Original Research Article

Detection and validation of serum C-reactive protein and procalcitonin as diagnostic markers for bacterial infections in patients with cirrhosis of liver

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Abstract

Background: The role of inflammatory markers like CRP and procalcitonin in predicting various outcomes in patients with cirrhosis is gaining lot of attention. There is a need for extensive studies, to be carried out in India as there is no adequate literature available on the subject.

Objectives: To assess the predictive validity of c-reactive protein and procalcitonin in predicting bacterial infection and mortality in patients with cirrhosis.

Materials and methods: A prospective observational study conducted in the Department of Hepatology, at Madras Medical College, Chennai. Patients admitted to the Hepatology ward from March2016 to February 2017with acute decompensation of liver cirrhosis were studied. The serum procalcitonin level was assessed by Electro Chemi Luminescence Immuno Assay (Eclia) with a measuring range of 0.02-75ng/ml. and C-Reactive Protein level was assessed by ImmunoTurbido

Metric Assay, with a measuring range of 1.00-200mg/l. The utility of CRP and procalcitonin in predicting the infection and mortality was assessed by Receiver Operative curve (ROC) analysis.

Results: Procalcitonin had a better predictive validity than C-reactive protein in predicting the bacterial infection in the study population as indicated by their AUC curve as 0.99 (95% CI 0.99, 1.00, p value <0.001), for Procalcitonin and 0.84 (95% CI 0.76, 0.92, p value <0.001) for C-reactive protein. In predicting the mortality, C-reactive protein had a better predictive validity when compared to Procalcitonin as indicated by their AUC curve as 0.804 (95% CI 0.68, 0.92, p value <0.001) for C-reactive protein and 0.63 (95% CI 0.48, 0.77, p value <0.001) for Procalcitonin.

Conclusion: More than one third of hospitalized Cirrhosis patients had infection and mortality rate was just over 20%. PCT has shown better predictive validity as compared to CRP in predicting infection, but CRP had better predictive validity in predicting mortality.

Key words

Cirrhosis, CRP, Procalcitoni, Infection, Mortality, Predictive validity.

Introduction

The role of inflammatory markers in predicting various outcomes in many chronic diseases has received lot of attention in recent years [1-3]. With increase in burden of cirrhosis [4-6] of various etiologies and the resulting increase in morbidity and mortality, the search for appropriate predictors for sepsis in cirrhosis patients is point of focus in many recent studies across the globe [7].

Patients with cirrhosis are highly prone to bacterial infections [8], and it is one of the major causes of mortality. Identifying specific bacterial infections is a challenging task, as clinical presentations could be almost similar from other agents which are causing them [9]. In order to treat the infections, antibiotics are frequently being prescribed in higher doses and frequencies, which leads to bacterial resistance, which is again a serious issue. Few studies have suggested that, identifying markers specific for bacterial infections would be helpful in treating particular infection and restricting the use of antibiotics in parallel [10].

Culture tests are the most common and accurate way to identify bacterial infections. Procalcitonin (PCT) and C-reactive protein (CRP) markers, among different markers of inflammation are most commonly being studied for the diagnosis of bacterial infections [11]. Some authors have reviewed various studies, and also have suggested that the accuracy of Procalcitonin diagnosing the diseases were much higher compared to CRP [10].

Few models with scores and scales have been designed for predicting the bacterial infections and mortality. One of the mostly used models is CTP (Child–Turcotte–Pugh) score used for assessing the severity of the illness and mortality. This scale is not used very often as it has various limitations [12]. MELD (Model for end stage liver disease), greater the score, higher is the rate of mortality [13]. SOFA (Sequential Organ Failure Assessment) is also a good scale for predicting mortality in critically ill patients with liver diseases [14]. There is a need for extensive studies, to be carried out in India as there is no adequate literature available regarding the, factors predicting bacterial infection and mortality in patients with chronic liver diseases.

Objective

- To assess the validity of c-reactive protein and procalcitonin in predicting bacterial infection and mortality in patients with cirrhosis.

