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REVIEW ARTICLE

DIAGNOSTIC USEFULNESS OF PROCALCITONIN AND C-REACTIVE PROTEIN IN GRAM NEGATIVE BACTERIAL INFECTIONS.

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Abstract

Any biomarker used to substantiate bacterial infections should aid in the rapid diagnosis, initiation of treatment and during prognosis monitoring. As of now a wide range of biomarkers have been established and more researches are being done in this field. Markers such as ESR, C-Reactive Protein, Procalcitonin and Leucocyte count have been extensively studied for a wide range of bacterial infections. However, studies related to biomarkers, C-Reactive Protein and Procalcitonin have been found to be very useful in early diagnosis, treatment and monitoring the effect of antibiotic treatment, Both the above markers were found to be very useful in the diagnosis of gram negative bacterial infection compared to other type of infections such as by gram positive. Moreover, both these markers are found to be useful in infective fever, meningitis, sepsis, critical care patients, graft acceptance/rejection and in pneumonia. This review article present the various research findings related to the clinical usefulness of these biomarkers in the diagnosis of infections caused by gram negative bacteria.

Introduction:-

Biomarkers are very useful in the diagnosis of various types of infections caused by a wide range of bacteria infections. Many biomarkers such as Erythrocyte Sedimentation Rate (ESR), Complete Blood count (CBC), C-reactive Protein (CRP) , Procalcitonin (PCT), Interlukins (ILS) and many infection specific protein molecules have been identified. Among the various types of infections, Gram negative (G-) bacterial infection have been extensively studied. The aim of this review article is to bring out the research findings done during the past two decades on the diagnostic usefulness of measuring PCT and CRP.

PCT levels can distinguish between infectious and non-infectious systemic inflammatory response. However, there are some differences between G-, G+, and fungal bloodstream infections (BSIs), particularly in different cytokine profiles, severity and mortality. PCT levels were significantly higher in G- compared to other cohorts and CRP concentrations did not differ significantly in groups. Significantly higher PCT levels could differentiate G- sepsis

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from G+ and fungemia. In contrast to CRP, PCT is a good discriminative biomarker in different BSIs[1]. In diagnostic episodes with positive blood Blood Culture (BC) results, a cutoff value of ≥6.47 ng/mL for PCT yielded a sensitivity of 74%, a specificity of 81%, a positive predictive value of 82%, a negative predictive value of 75% and an area under the curve of 0.81 for G-bacteraemia identification.PCT may represent a useful tool for differentiating G+ from G- BSIs with a high significant.[2] Serum PCT levels differ in patients with bacterial or fungal infections and are significantly elevated in patients with G-bacteraemia. An optimal cut-off value of 3.11 ng/mL for PCT in discriminating G- sepsis from fungal sepsis, led to a sensitivity of 63.9% and specificity of 93.3%. Neither PCT nor other inflammatory markers could be used to distinguish between G+ and fungal sepsis. PCT is a potential sensitive biomarker for distinguishing G- sepsis from G+ and fungal sepsis.[3]

PCT can discriminate bacterial from viral systemic infections and true bacteraemia from contaminated BC. Additional results showed a significant difference in median PCT values between Enterobacteriaceae and nonfermentative G- bacteria.[4] An early diagnosis of bacteraemia is crucial to facilitate adequate treatment of severe infections. A PCT level > 2 ng/mL was reported in 71% cases in G-bacteraemia patients, whereas in patients with G+ bacteraemia this level of PCT was reported only in 33%. The analysis of mortality in patients with systemic infection (PCT > 2 ng/mL + bacteraemia) has shown comparable data in groups of patients with G+ and G- bacteraemia.[5] G- and G+ infections have been considered the most important causes of morbidity and mortality in patients with leukopenia following chemotherapy. However, discrimination between bacterial infections and harmless fever episodes is difficult. Classical inflammatory signs of infection are often absent and frequent fever is the only sign of infection. Compared to normal rats, immunosuppressed animals exhibited significantly higher fevers and lesser production of all mediators, except IL-6, after toxin challenge. Moreover, compared to rats that received Manic Depressive Psychosis (MDP), both groups of animals that received an equivalent dose of lipopolysaccharide showed significantly higher fevers and greater increase in serum cytokine levels. Furthermore, in contrast to those in immunocompetent rats, serum levels of IL-6 and Magrophage Inflammatory Protein -2 (MIP-2) were not significantly changed in leukopenic animals after MDP injection. Other serum markers such as PCT and CRP failed to discriminate between bacterial stimuli in both groups of animals. These results suggest that the use of serum markers at an early stage of fever could give useful information for the clinicians for excluding G - from G + infections.[6]

