Journal of Rawalpindi Medical College (JRMC); 2018;22(2): 99-103

Original Article

Pro-Calcitonin and C Reactive Protein as Marker of Infection: Evaluation of Systemic Inflammatory Response Syndrome (SIRS) in Patients with Normal and Impaired Renal Function

Nadeem Anjum [1], Muhammad Khurram [2], Madiha Sultan [2], Jianan Ren [1] ,Guanwei Li [1], Xiuwen Wu [1]

1.Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, Nanjing, China;
2. Department of Medicine Rawalpindi Medical University, Rawalpindi, Pakistan

Abstract

Background: To investigate Pro-Calcitonin (PCT) and C reactive protein (CRP) as predictor of infectious systemic inflammatory response syndrome (SIRS) in patients with normal and impaired renal function.

Methods: In this cross sectional study >18 year old patients with features suggestive of SIRS were included.PCT and CRP were done on first day of admission. Based on clinical features and results of cultures, patients were divided into non-infection and infection (sepsis) groups. Based on glomerular filtration rate (GFR) patients were further divided to Group A (GFR ≥60ml/min) and Group B (GFR <60ml/min).Receiver operating characteristic (ROC) curve was used for statistical analysis.

Results: Out of 740 patients, 48.3% were diagnosed to be suffering from infection (sepsis). GFR of 50.8% patients was ≥ 60 ml/min/1.73m^2 (Group A), and GFR of 364 (49.2%) patients was < 60 ml/min/1.73m^2(Group B).For prediction of infection in SIRS patients, ROC curve based AUC for PCT in all, Group A, and Group B patients was 0.84, 0.86, and 0.71 respectively. Similarly for CRP AUC was 0.81, 0.78, and 0.83 respectively. Best cut off value of PCT predicting infectious cause of SIRS in all, Group A, and Group B patients was 0.24, 0.13, and0.93 ng/mL respectively. Similar best cut off value of PCT for all, Group A and B patients were 13.10 and 11.10 mg/L respectively.

Conclusion: Initial PCT≥ 0.24ng/mL and CRP ≥ 13.10 mg/L are predictors of sepsis in SIRS patients. PCT is better predictor for patients with normal and CRP better predictor for patients with deranged renal function.

Key Words:Pro-calcitonin, C-reactive protein,Systemic Inflammatory Response Syndrome,SIRS,Glomerular filtration rate.

Introduction

Systemic inflammatory response syndrome (SIRS) results from immune system activation. It is diagnosed when two or more of following conditions are fulfilled , i.e., (i) fever or hypothermia,(ii) tachycardia, (iii) tachypnea or hyperventilation, and (iv) leukocytosis or leukopenia, or bandemia.[1] In addition to infections SIRS may be caused by myocardial infarction, trauma, burns, and pancreatitis etc. A patient with SIRS is considered to be suffering from sepsis if he or she has confirmed or suspected infection.[1]

Initial clinical features of infection and sepsis are nonspecific and overlap with those of SIRS. Pro-calcitonin (PCT) and C-reactive protein (CRP) are being used as predictor of infection in such patients. Studies have shown that PCT is better parameter then CRP for early detection of bacterial infection.[2]Patients with renal dysfunction have impairment of immune system that predispose to infection.[3] Severe infection and multiple organ dysfunction (MOD) are one of the main causes of morbidity and mortality in CKD patients.[4] In patients with renal impairment there is uncertainty about accuracy of PCT.[5]

Diagnostic and the best cut off value of PCT and CRP suggestive infectious cause of SIRS have been extensively worked in patient with normal renal function. Such values for patients with impaired renal function are still being evaluated. This study was conducted to investigate PCT and CRP levels as predictor of infectious SIRS in patients with normal and impaired renal function.

Patients and Methods

This cross sectional study was conducted at Nanjing Jinling Hospital, Nanjing University, China from April 2013 to August 2015, after approval from Ethical Committee of the Hospital. Patients with features suggestive of systemic inflammatory response syndrome (SIRS) along with positive or

negative microbiological culture reports were included after informed consent from the patient or surrogate, provided they were >18 years old . PCT and CRP were measured on first day of admission.[1,6] Patients were recruited irrespective of their disease status and hospital settings such as wards, intensive care unit or elective procedures. Patients with non-conclusive diagnosis of infection status were also excluded from the study. Patients were divided into infection and non-infection groups depending upon their clinical features and results of microbiological evaluation. Based on estimation of at admission glomerular filtration rate (GFR) ≥60 mL/min/1.73 m^2, and <60 mL/min/1.73 m^2 each group was subdivided into normal (Group A) and impaired renal function subgroup (Group B). PCT was analyzed by using semi-automated chemoluminescent immunoassay .CRP was measured on an immunoturbidimetric assay .Mann-Whitney U test was used for analysis of continuous data. Chi^2test analysis was done for categorical data. Receiver operating characteristic (ROC) curve was used for prediction of infection, sensitivity, specificity, and area under the curve (AUC) for PCT and CRP. Pearson correlations were sought for PCT and CRP association with GFR. P-value of <0.05 was considered statistically significant.