Materials and methods

The current study was a prospective observational study conducted in the Department of Hepatology, at Madras Medical College, Chennai, which is a tertiary care teaching hospital. All the patients who were admitted to the Hepatology ward with acute decompensation of Liver Cirrhosis were considered as study population. The data collection for the study was done for a period of twelvemonths from March 2016 to February 2017.

All the participants were evaluated following admission, and the following clinical variables were collected: age, gender, current alcohol intake (defined as any alcohol intake within a month prior to hospitalization), illicit drug use, associated diseases, prophylactic antibiotics, known chronic liver disease, current and previous decompensation. All subjects underwent laboratory evaluation at admission, and the following tests were performed for this study: Haemoglobin, total leukocytes, platelet count sodium, creatinine, albumin, total bilirubin, international normalized ratio (INR), CRP and PCT. They were also subjected to etiological work up for cirrhosis. Individuals with suspected infection at hospital admission were submitted to clinical examination and laboratory analysis (culture) to confirm this diagnosis and to establish the primary source of infection.

The diagnosis of systemic inflammatory response syndrome (SIRS) and sepsis was established based on the definition of the Society Of Critical Care Medicine (SCCM). Severity of liver disease was estimated by the Child-Pugh score and MELD (Model for End-Stage Liver Disease) calculated based on laboratory tests performed on admission.

CRP and PCT measurements were performed on samples collected on hospital admission. The serum procalcitonin level was assessed by Electro Chemi Luminescence Immuno Assay (Eclia) with a measuring range of 0.02-75ng/ml. and C-Reactive Protein level was assessed by Immuno Turbido Metric Assay, with a measuring range of 1.00-200 mg/l.

Inclusion criteria

- Axillary temperature >/ 37.5 C
- SIRS
- New onset encephalopathy or worsening of pre onset encephalopathy by at least one grade according to West Heaven criteria.
- New onset ascites or hydrothorax or worsening of preexisting ascites or hydrothorax
- Abdominal pain
- Respiratory tract symptoms (cough, dyspnea, or tachypnea)
- Urinary tract symptoms (loin pain ,dysuria, polyuria)
- Clinical evidence of pyodermatitis (cellulitis)
- Upper gastro intestinal bleeding (esophageal or gastric varices or portal hypertensive gastropathy)
- White blood cell count >/ 10,000 cumm
- Increase in creatinine by 50 % from the baseline or increase in bilirubin by 3 mg/dl from baseline
- Patients receiving prophylaxis for spontaneous bacterial peritonitis could be included

Exclusion criteria

- Patient receiving therapeutic antibiotics at screening or over the previous 7 days and/ or receiving immunosuppression were excluded.
- Patient with hepatocellular carcinoma and portal vein thrombosis.

Sample size

The sample size was calculated basing on the expected prevalence of bacterial infection of about 30%, expected Area under the curve values

for CRP and procalcitonin as 0.73 and 0.82 as per study by Simon L, et al. [10], with an alpha error of 0.05 and 80% power of study. The required sample as per the above mentioned parameters was 81 subjects. To account for 10% loss to follow up about 90 was considered as final sample size.

Statistical Analysis

Mortality and occurrence of any bacterial infection was considered as primary outcome variables. C-reactive protein and Procalcitonin levels were considered as explanatory variables Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. The mean c-reactive protein and procalcitonin values were compared across the infection and mortality categories using independent sample t-test. The utility of CRP and procalcitonin in predicting the infection and mortality was assessed by Receiver Operative curve (ROC) analysis. Area under the ROC curve along with its 95% CI and p value are presented. Basing on co-ordinates of ROC curve. The cut off level for CRP and procalcitonin were identified as 30 and 1.5 units respectively. The values above the mentioned cut off level were considered as screening positive. The sensitivity, specificity, predictive values and diagnostic accuracy were calculated for these cut-off levels. P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis [15].

Results

A total of 90 subjects were included in analysis. Majority (66.7%) of the study population was between 41 to 60 years of age. The proportion of males was 72.2%), Ascites was present in 63 (70.0%) subjects, followed by jaundice and encephalopathy in 56 (62.2%) and 50 (55.6%) of the subjects, respectively. Upper GI bleeding was reported by 33 (36. 7%).Alcoholic cirrhosis was the most common etiology seen in 41 (45.6%) subjects, followed by HBV (22.2%) and HCV (12.2%). Infiltrate in chest X-ray was present in only 8 (8.9%) of the study population (**Table - 1**).

