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"SERUM PROCALCITONIN VERSUS CRP LEVELS AS EARLY DIAGNOSTIC MARKERS OF SEPSIS IN CANCER PATIENTS WITH FEBRILE NEUTROPENIA"

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ABSTRACT

Objective: Procalcitonin as a predictive factor and a diagnostic marker for the diagnosis of sepsis in febrile neutropenic patients in comparison to CRP.

Material &Methods: This study was conducted in Medical Oncology department, SVIMS from May 2018 to December 2019. Patients were divided in to two groups based on presence or absence of sepsis. Baseline characteristics and MASCC score were noted. PCT value >0.25ng/ml was taken as positive. CRP value > 6 mg/dl in serum was taken as positive.

Statistical Analysis: Differences between the groups were tested for statistical significance using Independent Student's t-test & Fischer's exact test for continuous and categorical data respectively .Pearson correlation test was performed to find out the relationship between MASCC score, CRP and Procalcitonin. Receiver Operator Characteristic (ROC) curve analysis was performed to find out the Sensitivity, Specificity, PPV and NPV.

Results: Mean CRP in sepsis vs non sepsis is 129.69±11.64 vs 85.73±11.22 (p=<0.05).Mean PCT in sepsis vs non sepsis is 22.20±5.18 vs 3.53±2.53 (p=<0.05).ROC curve analysis suggestive of PCT had more sensitivity (81.4%vs67.4%) and specificity when compared to CRP (90.0%vs67.5%). On correlation MASCC score was significantly negatively correlated with PCT (r = -0.594, p=<0.0001).

Conclusions: Procalcitonin has more sensitivity and specificity in diagnosing sepsis in FN patients.

KEYWORDS : Sepsis, Procalcitonin, C-reactive protein, febrile neutropenia, MASCC score

INTRODUCTION:

Febrile neutropenia (FN) is a common complication related to chemotherapy in cancer patients. The early diagnosis of bacterial infection among patients with FN is challenging. Few clinical signs such as fever, headache, and hypotension may indicate bacterial infections in many cases of FN (1) and the focus of infection is uncertain. For the diagnosis of bacteraemia, even though blood cultures are the gold standard for the diagnosis of bacteraemia (2), obtaining and testing cultures are time-consuming and their results are not available immediately. Therefore, a predictive tool to diagnose bacterial infections in FN is crucial for early diagnosis. Many authors suggested interleukin-6, C-reactive protein (CRP), and Procalcitonin (PCT) as predictive biomarkers to diagnose bacterial infections.CRP is an acute-phase protein. Procalcitonin (PCT) is produced by thyroid C cells and converted to calcitonin before being released into the bloodstream. PCT rises within 3 hours after the onset of symptoms to a level which can be measured. PCT concentrations were below the detection limit in healthy individuals but levels increased with increasing severity of the bacterial infection. Febrile neutropenia patients were classified as low risk, and high risk based on the Multinational Association for Supportive Care in Cancer (MASCC) score(3) . The MASCC risk index is a valuable part of the selection of patients who can safely be treated at home. MASCC score needs to be correlated with a biomarker like procalcitonin or CRP in order to increase the specificity and sensitivity of the scoring system. The utility of PCT has been demonstrated in recent studies, and as there is a need of early detection of infection in febrile neutropenic patients. This study aimed to determine the role of Serum Procalcitonin as early diagnostic marker of sepsis in comparison to CRP in cancer patients with febrile neutropenia.

MATERIALAND METHODS:

This was a prospective observational study conducted on patients presenting to Medical Oncology department SVIMS from May 2018 to December 2019. All cancer patients (both solid and haematological) with chemotherapy-induced febrile neutropenia between the ages of 4 to 70 years with febrile neutropenia and not received prior antibiotic therapy at initial presentation were included. Patients with neutropenia unrelated to chemotherapy, afebrile neutropenia and medullary carcinoma of thyroid were excluded. Recruitment of patients was started after getting approval from the institutional Ethics Committee. A written informed consent was taken from all patients. Patients who have a single oral temperature of > 38.3^{0}C (101^{0}F) or temperature >38^{0}C (100.4^{0}F) for one hour with an absolute neutrophil count of < 500 cells/mm^3 or expected to fall below 500/mm^3 within 48 hours were considered as having FN. Blood samples were collected for analysing haemoglobin level, white blood cell count, platelet count, absolute neutrophilic count, CRP, PCT, culture and sensitivity. Patients were divided in to two groups based on presence or absence of sepsis after the diagnosis of febrile neutropenia. Patients with sepsis (documented sepsis by culture or clinical sepsis with symptoms like tachycardia, tachypnea, and hypotension) were allotted to group 1; Patients with no sepsis (fever, neutropenia with sterile blood cultures, and no signs of clinical sepsis) were allotted to group 2. Sepsis presence was proven by blood culture or clinical sepsis with fever, tachycardia, tachypnea and hypotension. Baseline characteristics including age, sex, malignancy, chemotherapy received, degree of neutropenia, vital signs (pulse rate, temperature, respiratory rate, oxygen saturation, blood pressure) and MASCC score were noted.PCT value >0.25ng/ml was taken as positive**.** PCT was measured by sandwich immunodetection method. CRP value >6 mg/dl in serum was taken as positive and measurement was done by nephelometric methodology (passive agglutination).