Microbial challenges to the host initiate an array of defense processes through the activation of innate and adaptive immunity. Innate immunity consists of sensors or pattern-recognition receptors (PRRs) that are expressed on immune and non-immune cells and sense conserved pathogen-derived molecules or pathogen-associated molecular patterns (PAMPs) in various compartments of the host cells. Recognition of the PAMPs by PRRs triggers antimicrobial effector responses via the induction of proinflammatory cytokines and type I Interferon (IFNs). Several families of PRRs, such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and DNA sensors and their respective PAMPs have been well studied in innate immunity and host defense.[7] PCT and CRP serve as biomarkers of infection in patients with sepsis/bacteraemia. Patients who were PCT positive were older and more frequently male, had reduced levels of platelets and albumin, and increased levels of aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, and CRP. Patients who were PCT positive had significantly higher BC positivity compared with those who were PCT negative, and the sensitivity and specificity of PCT for detecting positive BCs were 74.5% and 59.1%, respectively. *Escherichia coli* was detected in PCT-positive patients, whereas *Staphylococcus epidermidis* and *Staphylococcus lugdunensis* were frequently detected in PCT-negative patients. Levels of PCT were higher in patients infected with G- rods than those with G +cocci. Furthermore, extended-spectrum β-lactamase (ESBL)-producing bacteria cases showed higher levels of PCT than those of non-ESBL cases. PCT may be a useful biomarker of sepsis, and it might serve as a strong tool to detect patients with severe G- rod bacteraemia including ESBL-producing bacteria cases early due to its relative high sensitivity.[8]

The diagnostic utility of PCT and CRP to discriminate between infective fever and fever due to inflammation was assessed in hemato-oncological patients treated with aggressive chemotherapy. PCT determination may contribute significantly to the management of hemato-oncological patients who experience febrile episodes.[9] The average values of PCT from patients with sputum culture positive and negative were 0.42 and 0.12 ng/mL respectively, and the average values of PCT from patients with BC positive and negative were 9.54 and 0.28 ng/mL respectively. In sputum culture, positive rate of PCT in cases with growth of pathogens was 47.1%. In BC, positive rate of PCT in cases with growth of pathogens was 89.2%. PCT is useful in early diagnosis of respiratory infections and BSIs, but the specificity of PCT in diagnosing respiratory infections is not as high as it is in BSIs.[10]In the ICU, bacteraemia is

a life-threatening infection whose prognosis is highly dependent on early recognition and treatment with appropriate antibiotics. PCT levels have been shown to distinguish between bacteraemia and noninfectious inflammatory states accurately and quickly in critically ill patients. However, we still do not know to what extent the magnitude of PCT elevation at the onset of bacteraemia varies according to the Gram stain result.A high PCT value was found to be independently associated with G-. A PCT level of 16.0 ng/mL yielded an 83.0% positive predictive value and a 74.0% negative predictive value for G-related bacteraemia in the study cohort. In critically ill patients with clinical sepsis, G-bacteraemia could be associated with higher PCT values than those found in G+ bacteraemia, regardless of the severity of the disease.[11]

To compare semi-quantitative PCT with CRP in predicting bacteraemia in haematological patients with neutropenic fever, bacteraemia was observed in 23% and the criteria for severe sepsis were fulfilled in 14%. Half of the bacteraemic episodes were caused by G- bacteria. The kinetics of PCT and CRP were similar, with increasing levels for 2 to 4 days after the onset of fever. The PCT level on days 1, 2, 3 and 4 was associated with bacteraemia and G- bacteraemia, but not with the development of severe sepsis. On day 1, a PCT level above 0.5 ng/mL had a sensitivity of 57% and 70% and specificity of 81% and 77% to predict bacteraemia and G- bacteraemia, respectively.An elevated level of PCT within 24 h after the onset of neutropenic fever predicts bacteraemia and G- bacteraemia in haematological patients.[12]There are a number of limitations to using conventional diagnostic markers for patients with clinical suspicion of infection. As a consequence, unnecessary and prolonged exposure to antimicrobial agents adversely affect patient outcomes, while inappropriate antibiotic therapy increases antibiotic resistance. A growing body of evidence supports the use of PCT to improve diagnosis of bacterial infections and to guide antibiotic therapy. For patients with upper and lower respiratory tract infection, post-operative infections and for severe sepsis patients in the intensive care unit, randomized-controlled trials have shown a benefit of using PCT algorithms to guide decisions about initiation and/or discontinuation of antibiotic therapy. For some other types of infections, observational studies have shown promising first results, but further intervention studies are needed before the use of PCT in clinical routine can be recommended.[13]

