

EVALUATION OF PROCALCITONIN AND C-REACTIVE PROTEIN IN PATIENTS OF CIRRHOSIS OF LIVER WITH SEPSIS- A CROSS-SECTIONAL STUDY

Vivek Kumar¹, Sudhir Kumar Verma², Dinesh Kumar Singh³, Nikhil Panjabrao Joge⁴, Ravi Misra⁵

¹Professor (Junior Grade), Department of Internal Medicine, King George Medical University, Lucknow, Uttar Pradesh.

²Assistant Professor, Department of Internal Medicine, King George Medical University, Lucknow, Uttar Pradesh.

³Senior Resident, Department of Internal Medicine, King George Medical University, Lucknow, Uttar Pradesh.

⁴Senior Resident, Department of Internal Medicine, King George Medical University, Lucknow, Uttar Pradesh.

⁵Professor and HOD, Department of Internal Medicine, King George Medical University, Lucknow, Uttar Pradesh.

ABSTRACT

BACKGROUND

Sepsis is commonly encountered in patients of cirrhosis of liver and is associated with worse outcome. Traditional culture methods commonly used to diagnose sepsis in such patients is positive only in 50-70% of cases and take longer time. Therefore, surrogate marker such as Procalcitonin (PCT) and C-Reactive Protein (CRP) may be useful to identify patients of early sepsis with increased sensitivity and in shorter time.

The aim of the study is to-

1. Evaluate the role of PCT and CRP in patients with cirrhosis of liver with and without sepsis.
2. Find correlation of levels of procalcitonin and CRP with clinical and biochemical parameters of severity of cirrhosis as well as to find out its prognostic implications.

MATERIALS AND METHODS

A cross-sectional observational study was conducted in the Department of Medicine, King George Medical University, Lucknow, India, over a period of one year. A detailed history and clinical examination was performed in all enrolled patients. Along with routine tests done in patients of cirrhosis of liver, procalcitonin and CRP levels are performed.

RESULTS

PCT and CRP levels were significantly higher in patients with sepsis as compared to patients without sepsis. PCT and CRP levels were also significantly higher in patients who presented with complications of cirrhosis like variceal bleed, hepatic encephalopathy and severe ascites as compared to patients without these complications. Significantly higher rate of mortality and longer duration of hospital stay was observed in patients with higher values of PCT and CRP levels.

CONCLUSION

Procalcitonin and CRP levels are significantly raised in patients of cirrhosis with sepsis. These biomarkers gives us an opportunity to diagnose sepsis in early stages, so that early antibiotic therapy can be initiated and sepsis precipitated complications of cirrhosis can be prevented leading to favourable outcome of the patient. So, we recommend that PCT and CRP levels should always be measured in patients of cirrhosis with suspected sepsis.

KEYWORDS

Cirrhosis of Liver, Sepsis, Procalcitonin, C-Reactive Protein.

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BACKGROUND

Sepsis is commonly encountered in patients of cirrhosis of liver and is associated with poor survival outcomes.¹ Cirrhosis-Associated Immune Dysfunction Syndrome (CAIDS) is a multifactorial state of systemic immune

dysfunction, which makes the patients of cirrhosis of liver more susceptible to acquiring infection.²

The severity of liver disease determines the development of sepsis, while sepsis leads to increased occurrence of complications like variceal bleeding and hepatic encephalopathy, which adversely affects survival outcome.¹ Traditional culture methods commonly used to diagnose sepsis in such patients is positive only in 50-70% of cases and take longer time. Therefore, surrogate marker such as C-Reactive Protein (CRP) and Procalcitonin (PCT) may be useful to identify an early infection.³

Under normal conditions, the PCT levels in the circulation are very low (<0.05 ng/mL). Bacterial infections induce a ubiquitous increase of CALC-1 gene expression and a constitutive release of PCT from all parenchymal tissues

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Corresponding Author:

Dr. Vivek Kumar,

Professor, Department of Internal Medicine,

King George Medical University, Lucknow, Uttar Pradesh.