Statistical Analysis:

Data was analysed using SPSS version 25.0 (IBM SPSS, Armonk, NY, USA) and expressed as mean±SE (variables with normal distribution) or mean±SE (variables without normal distribution) and frequencies with percentages for continuous and categorical variables respectively. Differences observed between the groups were tested for statistical significance using Independent Student's t-test & Fischer's exact test for continuous and categorical data respectively. Pearson correlation test was performed to find out the relationship between MASCC score, CRP and Procalcitonin. Receiver Operating Characteristic (ROC) curve analysis was performed to measure the accuracy of CRP and Procalcitonin in predicting sepsis among cancer patients. With ROC curve analysis we have measured cut-off point, sensitivity (True positive), specificity (True negative), negative predictive value (PPV) and positive predictive value (NPV) for both CRP and Procalcitonin in differentiating between sepsis and non-sepsis groups. The cut-off values for both the parameters CRP and Procalcitonin were taken from the Youden index. A p-value ≤0.05 (probability value) was considered as significant.

RESULTS:

The present study enrolled a total of 83 cases of Febrile Neutropenia. The mean age of the study population was 27.59±1.82 years. Majority of cases were male gender. The frequency of FN was highest in AML patients followed by ALL patients. Mean CRP in sepsis vs non sepsis is 129.69±11.64 vs 85.73±11.22 (p=<0.05).Mean PCT in sepsis vs non sepsis is 22.20±5.18 vs 3.53±2.53 (p=<0.05).Sepsis (both clinical and documented sepsis) was found in 51.8% cases (n=43).Blood culture

was positive in 36.1% (n=30) of the cases of which majority were positive with gram negative organisms. MASCC high risk was statistically significant in cases with sepsis. Both CRP and PCT were high in sepsis cases when compared to non sepsis cases with significant p value. ROC curve analysis suggestive of PCT had more sensitivity (81.4%vs67.4%) and specificity when compared to CRP (90.0%vs67.5%) (Figure 1) .On correlation MASCC score was significantly negatively correlated with PCT (r = -0.594, p=<0.0001) and it indicates patients with low MASCC score < 21 (high risk) were having high PCT values.CRP was not correlated with the MASCC score (r = -0.114,p=0.305) (Figure 2).

DISCUSSION:

Febrile neutropenia is one of main complications of chemotherapy and is considered as oncological emergencies. Identifying the causative agent for treatment may take time and may cause delay in the initiation of treatment. Hence we require markers that help in early diagnosis.

Patient Characteristics:

The mean age of the study population was 27±1.82 years which is similar to study done by Andre et al, Roy et al (4). Majority of patients in the current study were male (n=55, 66.3% vs 33.7%). Among the 83 cases, 68 cases were diagnosed with haematolymphoid malignancies and remaining 15 cases were diagnosed with solid malignancy group (81.9% vs 18.1%). More than half of the cases were leukemia (74.7%), with highest frequency in AML cases (49.4%) followed by ALL (25.3%).This is similar to studies done by Heinz Ludwig et al and Mahmouds-Ahwal et al (5). This is also evident by studies done by Klastersky J et al, Lyman GH et al. (6)

Sepsis, PCT and CRP:

