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Original Research

Pentraxin 3 (PTX3) as a Predictor of Severity of Sepsis in Patients Admitted to an Intensive Care Unit

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ABSTRACT

Introduction – In the medical intensive care unit, sepsis is a prevalent clinical syndrome in critically ill patients. Numerous biomarkers and grading schemes are developed to identify adverse outcomes in sepsis patients. The purpose of this research is to determine if pentraxin 3 (PTX3) is a reliable predictor of sepsis in critically sick patients who have been hospitalized to intensive care units.

Material and methods- The present cross-sectional study was conducted at a tertiary care centre among 100 patients of sepsis for a period of one year. A standardized and verified checklist was used to capture socio-demographic characteristics and baseline investigations. SOFA and APACHE-II scores were calculated. Lactate and PCT were also calculated .Results were analyzed using SPSS version 26.0

Results – The mean age of patients was 49.89 years. Out of 100 patients 60% were male and 40% were female. Hypertension was found in 15 and diabetes in 13 patients. The mean value of Pentraxin 3 (ng/ml) was 5.25±3.13. The mean value of SOFA score was 8.98±2.64 and of APACHE II score was 15.89±5.02. The findings show a significant positive correlation of PXT3 with the fraction of inspired oxygen (FiO2), partial pressure of carbon dioxide (PCO2), lactate, PCT, and blood urea. Further, the PXT3 level reported a significant positive relationship with the SOFA score (r = 0.745) and APACHE-II scores (r = 0.345).

Conclusion – The severity of sepsis as determined by the SOFA score and other markers such as lactate, procalcitonin, and APACHE-II was found to be correlated with PTX3.

Keywords – Biomarker, Intensive Care Unit, Pentraxin, Sepsis

INTRODUCTION

Sepsis is a prevalent clinical phenomenon resulting from widespread infection in the body, which frequently results in death for very unwell patients. The definition provided by the Global Sepsis Alliance characterizes sepsis as a state in which the body's response to infection becomes disordered, leading to life-threatening malfunction of the organs. It has been a major factor leading to the admission of patients to intensive care units around the world. Sepsis arises from the intricate interplay between the host immune system and invading viruses and bacteria [1]. Sepsis has a substantial fatality rate worldwide, surpassing the combined mortality rates of breast and lung cancer. Moreover, the absence of targeted therapy for sepsis leads to an increased occurrence of many consequences, such as septic shock, multiple organ dysfunction syndrome, and ultimately, death. Sepsis is most frequently fatal in patients due to multiorgan failure and septic shock [2].

Sepsis diagnosis is challenging for healthcare workers due to factors such as organ support, malfunction, pre-admission treatment, and absence of a "gold standard" test. Numerous scoring systems, such as SOFA (Sequential Organ Failure Assessment) and APACHE-II (Acute Physiology and Chronic Health Evaluation II), have been developed to predict organ dysfunction risk in patients with proven or suspected infection [3-5]. Numerous biomarkers have been developed for predicting risk in critically ill individuals. [6]

Pentraxin-3 (PTX3) is a member of the long-chain pentameric protein superfamily and is classified as an acute-phase protein. As a crucial element of the human innate immune system, it plays a vital role in the regulation of inflammation. It could be released by several cell types, such as neutrophils, monocytes, and vascular endothelial cells in response to diverse stimuli.[7] PTX3 has recently gained recognition as a promising biomarker for sepsis along with other biomarkers (such as Interleukin-6 (IL-6), PCT, troponin T, monocyte chemoattractant protein 1

(MCP), proadrenomedullin (proADM), or angiopoietin (Ang) 1/2)) [8]. Studies have shown that the concentration of PTX3 is increased in individuals suffering from sepsis.

The use of PTX3 as a biomarker for sepsis, and its diagnostic effectiveness in a tertiary care setting, would assist in assessing the potential for future applications in sepsis patients. Several research in the Indian subcontinent have highlighted the need of evaluating the diagnostic effectiveness of PTX3 in sepsis patients. However, none of these studies are considered to be the best available evidence. Consequently, the present study was conducted to establish a connection between serum PTX3 levels and the intensity of sepsis.