Sepsis is a leading cause of mortality in critically ill patients. Delay in diagnosis and initiation of antibiotics have been shown to increase mortality in this cohort. However, differentiating sepsis from non-infectious triggers of the systemic inflammatory response syndrome (SIRS) is difficult, especially in critically ill patients who may have SIRS for other reasons. PCT has emerged as the most studied and promising sepsis biomarker. For diagnostic and prognostic purposes in critical carePCT is a better marker than CRP and other traditional markers of sepsis, but is not accurate enough for clinicians to dispense with clinical judgement. There is stronger evidence, however, that measurement of PCT has a role in reducing the antibiotic exposure of critical care patients. For units intending to incorporate PCT assays into routine clinical practice, the cost-effectiveness of this is likely to depend on the pre-implementation length of an average antibiotic course and the subsequent impact of implementation on emerging antibiotic resistance. In most of the trials to date, the average baseline duration of the antibiotic course was longer than is currently under standard practice in many UK critical care units. Many other biomarkers are currently being investigated. To be highly useful in clinical practice, it may be necessary to combine these with other novel biomarkers and/or traditional markers of sepsis.[14]

High PCT levels are strongly associated with systemic bacterial infections. PCT is produced in response to bacterial endotoxin and inflammatory cytokines. Few studies are available in the literature on PCT ability to distinguish different strains of BSIs in patients with hematologic diseases.[15] PCT as a diagnostic marker for bacteraemia and sepsis has been extensively studied. PCT levels in *Salmonella* infections are near normal or minimally increased which differentiates it from other systemic G- infections. PCT cannot be used as a specific diagnostic marker of typhoid.[16]PCT has proven to be a very sensitive marker of sepsis for non-leucopenic patients. Little is known about its relevance in immunosuppressed and leucopenic adults. Regardless of the leucocyte count, the median PCT level in bacteraemia cases always remained $<0{\cdot}5$ ng/mL. In heavily leucopenic situations, PCT levels were never >2 ng/mL even in the sepsis and severe sepsis/septic shock groups, whereas a WBC count $>1{\cdot}0 \times 10^9$/L resulted in median PCT values of 4·1 ng/mL and 45 ng/mL respectively. The positive predictive value for sepsis (cut-off 2 ng/mL) was 93% in cases of WBC count $>1{\cdot}0 \times 10^9$/L, but only 66% in leucopenic conditions. The negative predictive value (cut-off 0·5 ng/mL) was 90% when the WBC count was $>1{\cdot}0 \times 10^9$/L and 63% in leucopenic conditions. PCT is an excellent sepsis marker with a high positive- and negative-predictive value in patients with WBC count $>1{\cdot}0 \times 10^9$/L, but it does not work satisfactorily below this leucocyte count.[17]

Rejections and viral infections did not interfere with the PCT release.PCT is a reliable predictor with discriminating power for non-viral systemic infections in patients after heart and/or lung transplantation. PCT allows an early differential diagnosis between rejection and bacterial/fungal infection (IF) and thus a rapid and focused therapeutic intervention. It avoids unnecessary antibiotic treatment which could be toxic for the graft itself in patients with rejection only. PCT provides vital information early to clinicians and allows them to improve the management of bacterial/fungal infections in immunocompromized transplant patients. PCT thus facilitates and improves the outcome of survival rate and the quality of life in the postoperative period of patients with heart and/or lung grafts.[18]

The mean levels for PCT was higher in bacterial meningitisthan in viral meningitis. As a predictor of bacteraemia in bacterial meningitis, only PCT delivered a significantdifference. A cutoff of ≥1.1ng/mLachieved 94.6% sensitivity, 72.4% specificity, NPV of 95.4%, and PPV of 69.2%; the AUC was 0.965. PCT has a highdiagnosticpowerforacute meningitis in emergency department patients. PCT out performs CRP in the detection of bacterialaetiology and is a good predictor of bacteraemia in bacterial meningitis.[19] PCT level showed significant association with septic shock, positive BC and mental dysfunction. The high level of PCT can differentiate septic shock from SIRS and other stages of infection. Dysfunction of mental status and high level of PCT can determine septic shock.[20] PCT is a well-known prognostic marker after elective cardiac surgery. However, the impact of elevated PCT in patients with an initially uneventful postoperative course is still unclear. Patients with PCT levels above 2.95 ng/mL on the first postoperative day had a highly increased risk of delayed complications.A single measurement of PCT seems to be a useful tool to identify patients at risk of delayed complications despite an initially uneventful postoperative course.[21]