Results

Six thousand three hundred and fifty (6350) patients were screened for the study. Of these 920 patient's PCT and CRP were measured on first admission day. 740 patients were included finally as 180 patients were excluded due to ambiguous nature of infection. Most common non-infectious illnesses included cardiovascular diseases, and diabetes mellitus. Patients categorized to infection were 48.37% and 51.62% to non-infection categories (Table 1). GFR of 376 (50.8%) patients was ≥ 60 ml/min/1.73m^2 (Group A), while GFR of 364 (49.2%) patients was < 60ml/min/1.73m^2(Group B)(Table 2). Most common infectious illnesses were intra-abdominal infections, and pneumonia. Patients with infective causes of SIRS (sepsis) had significantly higher at admission PCT and CRP values compared to non-infection SIRS patient, whether they have renal dysfunction or not (Table 3; Figure 1&2)). For prediction of infection cause of SIRS, ROC curve based AUC for PCT in all patients was 0.84 (95% CI: 0.81-0.87). For CRP, it was 0.81 (95% CI: 0.78-0.84). In Group A patients, AUC of
PCT was 0.86 (95% CI: 0.82-0.90) and of CRP was 0.78 (95% CI: 0.74-0.83). In group B for PCT, AUC was 0.71 (95% CI: 0.66–0.77) and for CRP it was 0.83 (95% CI: 0.78–0.87)(Figure 3).The best cutoff value of PCT in all patients was 0.24 ng/mL (sensitivity 80%, specificity 78%, positive predictive value 0.81, and negative predictive value 0.78 resepctively.

Table 1. Baseline characteristics

Characteristics	N (%) or Median (IQR)
Age (years)	56.02 (19.8)
Gender (male/female)	497(67.16%)/243 (32.83%)
Serum albumin (g/L)	32.4 (8.09)
Serum hemoglobin (g/L)	101.6 (26.2)
Glucose (mmol/L)	6.76 (2.87)
Infectious diseases	
Abdominal infection	174 (47.2)
Pneumonia	112 (30.4)
Skin and soft tissue infections	45 (12.21)
Urinary tract infection	27 (7.33)
Central nervous system infections	5 (1.35)
Catheter associated infections	4 (1.08)
Non Infectious diseases	
Cardiovascular diseases	269 (36.3)
Diabetes Mellitus	130 (15.5)
Malignancies	114 (15.4)
Cerebrovascular diseases	58 (7.81)
Ischemic bowel injury	38 (5.13)
Chronic obstructive pulmonary disease	50 (6.75)
Autoimmune diseases	84 (11.3)
Inflammatory bowel diseases	52 (7.02)
History of trauma	51 (6.89)
Pancreatitis	27 (3.64)
Syndromes	4 (0.54)

Table 2. Comparison of patients with and without infection (N (%) or Median (IQR)

	Infection	No Infection	P value
Total	358 (48.37)	382 (51.63)	-
Age > 60 Year	155 (43.2)	159 (41.6)	0.96
Gender (male/female)	256/102 (71.50/28.5)	241/141 (63.1/36.9)	0.55
Cardiovascular disease	131 (36.5)	138 (36.1)	0.82
Diabetes mellitus	61 (17)	69 (18);	0.52
Group A* (N=376, 50.8%)			
Age (years)	51 (14.2)	58 (15.1)	0.74
Gender (male/female)	135(35.9)/45 (11.9)	120 (31.9)/76 (20.2)	0.31
Cardiovascular diseases	40 (11.1)	34 (8.9)	0.09
Diabetes mellitus	18 (5.02)	15 (3.92)	0.27
Group B** (N=364, 49.1%)			
Age> 60 Year	104 (29)	101 (26.4)	0.66
Gender (male/female)	12 (33.2)/57 (15.63)	121 (33.2)/65 (17.85)	0.79
Cardiovascular diseases	91 (25.4)	104 (27.2)	0.21
Diabetes mellitus	43 (12)	54 (15)	0.20