E-mail: vivekkumar@kgmcindia.edu

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throughout the body. So, that significant concentration of PCT (up to 1000 ng/mL) is detected in the blood of patients with severe bacterial sepsis making it a useful marker of sepsis.⁴

C-Reactive Protein (CRP) and procalcitonin are two plasma biomarkers included among the inflammatory variables in the diagnosis of sepsis. Plasma levels of CRP and procalcitonin are similar in critically ill patients with and without liver cirrhosis, despite concerns regarding the ability of the liver to produce these proteins. PCT has the best diagnostic values among these biomarkers.⁵

We conducted the present study to evaluate the role of procalcitonin and CRP in patients with cirrhosis of liver with and without sepsis and to find correlation of levels of procalcitonin and CRP with clinical and biochemical parameters of severity of cirrhosis as well as to find out its prognostic implications.

MATERIALS AND METHODS

A cross-sectional observational study was conducted in the Department of Medicine, King George Medical University (KGMU), Lucknow, India over a period of one year (August 2012-July 2013). A total of 50 patients were enrolled in the study.

Patients with cirrhosis of liver aged more than 18 years, who were admitted with evidence of hepatocellular dysfunction and portal hypertension as evident clinically and by portal vein diameter >13 mm on USG and presence of oesophageal varices by upper gastrointestinal endoscopy.

Patients with cardiac disease, hypertension, diabetes mellitus, renal, pulmonary disease and malignancy were excluded.

Detailed history and clinical examination was performed in all enrolled patients. Complete haemogram, random blood sugar, serum Na⁺, K⁺, blood urea, serum creatinine, urine examination, liver function tests (serum bilirubin, SGOT, SGPT, ALP, serum protein, serum albumin), prothrombin

time, INR, viral markers (HIV, HCV, HBsAg) were carried out. Ultrasound whole abdomen with special attention to portal vein diameter, echotexture of liver, splenomegaly and ascites was performed by an expert radiologist. Upper gastrointestinal endoscopy, ascitic fluid examination, procalcitonin and CRP was carried out in all patients.

Procalcitonin was measured by immunoluminometric assay and a cut-off value of 0.5 ng/mL was taken for clinical use for indicating sepsis. C-reactive protein measured by coagulation assay with a cut-off value of 24.7 mg/L was taken as suggestive of sepsis. SIRS criteria were used for diagnosis of sepsis.

Statistical Analysis

All the statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, USA). Data were presented as mean \pm SD or number (%) unless specified. All parametric data were analysed using student's (t) test in categorical groups. All nonparametric data were analysed by Chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 50 patients were enrolled randomly fulfilling inclusion criteria. Out of 50, 30 patients were of liver cirrhosis with any one or combination of complications like hepatic encephalopathy, sepsis and gastrointestinal haemorrhage and 20 patients were of cirrhosis without these complications as control. Mean age of our enrolled patient was 48.35 ± 8.2 with 35 males and 15 females.

Table 1 shows mean PCT and CRP values in patients of cirrhosis of liver with and without sepsis. PCT and CRP levels were significantly higher in patients with sepsis as compared to patients without sepsis.

	Patients without Sepsis (n=17)		Patients with Sepsis (n=13)		Controls (n=20)		Significance of Difference	
	Mean	SD	Mean	SD	Mean	SD	F	p
PCT (ng/mL)	0.23	0.15	1.85	1.56	0.23	0.18	19.780	<0.001
CRP (mg/L)	20.82	20.19	81.00	83.10	15.10	6.87	10.102	<0.001

Table 1. Comparison of Procalcitonin and CRP in Patients With or Without Sepsis

Table 2 shows mean PCT and CRP values in patients of cirrhosis of liver with and without variceal bleed. PCT and CRP levels were significantly higher in patients with variceal bleed as compared to patients without variceal bleed.