MATERIAL AND METHODS

The present cross-sectional study was conducted at a tertiary care centre among patients of sepsis for a period of one year. Ethical clearance was taken from institutional ethics committee before commencement of study. Patients were asked to sign an informed consent form after explaining them the complete procedure of study.

Through convenience sampling method a total sample size of 100 patients was taken. Patients were selected on the basis of inclusion and exclusion criteria. The patients fulfilling the Surviving Sepsis Campaign guidelines and willing to write consent were included in the study. Patients who were on steroid therapy, diagnosed with immunodeficiency disorders, pregnant, and diagnosed with tuberculosis and acute coronary artery disease were excluded from the study.

A standardized and verified checklist was used to capture socio-demographic characteristics and baseline investigations. SOFA and APACHE-II scores were calculated. PCT was determined by chemiluminescence and lactate by arterial blood sample using a blood gas analyzer. EDTA and plain vials were used to collect blood samples. All blood samples were centrifuged. Plasma and serum were aliquoted. The aliquoted samples were kept at -80°C until analysis. Sandwich ELISA was used to analyze pentraxin per manufacturer instructions after getting a good standard curve.

The Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY) was used to analyze the data after they were converted to a Microsoft Excel sheet characterize the patients, the following metrics were used: frequency, percentage, means, and standard deviation (SD). Proportions were used to represent categorical variables. When reporting continuous or discrete data, means and SD were used. PTX3 and other continuous variables were correlated using the Spearman correlation coefficient, taking into account the non-normal distribution of the variables. To compare the distribution of mean PTX3 levels with genders, the Mann-Whitney U test was employed. Multivariate regression analysis was done to see if PTX3 is a predictor of sepsis severity. Every test statistic was calculated at the two-tailed $p < 0.05$ level.

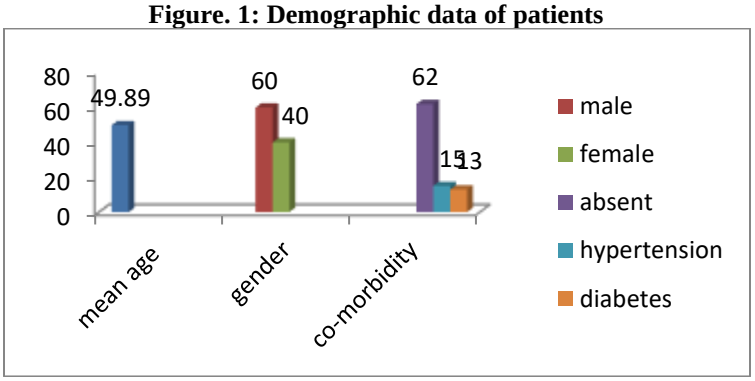
RESULTS

The mean age of patients was 49.89 years. Out of 100 patients 60% were male and 40% were female. Co-morbidities was absent in 62 patients while hypertension was found in 15 and diabetes in 13 patients as shown in table 1, figure 1.

Table: 1 Demographic data of patients

Variable		N/Mean±SD
Age (years)		49.89±5.8
Gender	Male	60
	Female	40
Co-morbidity	Absent	62
	Hypertension	15
	Diabetes	13
	Other	10

Figure. 1: Demographic data of patients



The mean value of Pentraxin 3 (ng/ml) was 5.25±3.13. The mean value of SOFA score was 8.98±2.64 and of APACHE II score was 15.89±5.02. Other values of laboratory parameters are shown in table 2.

Table: 2 Laboratory parameters of patients

Laboratory parameters	Mean±SD
Pentraxin 3	5.25±3.13
pH	7.6±0.11
FiO2	44.78±17.90
PaO2	83.45±18.9
PCO2	39.04±11.34
HCO3	21.39±5.98
Lactate	1.98±1.0
PCT	9.80±5.7
HR	118.2±13.4
RR	26.57±5.12
TLC	17890.15±11679.3
Platelets	123098.24±120876.1
Urea	68.34±39.8
Creatinine	2.03±2.28
Total bilirubin	1.89±2.3
SGOT	87.90±100.23
SGPT	78.34±108.2
INR	1.69±1.02
SOFA score	8.98±2.64
APACHE-II	15.89±5.02

The findings show a significant positive correlation of PXT3 with the fraction of inspired oxygen (FiO2), partial pressure of carbon dioxide (PCO2), lactate, PCT, and blood urea. Further, the PXT3 level reported a significant positive relationship with the SOFA score (r = 0.745) and APACHE-II scores (r = 0.345) as shown in table 3.