*Group A-GFR ≥ 60 ml/min/1.73m^2, **Group B- GFR < 60 ml/min/1.73m^2

Table 3. PCT and CRP levels of patients without and with infections with reference GFR based sub-grouping

	PCT (ng/mL)			CRP (mg/dL)		
	No infection	Infection	P value	No infection	Infection	P value
Total	0.19 (0.44)	2.78 (15.15)	<0.001	7.40 (17)	86.85 (115.42)	<0.001
Group A	0.05 (0.08)	0.76 (2.70)	<0.001	11.10 (14)	76.10 (94.73)	<0.001
Group B	0.09 (0.09)	2.13 (6.97)	<0.001	5.70 (12)	88.25 (111.23)	<0.001

*Group A- GFR ≥ 60 ml/min/1.73m^2, **Group B- GFR < 60 ml/min/1.73m^2

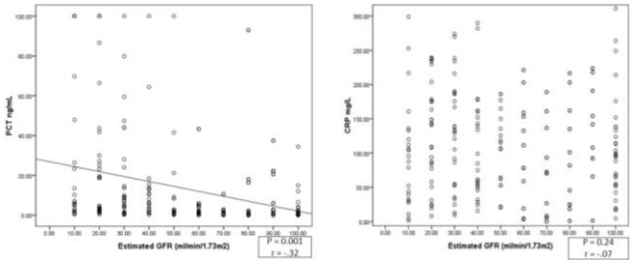

Figure 1. Pearson correlation PCT and CRP according to the eGFR level in patients with infection

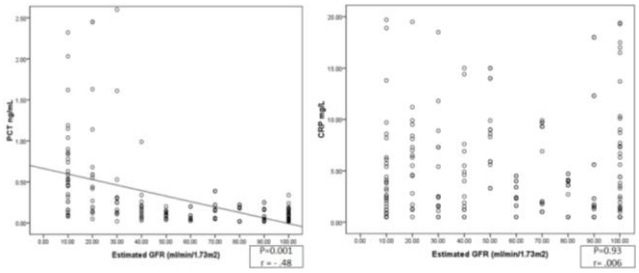

Figure 2. Pearson correlation PCT and CRP according to the eGFR level in patients without infection

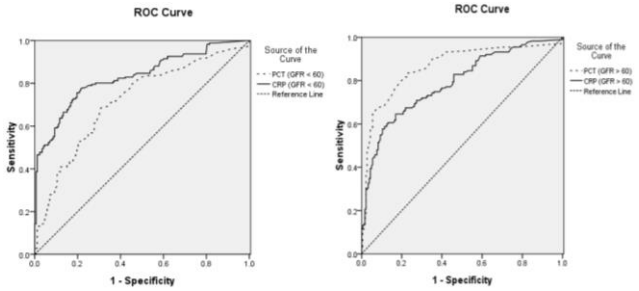

Figure 3. ROC curve of PCT and CRP in patients with and without renal dysfunction

In Group A patients best cutoff value of PCT was 0.13 ng/mL (sensitivity 80%, specificity were 78% PPV0.86, and NPV 0.81). In patients with impaired renal function best cutoff value of PCT was 0.93 ng/mL (sensitivity 80%, specificity 79%, PPV 0.78, NPV 0.83).The best cutoff value of CRP in all patients was 13.10 mg/L (sensitivity 85%, specificity 79%, PPV 0.81, NPV 0.80). In Group A patients this value was 11.10 mg/L (sensitivity 90%, specificity 65%, PPV 0.70, and NPV 0.87). In Group B, patients it was 11.10 mg/L (sensitivity 80%, specificity 82%, PPV 0.79, and NPV 0.84).

Discussion

In present study patients with infective causes of SIRS (sepsis) have significantly higher at admission PCT and CRP values compared to non-infection SIRS patient, whether they have renal dysfunction or not. PCT is better predictor of infectious cause of SIRS (sepsis) in patients with normal renal function while CRP similarly is better predictor in patients with renal dysfunction and 0.13 ng/mL, 0.93 ng/mL are best cut off values of PCT suggestive of sepsis in SIRS patients without and with renal dysfunction respectively, and 11.10 mg/L is best cut off value of CRP suggestive of sepsis inSIRS patients with and without renal dysfunction.

CRP is acute phase reactant. Its production is controlled by cytokines that mainly include IL-6, IL-1β, and tumor necrotic factor alpha. Higher CRP levels have been noted to be significantly associated with diagnosis of sepsis in patients with SIRS.[7,8]PCT because of comparatively rapid rise in sepsis and normalization with effective management is considered better biomarker of sepsis. It has been noted in various studies that sepsis patients have significantly higher PCT levels compared to patients with non-infectious SIRS.[8,9] Our results are comparable in this regard.