	Patients without VB (n=14)		Patients with VB (n=16)		Controls (n=20)		Significance of Difference	
	Mean	SD	Mean	SD	Mean	SD	F	P
PCT (ng/mL)	0.51	0.55	1.30	1.64	0.23	0.18	5.556	0.007
CRP (mg/L)	26.61	28.18	64.65	79.56	15.10	6.87	5.077	0.010

Table 2. Comparison of Procalcitonin and CRP in Patients With or Without Variceal Bleed (VB)

Table 3 shows mean values of PCT and CRP were higher in patients with hepatic encephalopathy than those without HE, though this was statistically significant only for PCT (p <0.017).

	Patients Without HE (n=8)		Patients With HE (n=22)		Controls (n=20)		Significance of Difference	
	Mean	SD	Mean	SD	Mean	SD	F	p
PCT (ng/mL)	0.43	0.28	1.12	1.47	0.23	0.18	4.416	0.017
CRP (mg/L)	34.00	39.26	51.59	70.19	15.10	6.87	2.847	0.068

Table 3. Comparison of Procalcitonin and CRP in Patients With and Without Hepatic Encephalopathy (HE)

Table 4 shows that Upper Gastrointestinal (UGI) bleed had the trend of being higher in patients with sepsis than in patients without sepsis, but this was not statistically significant.

UGI Bleed	Patients Without Sepsis (n=17)		Patients With Sepsis (n=13)	
	No.	%	No.	%
No	9	52.9	5	38.5
Yes	8	47.1	8	61.5

Table 4. Comparison of Different Groups for UGI Bleed

Table 5 shows that prevalence of hepatic encephalopathy was significantly higher in patients with sepsis as compared to patients without sepsis (p=0.011).

HE	Patients Without Sepsis (n=17)		Patients With Sepsis (n=13)	
	No.	%	No.	%
No	6	35.3	2	15.4
Yes	11	64.7	11	84.6

Table 5. Comparison of Different Groups for Presence of Hepatic Encephalopathy (HE)

Parameter	Expiry (n=7)		Survival (n=23)		Significance	
	Mean	SD	Mean	SD	t	p
PCT (ng/mL)	2.33	2.05	0.51	0.52	4.011	<0.001
CRP (mg/L)	97.43	111.95	31.52	28.25	2.653	0.013

Table 7. Role of Procalcitonin and CRP in Prediction of Survival

Table 8 shows that PCT and CRP levels were significantly higher in patients with longer duration of hospital stay.

	Outcome A Hospital Stay <5 Days (n=9)		Outcome B Hospital Stay 6-14 Days (n=10)		Outcome C Hospital Stay >14 Days/Expiry (n=11)		Significance of Difference	
	Mean	SD	Mean	SD	Mean	SD	F	P
PCT (ng/mL)	0.19	0.11	0.44	0.31	1.99	1.69	8.981	0.001
CRP (mg/L)	10.71	7.27	43.46	32.75	79.64	90.72	3.463	0.046

Table 8. Role of Procalcitonin and CRP in Prediction of Outcome

Table 9 shows that PCT had 100% predictive accuracy at a cut-off value >0.744, whereas CRP had a lower sensitivity and specificity.

Biomarker	Projected Cut-Off Value	Predicted Sensitivity	Predicted Specificity
PCT	>0.744	100%	100%
CRP	>23.50	84.6%	82.4%

Table 9. Derived Cut-Off Points and Predicted Sensitivity and Specificity of CRP and PCT

Table 6 shows that patients with sepsis had significantly more frequency of having poorly-controlled ascites as compared to patients without sepsis and controls indicating sepsis was determinant to effective control of ascites (p=0.011).

Ascites	Patients Without Sepsis (n=17)		Patients With Sepsis (n=13)		Controls (n=20)	
	No.	%	No.	%	No.	%
Easily controlled	7	41.2	1	7.7	10	50.0
No ascites	8	47.1	4	30.8	4	20.0
Poorly controlled	2	11.8	8	61.5	6	30.0

Table 6. Comparison of Different Groups for Ascites

$\chi^2=11.965$ (df=4); p=0.018 (S).