Table - 1: Descriptive analysis of baseline parameters (N=90).

Parameter	Frequency	%
Age Groups		
21 - 40years	18	20.0%
41 - 60years	60	66.7%
61 - 80years	12	13.3%
Gender		
Male	65	72.2%
Female	25	27.8%
Clinical characteristics		
Ascites	63	70.0%
Jaundice	56	62.2%
Encephalopathy	50	55.6%
Known Chronic liver disease	42	46.7%
Previous Decompensation	40	44.4%
Upper GI bleeding	33	36.7%
Recent alcohol abuse	32	35.6%
Prophylactic antibiotic therapy	23	25.6%
Etiology		
Alcohol	41	45.6%
HBV	20	22.2%
HCV	11	12.2%
Auto immune hepatitis	6	6.7%
More than one etiology	7	7.8%
Budd chairi syndrome	3	3.3%
NASH	2	2.2%
CTP		
CTP C	55	61.1%
CTPB B	33	36.7%
CTP A	2	2.2%
Chest X-Ray		
Infiltrate Absent	82	91.1%
Infiltrate present	8	8.9%

The mean Total bilirubin level was 8.66±7.505, mean albumin was 2.76±0.526, INR was 1.91± 0.466 and MELD score was 23.34± 7.823 in study population. Mean C-reactive protein was found to be 37.61±29.74 and mean Procalcitonin level was 3.88 ±5.86 in study population (**Table - 2**).

Table - 2: Descriptive analysis of Laboratory parameters and inflammatory markers.

Parameter	Mean	Standard Deviation
Total bilirubin	8.66	±7.505
Albumin	2.76	±0.526
INR	1.91	±0.466
C-reactive protein	37.61	±29.74
Procalcitonin	3.88	±5.863
creatinine	1.55	±0.876
Serum Na+	128.72	±3.412

When all the culture and sensitivity tests were assessed together considering "any culture positive" 34 (37.8%) subjects had shown culture positivity. Mortality occurred in 20 (22.2%) subjects (**Table - 3**).

Table - 3: Descriptive analysis of culture and sensitivity tests.

Parameter	Frequency	Percentage
Culture		
Positive	34	37.8%
Negative	56	62.2%
Mortality		
Death	20	22.2%
Alive	70	77.8%

Mean CRP was 32.77 (95% CI 19.39 to 46.15, P value < 0.001) units higher in people with mortality compared with subjects, who were alive. Mean CRP level was 35.36 (95% CI 24.83 to 45.89, P value < 0.01) units higher in culture positive subjects, as compared to culture negative subjects. Mean procalcitonin level was 5.3 (95% CI 2.54 to 8.05, P value < 0.01) units higher in people with mortality and it was 8.27 (95% CI 6.43 to 10.12, P value < 0.01) units higher in people with infection (**Table – 4**).

Procalcitonin had a better predictive validity than C-reactive protein in predicting the bacterial infection in the study population as indicated by their AUC curve as 0.99 (95% CI 0.99, 1.00, p value <0.001) for Procalcitonin and 0.84 (95% CI 0.76, 0.92, p value <0.001) and p value <0.001 for C-reactive protein (**Figure – 1**).

Similarly, when predictive validity was assessed for predicting the final outcome, C-reactive protein had a better predictive validity when compared to Procalcitonin as indicated by their AUC curve as 0.804 (95% CI 0.68, 0.92, p value <0.001) for C-reactive protein and 0.63 (95%CI 0.48, 0.77, p value < 0.001) for Procalcitonin (**Figure – 2**).