Some patients with the phenotype of severe sepsis may have no overt source of infection or identified pathogen. In ICU patients with the phenotype of severe sepsis or septic shock and without an overt source of infection or a known pathogen, it was unable to confirm that a PCT-based algorithm may influence antibiotic exposure. However, the premature termination of the trial may not allow definitive conclusions.[22] Patients with Nursing Home Acquired Pneumonia (NHAP) present a distinct group of lower respiratory track infections with different risk factors, clinical presentation, and mortality rates.A PCT level upon admission > 1.1 ng/mL was an independent predictor of in-patient mortality. Of the pneumonia severity scores, CURB-65 showed greater accuracy in predicting in-patient mortality, PCT and CRP are reliable for the diagnosis of NHAP, and PCT and CURB-65 are accurate in predicting in-patient mortality in NHAP.[23]

CRP and Gram Negative Bacteria:-

G-bacteraemia has been associated with severe sepsis, although the exact mechanism and pathophysiological differences among bacterial species are not well understood. CRP and IL-6 levels were significantly higher in G-bacteraemia than in G+bacteraemia. These observations suggest a distinct immune pathophysiologic behavior of sepsis in patients with G-bacteraemia that may influence clinical outcomes. Future research exploring new biomarkers and danger signals and further characterizing differences in the virulence mechanisms between G- and G+ bacteria appears promising and could lead to new therapeutics and to improved clinical outcomes.[24] Only serum CRP was capable of distinguishing Gram stain-negative bacterial meningitis from viral meningitis on admission with high sensitivity (96%), high specificity (93%), and high NPV (99%). Exclusion of bacterial meningitis with only the conventional tests is difficult. Combined with careful physical examination and CSF analysis, serum CRP measurement affords substantial aid.[25] Injury and infection are characterized by the activation of the acute phase proteins response. CRP, an acute phase protein, has been mentioned as an useful indicator of infection and sepsis in critically ill patients.The course of serum CRP levels is different in the group of patients with severe blunt trauma and infection, compared with the non-infected group during the first week after injury and it could be an useful supplementary marker for infection after post injury day 4. A value of 110 mg/L or higher for CRP should suggest an underlying infectious complication.[26]

A significant difference between patients with major and minor infections was also found. No significant difference in the CRP level was found between patients with microbiologically and clinically documented infections, nor did the serum CRP levels differ between patients with infections due to G+ and G-organisms. The most favorable cut-off limit for detection of an inflammatory process was 25 mg/L. There was no quantitative difference between CRP levels measured by a latex-agglutination method and the nephelometry assay.[27] The antimicrobial activity of a recombinant CRP2 isoform (rCRP2) was tested against E. coli, Pseudomonas aeruginosa and Staphylococcus aureus. rCRP2 agglutinates bacteria exhibits bactericidal activity against G- bacteria. In addition, the antimicrobial activity of rCRP2 is calcium-independent. GST pulldown experiments suggest that in the naïve physiological state, CRP2 interacts with hemocyanin, native CRPs, a 35-kDa plasma lectin and an as yet unidentified 40-kDa protein.

This interaction was enhanced upon Pseudomonas infection, suggesting that rCRP2 is a PRR with potent antimicrobial activity and its interacting partners contribute to effective bacterial clearance.[28] CRP plays an important role in vivo in host defense against salmonellae during the early stages of infection. In addition, as the beneficial effect of CRP includes enhancement of the host's humoral immune response, CRP may also contribute indirectly to host defense during later stages of infection.[29] Infections with G+ (chiefly coagulase-negative staphylococci) and G- bacteria are accompanied by elevated concentrations of PCT. In the case of G+ bacteria, other laboratory signs of infection studied were not discriminatory, confirming the diagnostic usefulness of PCT measurements in nosocomial infections of the neonate with G- or G+ bacteria.[30]