Table: 3 Correlation of different parameters with PTX3

Parameters	r	P value
Age	0.156	0.167
Mean BP	-0.066	0.523
pH	-0.223	0.031
FiO2	0.268	0.004
PaO2	-0.435	<0.001
PCO2	0.265	0.004
HCO3	0.031	0.789
Lactate	0.789	<0.001
PCT	0.853	<0.001
HR	-0.023	0.891

RR	0.098	0.342
TLC	0.115	0.265
Platelets	-0.154	0.134
Urea	0.256	0.039
Creatinine	0.187	0.056
Total bilirubin	0.188	0.055
SGOT	-0.006	0.876
SGPT	0.096	0.342
INR	0.115	0.268
SOFA score	0.745	<0.001
APACHE-II	0.345	<0.001

Multivariate linear regression analysis was used to combine the cumulative effect of significant variables of simple linear regression. Findings reported that lactate ($p < 0.001$), PCT ($p < 0.001$), and SOFA score ($p = 0.001$) significantly predict the change in PXT3 level as shown in Table 4.

Table: 4 Predictors of pentraxin 3

Variable	B	Std . error	beta	P value
Constant	-45.567	18.567		0.023
FiO2	0.014	0.008	0.067	0.209
PaO2	-0.003	0.007	-0.011	0.817
PCO2	0.0014	0.012	0.048	0.310
Lactate	1.569	0.213	0.416	<0.001
pH	5.469	2.598	0.108	0.034
Pro- cal	0.209	0.037	0.389	<0.001
SOFA	0.278	0.088	0.234	0.001
APACHE-II	-0.008	0.037	-0.015	0.796
B urea	0.002	0.004	0.018	0.675

DISCUSSION

Sepsis is a significant contributor to global mortality, particularly in poor nations like India, due to the absence of standardized care and limited resources. It continues to be the primary factor leading to death in critically ill individuals. Prior research has shown that promptly recognizing and implementing treatment protocols for severe sepsis can enhance the chances of patient survival. Recently, several new biomarkers, such as PTX3, C-reactive protein (CRP), PCT, and plasma PTX3, have been discovered for the early detection and treatment planning of sepsis. Nevertheless, each individual biomarker has its own limitations and is not fully effective in diagnosing severely ill patients. This study examined the PTX3 levels in critically ill patients with sepsis and investigated its relationship with lactate, PCT, and critical illness indicators such as the SOFA score and APACHE-II score. [9,10]

The mean age of participants was 49.89±5.8 years with a predominantly male population. Maximum patients does not have any comorbidity, other have hypertension and diabetes. These findings were in line with most of the trials, including those by Chatterjee et al.[11]. Of 100 participants, only 65 had positive cultural results. Most of them had gram-negative bacteria in their culture, which included Acinetobacter, Pseudomonas, and Klebsiella species.

The relevant laboratory parameters were measured, and the SOFA score and APACHE-II score were calculated. We analyzed the relationship between PTX3 and various laboratory parameters. We observed that blood pH and PaO2 have a negative correlation with PTX3, whereas FiO2, PCO2, lactate, PCT, and blood urea had a positive correlation with PTX3. The primary objective of the study was to analyze PTX3 levels and see the correlation with SOFA scores. The study findings reported that lactate and PCT show a significant correlation with PTX3 in the studied cohort. These findings are in accord with several previously published studies that reported a significant relationship of PTX3 with lactate and PCT [12,13]. Hamed *et al* [14] found that patients with sepsis and septic shock had higher PTX3 levels than the control group in a study including 213 adult patients diagnosed with sepsis and septic shock. They reported that the ≥5 ng/ml cut-off point was significant for the diagnosis of sepsis and the ≥9 ng/ml cut-off point was significant for the diagnosis of septic shock. In a similar study on patients with sepsis, Kim *et al* found that the PTX3 level was 201.4 ng/mL in patients who died and 36.5 ng/mL in surviving patients ($P = 0.008$). They reported that the level of PTX3 measured during the admission of severe sepsis patients who underwent successful early targeted treatment was a strong predictor of 28-day mortality.[15]