In predicting infection, Procalcitonin had 100.0% sensitivity (95% CI 100% to 100.0%) 92.8% specificity (86.11% to 99.60%) in study population. The positive predictive value was 89.47 % (79.71% to 99.23%) and the negative predictive value was 100.0% (100.0% to 100.0 %) in the study population. The overall diagnostic accuracy was 96% (91.29% to 99.81%) in the study population. In predicting infection, C-reactive protein had 88.24% sensitivity (95% CI 77.40 to 99.06%), 75.00% specificity (63.65% to 86.34%) in study population. The positive predictive value was 68.18 % (54.41% to 81.94%) and the negative predictive value was 91.30% (83.16% to 99.44%) in the studypopulation. The overall diagnostic accuracy was 80% (71.73% to 99.72%) in the study population (**Table - 5**).

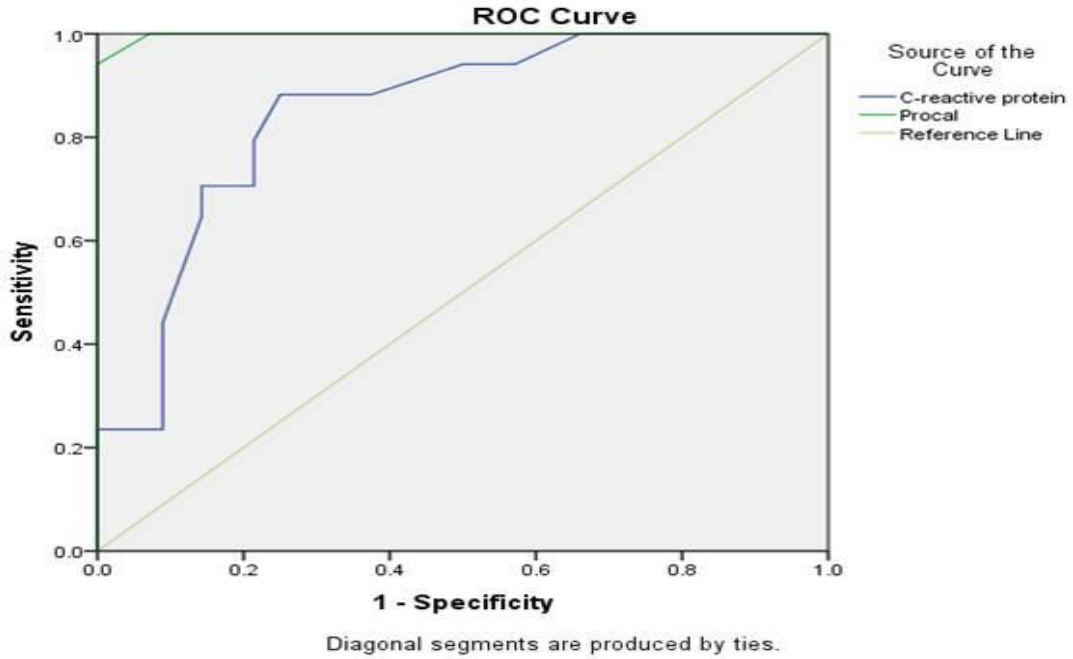
In predicting mortality, C-reactive protein had 65.00% sensitivity (95% CI 44.09% to 85.90%), 55.71% specificity (44.07% to 67.35%) in study population. The positive predictive value was 29.55% (16.06% to 43.02%) and the negative

predictive value was 84.78% (74.40% to 95.16%) in the study population. The overall diagnostic accuracy was 58% (47.57% to 67.98%) in the study population. In predicting mortality, Procalcitonin had 50.00% sensitivity (95% CI 28.08% to 71.91%), 60.00% specificity (48.52% to 71.47%) in study population. The positive predictive value was 26.32% (12.31% to 40.31%) and the negative predictive value was 80.77% (70.05% to 91.48%) in the study population. The overall diagnostic accuracy was 58% (47.57% to 67.98%) in the study population (**Table - 6**).

Table - 4: Association between mortality, Infection and the inflammatory markers (N=90).