Serial determinations of CRP resulted in enhanced sensitivity in the positive BC group, the negative BC-definite infection group, and the negative BC-possible infection group. Initial determinations by themselves were inadequately sensitive. Serial determinations did not enhance sensitivity of the negative BC-no infection group. High specificity (91%) is suggested by the low incidence of abnormal CRP levels among infants who were not infected. It would be appropriate to conduct a cautious, controlled trial to assess the safety of discontinuing antibiotic therapy if three serial CRP measurements are normal and if there are no other clinical factors suggestive of infection and it is necessity for serial determinations of CRP for optimal sensitivity.[31] The physiological role of CRP, the classical acute-phase protein, is not well documented, despite many reports on biological effects of CRP in vitro and in model systems in vivo. It has been suggested that CRP protects mice against lethal toxicity of bacterial infections by implementing immunological responses. In Achatinafulica CRP is a constitutive multifunctional protein in haemolymph and considered responsible for their survival in the environment for millions of years. The efficacy of Achatina CRP (ACRP) was tested against both Salmonella typhimurium and Bacillus subtilis infections in mice where endogenous CRP level is negligible even after inflammatory stimulus.[32]

There is currently no single test to diagnose the etiology of meningitis promptly and accurately. Given its high sensitivity and easy measurability, CRP may be a useful supplement for rapid diagnosis and categorization of bacterial meningitis. is recognized as a critical condition that influences the outcome of sepsis. Although large-scale surveillance studies of bacterial species causing bacteraemia have been published, the pathophysiological differences in bacteraemias with different causative bacterial species remain unclear.The incidence of G-bacteraemia was significantly higher in bacteremic ICU patients with septic shock than in those with sepsis or severe sepsis. Furthermore, CRP and IL-6 levels were significantly higher in G-bacteraemia than in G+bacteraemia. These findings suggest that differences in host responses and virulence mechanisms of different pathogenic microorganisms should be considered in treatment of bacteremic patients, and that new countermeasures beyond conventional antimicrobial medications are urgently needed.[34]

As a structural component of the outer membrane of G- bacteria, endotoxin, also known as lipopolysaccharide exhibits strong immunostimulatory properties, rendering it a pivotal role in the pathogenesis of G- septicaemia. An investigation of CRP response to Pseudomonas aeruginosa unveiled a robust innate immune system in the horseshoe crab, which displays rapid suppression of a dosage of 10(6) CFU of bacteria in the first hour of infection and effected complete clearance of the pathogen by 3 days. Such a high dose would have been lethal to mice. Full-length CRP cDNA was cloned. Analysis of the untranslated regions suggests their crucial role in post-transcriptional regulation of CRP transcript levels. Northern blot analysis demonstrated an acute up-regulation of CRP by about 60-fold in 6-48 h of Pseudomonas infection.[35] Clinical features and outcomes of neonatal sepsis caused by resistant G-bacteria are not well described in Jordan. Elevated CRP and thrombocytopenia were seen in 28% and 24% of infants with early-onset sepsis, and in 79.6%, 59.3% of infants with late-onset sepsis respectively.Both early- and late-onset neonatal sepsis are caused by highly resistant G- bacteria. Mortality of sepsis is high. Elevated CRP and thrombocytopenia is seen more commonly in late-onset neonatal sepsis.[36] Elevated CRP level is widely used in clinical practice as a marker to distinguish between neonates with or without sepsis. However, some neonates with bacteraemia have a CRP level within the normal range and they are not well characterized.The sepsis-attributable mortality rate was lower in the low CRP group (4.9 %) than in the high CRP group (13.6 %).A considerable proportion of neonatal BSIs had a normal or low initial CRP level (≤10 mg/L), which was more likely to occur in low birth weight or extremely preterm infants, those with earlier onset of sepsis, and those infected with Coagulase negative staphylococci NS. Plasma CRP level should not be used to rule out severe culture-proven sepsis or guide the empirical choice of antibiotics.[37]