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) recommended measuring lactate levels for septic shock [16]. It has been suggested that serum lactate levels can be used to screen for sepsis among adults with clinical suspicion of sepsis. Several studies were conducted to assess the use of lactate in this context [17,18]. We have also included lactate in our study, in which lactate was found to correlate with SOFA score, which is similar to the study done by Liu et al. in 2019 [12]. In our study, we have also found that PTX3 is positively correlated with lactate ($p = 0.000$). This is in line with a previous prospective study done by Hu et al. [10]. However, serum lactate alone is neither sensitive nor specific to rule in or rule out the diagnosis of sepsis on its own. The testing of lactate may not be available in resourcelimited settings [19]. Hence, it was given as a weak recommendation to use lactate levels in serum as an adjunctive test to detect the probability of sepsis in patients with suspected but not confirmed sepsis. A large observational study demonstrated that PTX3 levels higher than 6.4 ng/mL of non-hospitalized individuals were remarkably linked with higher mortality, independently of hospitalization causes.[20] Thus, PTX3 may be an independent predictor of bad outcomes in sepsis. Notably, in most of these studies, healthy volunteers or relatively mild patients were enrolled as controls.

PCT fulfills the need for high diagnostic accuracy in detecting sepsis, which is needed to be used as a biomarker, especially in comparison to conventional. PCT alone cannot identify specific pathogens of sepsis, but the level of PCT might be useful to estimate the probability of severe bacterial infection [21]. We measured the level of PCT of all the participants, and it was found to correlate with the SOFA score. A prospective study done by Sudhir et al. depicted that there was a significant association between PCT and SOFA score [22]. But in a retrospective cohort study done by Yunus et al., there was a weak correlation between PCT and SOFA score [23]. In our study, PTX3 has a significant positive correlation with PCT which is similar to the previous study [24].

APACHE-II score is one of the scoring systems used to determine the severity of disease and predict the mortality of sepsis patients. Hill et al., in a pilot study, found that PTX3 levels were increased in patients with sepsis and are related to APACHE-II scores when plotted according to the APACHE-II score quartile [25]. Our study found that PTX3 levels are correlating significantly with the APACHE-II score ($p = 0.00$).

We did multistep-wise forward linear regression analysis and interestingly we found that the best individual marker to predict PTX3 is PCT. The predictability increased with PCT and lactate together . The predictability of PTX3 is further increased with PCT, lactate, and SOFA scores together significantly. The efficacy of PTX3 as a biomarker tool in sepsis has been demonstrated in the work of many studies.[26,27] PTX3, in combination with established other markers, might improve the correlation with sepsis severity and needs to be studied.

This is a single-center study, and we have not included the mortality data; hence, an association between PTX3 and mortality cannot be established. In this survey, we measured PTX3 once, which may not be sufficient to conclude, and the authors recommend a longitudinal large-scale study to understand the exact role of PTX3 in sepsis development and other health consequences.

CONCLUSION

Presently, the precision of several biomarkers in sepsis and septic shock and their association with severity has resulted in contradictory findings, with numerous studies presenting divergent outcomes. In this work, we examined and analyzed PTX3 in accordance with the most recent Sepsis-3 recommendations. We discovered that PTX3 is closely associated with the severity of sepsis, as shown by the SOFA score, as well as other markers such as lactate, PCT, and the APACHE-II score. The study examined the relationship between PTX3 levels and PCT and lactate, which are well-established indicators in sepsis, unlike newer markers. In the future, using novel biomarkers like PTX3 along with lactate, PCT, and SOFA score could be beneficial in enhancing the assessment of risk for patients with sepsis.

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