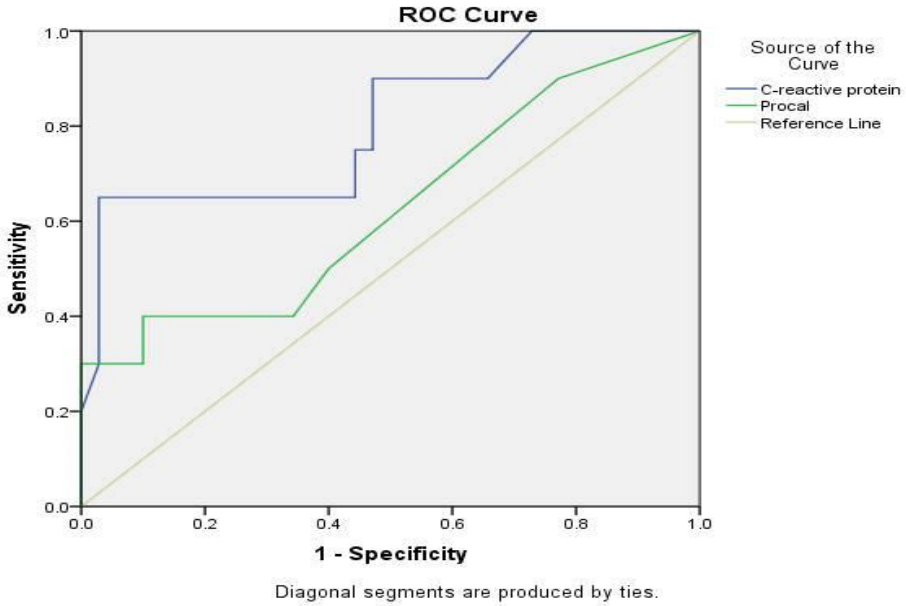
Outcome		Mean	Stand Deviation	Mean Difference	P Value	95% CI	
						Lower	Upper
C-Reactive protein							
Mortality	Death	63.10	34.27	32.77	<0.001	19.39	46.15
	Alive	30.33	23.99				
Culture	Positive	59.62	25.08	35.36	<0.001	24.83	45.89
	Negative	24.25	23.93				
Procalcitonin							
Mortality	Death	8.00	9.78	5.3	<0.001	2.54	8.05
	Alive	2.70	3.41				
Culture	Positive	9.03	6.94	8.27	<0.001	6.43	10.12
	Negative	0.75	0.58				

Figure - 1: Predictive validity of CRP and PROCALCITONIN in predicting bacterial infection.



Inflammatory marker	Area under the curve	95% Confidence Interval		P value
		Lower Bound	Upper Bound	
C-reactive protein	0.848	.0768	0.928	< 0.001
Procalcitonin	0.998	0.993	1.000	<0.001

Figure - 2: Predictive validity of CRP and PROCALCITONIN in predicting mortality.



Inflammatory marker	Area under the curve	95% Confidence Interval		P value
		Lower Bound	Upper Bound	
C-reactive protein	0.804	0.686	0.923	< 0.001
Procalcitonin	0.630	0.481	0.779	<0.001

Table - 5: Comparison of CRP and Procalcitonin in predicting infection.

Parameter	Procalcitonin (95% CI)	CRP (95% CI)
Sensitivity	100.0% (100% to 100%)	88.24% (77.40% to 99.0%)
Specificity	92.86% (86.11% to 99.60%)	75.00% (63.65% to 86.34%)
False positive rate	7.14 (0.397 to 13.88)	25.00 (13.65 to 36.34)
False negative rate	0.00 (0 to 0)	11.76 (0.934 to 22.59)
Positive predictive value	89.47 (79.71 to 99.23)	68.18 (54.41 to 81.94)
Negative predictive value	100.00 (100 to 100)	91.30 (83.16 to 99.44)
Diagnostic accuracy	96 (91.29 to 99.81)	80 (71.73 to 88.26)

Table - 6: Comparison of CRP and Procalcitonin in predicting mortality.