Sepsis was seen in 51.8 %(n=43) of FN cases. Blood culture positivity was found in 30 FN cases (36.1%) in which 24 were gram-negative (n=28.9%), 6 were gram-positive (7.2%).Urine culture was positive in 11 cases with all cases showing gram-negative bacteria. In 1970s the predominant bacteria in FN patients were gram-negative bacteria which were shifted to gram-positive spectrum since mid-1980s. An analysis done by EORTC antimicrobial group, found that the frequency of gram positive organisms increased from 29% to 69 % in the trials conducted between 1973 to 1994(7, 8). In contrast to this, the present study revealed increased frequency of gram-negative bacteria in FN patients. This could be related to the microbiological spectrum of our institute. Prakas Kumar mondal et al (9) studied 268 FN cases among them 78 cases showed culture positivity with more than half of the culture positive cases showed gram negative bacteria, which is similar to the present study. This is also evident by studies done by Bodey GP et al, Cometta et al (10, 11, 12, 13, and 14). In the present study the mean CRP and procalcitonin levels in sepsis group are high compared to non sepsis group with significant probability value. However ROC curve analysis revealed PCT (cut off point >0.98) is better in predicting the sepsis than CRP (cut off point >111) in FN patients. The sensitivity, specificity, positive and negative predictive value of PCT was 81.4%, 90%, 89.7% and 81.8% respectively. The sensitivity and specificity, positive and negative predictive value of CRP was 67.4%, 67.5%, 69% and 69.5% respectively. Dae yong et al (15) studied diagnostic accuracy of PCT and CRP in 286 FN patients and reported a higher sensitivity and specificity for PCT when compared with CRP which is similar to the present study. In this study sensitivity and specificity for PCT were 60.5% and 82.3% respectively and for CRP it was 57.8% and 67.3% respectively. Similar observations were noted in a retrospective study done by Mohsen Meidani et al (16). A prospective study done by Purkayastha k et al (17) compared PCT and CRP in 89 febrile neutropenic patients. They reported PCT had more sensitivity (73.3%vs13.3%) as compared to CRP but not specific (29.4%vs77.2%) in predicting sepsis. However, meta analysis done by Tan M et al(18) which included 495 patients with sepsis from nine studies and analyzed the diagnostic accuracy of PCT and CRP and found that the sensitivity and specificity of PCT(85% and 80% respectively) was higher when compared to CRP(80% and 61% respectively). Similar results were observed by Liliana simon et al (19) and Tasnim Arif et al (20) in their respective meta analysis.

MASCC score, CRP and PCT:

In the present study FN cases were classified into low risk (score >21) and high risk (score<21) based on MASCC score. Patients in high risk group had high frequency of sepsis when compared to low risk group. This is similar to the study done by Shin Ahn et al (21).On correlation of PCT and CRP with MASCC score revealed, MASCC high risk patients had significantly higher PCT values (r= -0.594;pvalue <0.0001) whereas correlation with CRP was not statistically significant (r=-0.114;p=0.305). Uys A et al (22) studied multiple biomarkers in FN patients and correlated with MASCC score. Of all the biomarkers PCT had strongest correlation with MASCC score (r−0.51; P<0.0001).

In conclusion, C reactive protein and Procalcitonin are useful biomarkers in detecting sepsis in FN patients. Procalcitonin has more sensitivity and specificity in diagnosing sepsis in FN patients when compared to CRP.MASCC high risk patients showed high frequency of sepsis as well as culture positivity. Gram negative bacteraemia is more common in the present study population. Procalcitonin has better correlation with MASCC score than C-reactive protein.

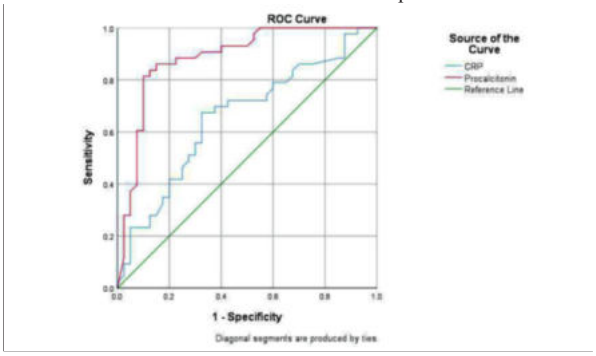

Figure 1: Receiver Operating Characteristic Curve Analysis Of CRP And Procalcitonin

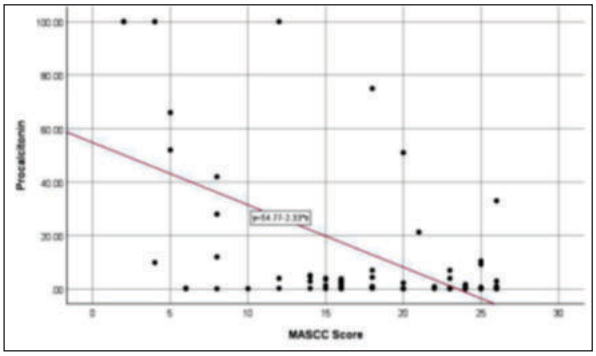

Figure 2: Correlation Between MASCC Score And Procalcitonin

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