Table 7 shows that mean values of both PCT and CRP were significantly (p <0.05) higher in those who expired than in those who survived.

DISCUSSION

In cirrhosis of liver, there is decreased activity of opsonin in ascitic fluid and neutrophil leucocyte dysfunction, decrement in reticuloendothelial function, deficiencies in C3 and C4 and changes in the intestinal flora and intestinal barrier, which leads to reduced bacterial clearance, which also facilitate bacterial translocation induced by increased intestinal permeability and bacterial overgrowth.^{6,7} In SIRS, anti-inflammatory cytokines (IL-10, IL-4, IL-13, prostaglandin E2) are unable to balance the proinflammatory cytokines, also known as a "cytokine storm," resulting in excessive inflammation. This leads to greater propensity of cytokine-induced hepatocyte apoptosis and necrosis leading to

greater incidence of decompensation and complications in patients of cirrhosis of liver who have sepsis.⁶

Sepsis is a common complication of cirrhosis of liver. According to Borzio et al⁸ hospital mortality of cirrhotic patient with infection is approximately 15%, more than twice that of patients without infection.

In our study, 33 patients (66%) belonged to Child Pugh's class C; 17 patients (34%) belonged to Child Pugh's class B while none (0%) belonged to Child Pugh's class A. Among these patients, hepatic encephalopathy was the most common complication (n=22; 73.3%) followed by variceal bleed (n=16; 53.3%) and sepsis (n=13; 43.3%).

Our study suggested that mean value of PCT and CRP in patients with sepsis was significantly higher than patients without sepsis. Procalcitonin was found to be 100% sensitive and specific for detecting sepsis and the predicted cut-off value is ≥ 0.744 $\mu\text{g/L}$. This was comparable to the observation made by Chih-Huang Li et al⁵ who observed a sensitivity of 81.5% and specificity of 87.3% for PCT in detecting sepsis with predicted cut-off of 0.5 $\mu\text{g/L}$. CRP was found to be 84.6% sensitive and 82.4% specific for detecting sepsis and the predicted cut-off value is ≥ 23.5 mg/L . This was similar to values derived by Chih-Huang Li et al⁵ who observed a sensitivity of 80.0% and specificity of 80.3% for CRP in detecting sepsis with predicted cut-off of 24.7 mg/L . Among the two variables being tested, procalcitonin had the highest sensitivity and specificity (100% each) for detecting sepsis.

In our study, the prevalence of variceal bleed was higher in patients with sepsis (n=8/13, 61.5%) than in those without sepsis (n=8/17, 47.1%), but this was not statistically significant $p > 0.05$. Bacterial infections are frequently associated with upper gastrointestinal bleeding in cirrhotic patients developing in up to 66% (20% within the first 48 hours, 35-66% within two weeks).⁹ Goulis J et al⁹ showed that proven bacterial infection or a surrogate of its presence (use of antibiotics) had the strongest independent association with failure to control bleeding in cirrhotic patients with variceal bleeding. According to Hou M C et al,¹⁰ bacterial infection severely hampers haemostatic mechanism in patients of cirrhosis of liver leading to upper gastroesophageal variceal bleed and concluded that antibiotic prophylaxis can prevent infection and rebleeding as well as decrease the amount of blood transfusion in patients with acute gastroesophageal variceal bleed following endoscopic treatment.

The prevalence of hepatic encephalopathy was significantly higher in patients with sepsis (n=11/13, 84.6%) than in those without sepsis (n=11/17, 64.7%). Sepsis may exacerbate the symptoms of both minimal and overt HE in patients of cirrhosis of liver and this is probably mediated by Tumour Necrosis Factor (TNF) and interleukin-6.¹¹ Permeability of brain endothelial cells is enhanced by TNF and interleukin-6 and TNF also increases the diffusion of ammonia into astrocytes.¹² In our study also, patients with sepsis presented with significantly higher grade of hepatic

encephalopathy (grade III/IV) as compared to those without sepsis (grade I/II) ($p < 0.05$).