Immune dysfunction predispose patients with deranged renal function to infection. Increased levels of inflammatory markers are frequently noted in such patients.[10] Of particular interest in this context is CRP, as its increased levels in patients with renal dysfunction may make it less specific marker of infection.[5] CRP inversely correlated with creatinine clearance in a study conducted by Panichi et al.[11] This was attributed to reduced clearance of CRP due to renal dysfunction. In another study.[5] CRP did not correlate with GFR. We also noted that there is no relationship between GFR and CRP levels.

We noted that PCT increases with deteriorating renal function. Exact details of PCT elimination are not known.P, C Meisner el al noted that major pathway of PCT elimination is renal.[12]Variable changes in PCT levels of renal dysfunction and dialysis patients have been noted.[5]In a study by Lee et al, higher PCT levels were noted in patients with end stage renal

disease.[13]Lu et al in a systemic review and meta-analysis pointed towards poor sensitivity and acceptable specificity of PCT in patients with renal impairment.[14]In a study similar to ours, Park et al, found statistically significant inverse relationship between PCT and GFR.[5]

PCT rise in non-infectious SIRS is not remarkable. This make it specific diagnostic marker of infection.[15] In patients with SIRS, PCT level > 2.0 ng/mL points towards infection.[13] Lee et al focused cut off value of PCT for diagnosing infection in patients with renal failure.[13]Accord;ing to them PCT cut off value of 0.75 ng/mL is suggestive of infection. In a meta-analysis that focused PCTs accuracy for of PCT for diagnosing infection in adult patients, PCT cut-off level of 0.5 ng/mL had 0.79 area under the summary receiver-operating characteristic.[16] Based on our results PCT level above 0.24ng/mL is suggestive of sepsis.

CRP increase with infection. It has been noted that if CRP rises 1mg above normal, risk of infection rises 2.9%.[17] Cut off value of CRP that differentiates non-infectious SIRS from sepsis has been focus of various studies. Farag NA et al noted that sepsis patients had significantly higher CRP levels compared to non-infectious SIRS patients on admission (61.2 ± 9:48.9 ± 7.1 mg/%), on day 2 (71.5 ± 9.6: 56.9 ± 8 mg/L), and on day 4 (196.8 ± 39.8: 73.7 ± 32.5 mg/L).[7]50-170mg/L cut off values of CRP have been considered suggestive of sepsis in various studies with >90% sensitivity, and ≥75% specificity.[7] Cut of value of CRP suggestive of infectious cause of SIRS in our study was 13.10 mg/L.

Most of the previously conducted studies show that PCT is better marker of sepsis.[8]In a cross sectional study focusing clinical relevance of PCT and CRP as infection markers in renal impairment, CRP had AUC 0.819 while PCT had 0.831. In sub group of patients with normal renal function CRP had AUC 0.684 while PCT had 0.766. In sub group of patients with abnormal normal renal function both CRP and PCT had AUC 0.876.[5] Interestingly we noted that for discrimination of SIRS patents with and without infection both CRP and PCT were almost equally effective. For infectious vs non-infectious categorization of SIRS patients without renal dysfunction PCT was better than CRP on one hand. On other hand in patients with renal dysfunction, CRP was better pointer of infection than PCT.

A number of limitations need to be kept in mind while generalizing the results. These include: 1) cross sectional type of study, 2) inclusion of variety of patients fulfilling SIRS criteria rather than SIRS patients of a particular illness, 3) differentiation of SIRS patients into infectious and non-infectious categories based on bacterial culture reports and suggestive clinical features, 4) relying on first CRP, and PCT levels rather than serial estimations, and 5) not focusing outcome etc. Despite these, one has to note that our study included comparably higher number of patients and its findings are comparable with previously conducted studies.[5]Employing our cut off values of CRP and HCT in related clinical scenario will help as a step for better management of SIRS patients.

Conclusion

1.Patients with sepsis (infectious cause of SIRS) have higher initial levels of PCT and CRP levels when compared to patients with non-infectious SIRS. At admission cut off values of 0.24ng/mL for PCT and 11.10 mg/L for CRP can be used for differentiating sepsis from non-infectious SIRS.

2.PCT is better predictor in SIRS patients with normal renal function while CRP is better predictor in patients with renal dysfunction.

Acknowledgment

This study was supported by the National Natural Science Foundation of China (grants number 81270478).NadeemAnjum, JiananRen,Guanwei Li, and Xiuwen Wu were responsible for study conduction, data collection and statistical analysis.

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