Parameter	CRP (95% CI)	Procalcitonin(95% CI)
Sensitivity	65.00% (44.09% to 85.90%)	50.00% (28.08% to 71.91%)
Specificity	55.71% (44.07% to 67.35%)	60.00% (48.52% to 71.47%)
False positive rate	44.29 (32.64 to 55.92)	40.00 (28.52 to 51.47)
False negative rate	35.00 (14.09 to 55.90)	50.00 (28.08 to 71.91)
Positive predictive value	29.55 (16.06 to 43.02)	26.32 (12.31 to 40.31)
Negative predictive value	84.78 (74.40 to 95.16)	80.77 (70.05 to 91.48)
Diagnostic accuracy	58 (47.57 to 67.98)	58 (47.57 to 67.98)

Discussion

Chronic liver disease patients are prone to various infections, which can adversely affect the course of the illness. Early detection of infection in these patients still remains a major challenge. Even though early institution of antimicrobial therapy may significantly reduce the morbidity and mortality, empirical treatment for all suspected patients is fraught with huge risk of anti-microbial resistance. Identification of a reliable marker which can identify the subjects with infection, early in the course will be extremely valuable in these patients.

Alcohol consumption (45.6%) was found to be the major etiology of cirrhosis in our study, where as in contrast to this HBV (55.3%) was reported by Cai ZH, et al. [16], but the results of Child Pugh score (CTP) were almost similar in both the studies, where the proportion of subjects with CTP C score were higher compared to A and C groups.

The current study has reported, culture positive infection rate of 37.8% and mortality in 22.2% of subjects during hospital stay. In their study on 184 cirrhotic patients in Korea, Kwon JH, et al. [1] have reported an infection rate of 31.5 % and mortality rate of 17.4 %.

Mean CRP level was 35.36 (95% CI 24.83 to 45.89, P value < 0.01) and mean PCT level was 8.27 (95% CI 6.43 to 10.12, P value < 0.01) units higher in people with infection, as compared to people without infection.Both the markers have documented strong positive association with infection in the study. Procalcitonin had a better predictive validity than C-reactive protein in predicting the bacterial infection in the study population as indicated by their AUC curve as 0.99 (95% CI 0.99,1.00, p value <0.001), for Procalcitonin and 0.84 (95% CI 0.76, 0.92, p value <0.001) and p value <0.001 for C-reactive protein .AUC value of 0.79% (95% CI,0.74-0.84) was reported by Li S, et al. [17], while assessing the diagnostic accuracy of using PCT over CRP for identifying the gram negative sepsis. Kwon JH, et al. [1] also reported CRP as a significant indicator of infection in hospitalized cirrhotic patients and a NLR was a useful predictor of 1-month survival [1].

Some studies 18] have reported the other way stating that the predictive validity was significantly higher in CRP, (AUC 0.83, 95% CI, 0.81–0.86) in predicting bacterial infections, compared to PCT (AUC 0.74, 95% CI, 0.71–0.77) ($p < 0.0001$),when studied among malaria patients. A Metaanalysis of studies published on all hospitalized subjects by Simon L, et al. [10], has tested the utility of procalcitonin (PCT) and C-reactive protein (CRP) in predicting the infection. The reported sensitivity (88% vs. 75%) and specificity (81% Vs 67%) was higher of PCT as compared to CRP in differentiating non infective causes of inflammation from infections. The area under the ROC curve was also higher for PCT, compared to CRP (0.82 vs. 0.73). In our current study the sensitivity and specificity were reported to be (100% vs 88.24%) and (92.86% vs 75.0%) in both PCT and CRP respectively, in predicting bacterial infection whereas sensitivity was reported (65.0% vs 50.0%) and specificity (55.71% vs 60.0%) in CRP and PCT in predicting mortality. Similar results were reported by Andreola B, et al. [19], with the AUC for CRP and PCT were 0.92 (95% CI, 0.80 – 0.98) and 0.75 (95% CI, 0.60 – 0.87) respectively. PCT was documented to be a better all-round marker, as compared to CRP by this meta-analysis.

Conclusion

More than one third of hospitalized Cirrhosis patients had infection and mortality rate was just over 20%. The mean CRP and PCT levels were significantly higher in people with infection and in people with mortality. PCT has shown better predictive validity as compared to CRP in predicting infection, but CRP had better predictive validity in predicting mortality.

Limitations

The role of potential confounders including demographic, disease related parameters could not be evaluated, considering the smaller sample size.

Recommendations

- Procalcitonin can be a very useful marker and should be assessed routinely in cirrhosis patients with high probability of infection.
- Further large scale studies on Indian population may help us in identifying the appropriate cut off level of these markers to institute antimicrobial therapy.

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