Sepsis was associated with greater likelihood for poorly-controlled ascites (n=8/13, 61.5%) when compared with patients without sepsis (n=2/17, 11.8%) and this was statistically significant $p > 0.05$. Sepsis causes cytokine-induced liver cell damage, altered liver reserve and also impaired renal function, which in turn might play a significant role in impeding effective control of ascites.¹³

Sepsis was associated with significantly longer duration of hospital stay than in patients without sepsis ($p < 0.001$). 76.9% (n=10/13) of the patients with sepsis having hospital stay greater than 15 days compared to only 5.9% (n=1/17) in patients without sepsis.

Overall, mortality in our study was 23.33% (n=7/30). Out of these patients, 20% had sepsis and 3.3% had no sepsis. In patients with sepsis (n=13), group mortality was 46.2% (n=6) while in patients without sepsis group mortality was 5.9%. This finding suggests that high index of suspicion for an infectious process should be emphasised despite the paucity of the signs and symptoms of an infection in all hospitalised patients of cirrhosis of liver. Prompt workup to determine the site of infection along with early antibiotic therapy and supportive measure might lower the observed mortality.¹⁴

CONCLUSION

Our study showed that procalcitonin and CRP levels are significantly raised in patients of cirrhosis with sepsis. These biomarkers gives us an opportunity to diagnose sepsis in early stages so that early antibiotic therapy can be initiated and sepsis precipitated complications of cirrhosis can be prevented leading to favourable outcome of the patient. So, we recommend that PCT and CRP levels should always be measured in patients of cirrhosis with suspected sepsis.

REFERENCES

- [1] Fernandez J, Navasa M, Gomez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002;35(1):140-148.
- [2] Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 2014;61(6):1385-1396.
- [3] Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010;139(4):1246-1256.
- [4] Hatzistilianou M. Diagnostic and prognostic role of procalcitonin in infections. *ScientificWorldJournal* 2010;10:1941-1946.
- [5] Li CH, Yang RB, Pang JH, et al. Procalcitonin as a biomarker for bacterial infections in patients with liver cirrhosis in the emergency department. *Acad Emerg Med* 2011;18(2):121-126.
- [6] Gustot T, Durand F, Lebrech D, et al. Severe sepsis in cirrhosis. *Hepatology* 2009;50(6):2022-2033.

- [7] Wiest R, Garcia-Tsao G. Bacterial Translocation (BT) in cirrhosis. *Hepatology* 2005;41(3):422-433.
- [8] Borzio M, Salerno F, Piantoni L, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. *Dig Liver Dis* 2001;33(1):41-48.
- [9] Goulis J, Armonis A, Patch D, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1998;27(5):1207-1212.
- [10] Hou MC, Lin HC, Liu TT, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. *Hepatology* 2004;39(3):746-753.
- [11] Häussinger D, Schliess F. Astrocyte swelling and protein tyrosine nitration in hepatic encephalopathy. *Neurochemistry Int* 2005;47(1-2):64-70.
- [12] Mostafa EF, Ibrahim AM, Elalawi SM. Effect of serum ammonia, TNF-alfa and IL-6 levels on the degree and outcome of hepatic encephalopathy in Egyptian cirrhotic patients. *International Journal* 2015;3(4):375-381.
- [13] Bonnel AR, Bunchorntavakul C, Reddy KR. Immune dysfunction and infections in patients with cirrhosis. *Clinical Gastroenterology and Hepatology* 2011;9(9):727-738.
- [14] Preda CM, Ghita R, Ghita C, et al. A retrospective study of bacterial infections in cirrhosis. *Maedica (Buchar)* 2011;6(3):185-192.