Septicemia is characterized by positive BC, thrombocytopenia& elevated CRP. Higher rise in CRP with prolonged duration following G- sepsis. However the incidence of both raised CRP and thrombocytopenia were more among

fungal sepsis. Though the onset was delayed, lower platelet nadir, more severe thrombocytopenia with prolonged duration was noted among fungal sepsis. may represent a useful tool for differentiating G+ from G-BSIs with a significantly higher PCT level indicating G-bacteraemia. A higher PCT level was found in patients with a G- BSIs than in those with G+ BSIs. Measurement of serum PCT may be adopted as a component of a diagnostic strategy to guide empirical antimicrobial therapy regimens in sepsis patients.[39] The highest PCT values were in patients with Klebsiella, Escherichia coli and Acinetobacter infections, respectively. CRP and PCT values were higher in G-bacteraemias compared to G+ and fungal infections. CRP and PCT levels may be beneficial for differentiation of G-bacteraemia, G+ bacteraemia and fungal infections and may be considered as a factor which may guide empirical antimicrobial treatments.[40]On initial lumbar puncture, CRP was detected in 100% of patients with culture-proven bacterial meningitis, compared to 6% of patients in the nonbacterial group. CRP in CSF had a sensitivity of 1.0 and a specificity of 0.94 for detecting culture-positive, bacterial meningitis. It was a more sensitive test for differentiating bacterial from nonbacterial meningitis on initial CSF examination than was the number of leukocytes, the absolute number of polymorphonuclear leukocytes, glucose concentration, protein concentration, or Gram staining of CSF. Detection of CRP by latex agglutination may prove to be a practical and reliable method for differentiating bacterial from nonbacterial meningitis.[41]

CRP levels were significantly elevated in patient with allo-and autoantibody- mediated thrombocytopenias compared with healthy controls. Within a week, intravenous immunoglobulin treatment in children with newly diagnosed immune thrombocytopenia led to significant decrease of CRP levels, increased platelet numbers, and clinically decreased bleeding severity. Furthermore, higher the level of CRP at diagnosis, the longer it took before stable platelet counts were reached. CRP amplifies antibody-mediated platelet destruction andmay in part explain the aggravation of thrombocytopenia on infections. Hence, targeting CRP could offer new therapeutic opportunities for these patients.[42] Acute bacterial meningitis which is a paediatric emergency with highmortality and morbidity must be diagnosed andtreated promptly. Often diagnosis of bacterial meningitis from viral meningitis is difficult after some days. Determination of some imflammatory mediators' such as IL-6 and hs-CRP may be useful in differential diagnosis of bacterial and viral meningitis. Mean hs-CRP in serum in bacterial meningitis was higher than in viral meningitis. The measurement of IL-6 in the CSF and serum is potentially a very useful diagnostic tool for differential diagnosis of bacterial and viral meningitis.[43] Early identification of bacterial infection in patients with fever is important forprompt treatment. However, the available parameters such as CRP and leukocyte counts are not very specific is a valuable marker of bacterial infections in febrile patients. PCT was superior to CRP, IL-6 or serum Amyloid a (SAA) in the early identification of bacterial infection. More prospective and large scale studies are warranted to confirm these findings.[44] Nosocomial pneumonia is the second most common nosocomial infection. It is usually bacterial in origin. Nosocomial pneumonia is responsible for 25% of infections in the ICU. Early-onset nosocomial pneumonia tends to carry a better prognosis than does late-onset nosocomial pneumonia. Enterobacter aerogenes represented 24% of nosocomial pneumonia. An Overall 70.8% of patients with E.aerogenes detected in culture and sensitivity were sensitive to both amikacin and levofloxacin and these patients received only amikacin.[45]

Conclusions:-

This review article on the diagnostic usefulness of PCT and CRP in G- bacterial infections has brought out the following conclusions for the use and clinical applications of patients infected with G- bacteria in a wide range of situations starting from the screening test, admissions, antibiotic treatment and prognostic monitoring. Significant higher PCT levels could differentiate G- sepsis from G+ and fungemia and it is a good discriminative biomarker in different BSIs. PCT can also differentiate between bacterial and viral infections measurement of PCT at an early stage of fever will enable to exclude both G+ and G- infections. PCT positive patients have reduced levels of platelets and albumin and increased AST, ALT, BUN, creatinine as well as CRP. Both PCT and CRP are very useful for diagnosing hemato-oncological patients. PCT improve diagnosis of bacterial infections and to guide antibiotic therapy and it is found to be useful to treat respiratory treat infections, post-operative infections and septic shock patients in ICU. CRP along with IL-6 are higher in G- bacterial infections compared to G+.The contents of this review article will be an eye opener to further explore this field and to bring out newer aspects on the diagnostic usefulness of both PCT and CRP.

Competing interest / Conflict of interest:-
The author(s) have no competing interests for financial support, publication of this research, patents and royalties through this collaborative research. All authors were equally involved in discussed research work. There is no financial conflict with the subject matter discussed in the manuscript.

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