymphocytes (lymphocytopenia) at an intensive care unit (ICU) admission are associated with increased mortality rates. However, the granulocyte count significantly increases during infection which is typically correlated with the severity of the infection.

The ability to diagnose sepsis from CBC alone is limited. For further progress in our investigations, CRP was documented as another diagnostic parameter. Positive CRP responses indicate the presence of infection and inflammation [4]. Although it is used to screen for early sepsis, CRP has low specificity in the case of bacterial sepsis detection. Statistically analysis of the results reveals that there is a significant difference between a healthy control group and hospitalized patients regarding to CBC and CRP results ($P < 0.001$) (Table 1). This conclusion proves the vital role of CBC and CRP estimation along with blood culture to detect bacterial sepsis. The pathogenesis of sepsis is progressive across the course of infection and each stage has its own biomarkers. As a result, different biomarkers must be used to detect and monitor the course of sepsis [18]. While no single sepsis biomarker is perfect, many are useful in identifying severely ill patients who require monitoring so that the condition can be detected and treated. In this research, some sepsis biomarkers such as PCT, PTX3, and PSN were used to identify their relatedness to develop the signs of septic patients.

Procalcitonin (PCT) is considered a sepsis biomarker. Different cells in various organs may generate PCT, raising the serum PCT value, which occurs when the human immune system is stimulated by an inflammatory response, particularly a bacterial infection [19, 20]. Since CRP level is associated with bacterial, viral and other non-infectious diseases, PCT was identified to be more effective and more specific than CRP for bacterial infection. Several studies have shown that it may be useful in predicting blood culture findings in patients suffering from severe sepsis [21]. In this study, PCT levels increased significantly in both CPS and CNS patients, in contrast to the low levels in the control group (Table 2). Elevated PCT levels in both the CPS and the CNS may help to primarily identify the causative agents of sepsis in uncultivated blood samples. Despite the fact that it refers to the significance of the PCT levels for primary detection of sepsis, keep in mind that more than one marker must be used to achieve accepted results for such infection.

Recently, presepsin (PSN) was discovered as a novel indicator whose value was used in the diagnosis and management of sepsis [22]. In a recent meta-analysis, Kondo *et al*. [23] discovered that PSN had even higher diagnostic accuracies than procalcitonin for identifying mixed-pathogen sepsis in critically sick adult patients. As with PCT, PSN is mainly used for early detection of a possible bacterial infection and to predict the risk of death due to its level gradually increasing with the progression of a sepsis episode [23]. In the current study, the mean levels of the PSN in both the CPS and CNS groups were considerably higher than in the control group (Table 2). According to this finding, there is an agreement between the current and

several previous investigations regarding the elevation of PSN levels in septic patients. The ambiguity of the sepsis events and their causative agents has led the researchers to exert more effort to find new biomarkers that could improve the diagnostic methodologies.

Pentraxin 3 (PTX3) is a new protein employed as a diagnostic marker for bacterial-originated sepsis. It is an acute phase protein that is produced by innate immune cells [24]. The results of our study showed no significant differences among the three groups (CPS, CNS and control) in terms of PTX3 concentrations which means PTX3 has no important role in the bacterial sepsis detection. However, further research is needed to prove the specificity of PTX3 in the diagnosis of bacterial sepsis.

Conclusion

The increasing PCT and PSN levels in hospitalized patients during the course of infection and inflammation, along with documented parameters (CBC, CRP) and blood culture results, indicate the critical importance of these biomarkers in correct and timely diagnosis. Furthermore, according to our findings, PSN appeared more valuable than PCT and, hence, may be considered a promising biomarker for this purpose.

Conflict of Interests

The authors declare that there was no competing interest.

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