Original Article

Serum C-reactive Protein Predicts Early Mortality in Patients with Decompensated Cirrhosis of Liver

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Abstract

Serum C-reactive protein is a marker of systemic inflammation, which has been studied to predict mortality and cirrhosis related complication in decompensated cirrhosis of liver. To evaluate the role of serum C- reactive protein as a predictor of early mortality in patients with decompensated cirrhosis of liver. This was a prospective observational study, carried out in the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka between October 2017 to February 2019. A total of 89 patients with decompensated cirrhosis of liver were included in the study. Baseline serum CRP was measured and patients were longitudinally followed for a period of 30 days. Patients were divided into two groups, survival and non-survival. The groups were compared of CRP level, CTP score, MELD score and cirrhosis related complications. Chi-Square test was used to analyze the categorical variables and Student t-test was used to analyze continuous variables. Receiver-operator characteristic curve was used to detect serum CRP level for prediction of mortality within 30 days. The mean age was found 49.02±13.90 years in survival group and 47.52±11.30 years in non-survival group. Male patients were predominant in both groups. Total WBC count, serum CRP, serum sodium, serum bilirubin, CTP score & MELD score were statistically significant (p<0.05) between the groups. In multivariate analysis, only serum CRP level (OR 1.075, 95% CI, 1.027-1.122%, p=0.001) was found significantly associated with mortality within 30 days. Receiver-operator characteristic (ROC) was constructed, using serum CRP level, which gave a cut off value of 31mg/L, with 78% sensitivity and 90% specificity for prediction of mortality within 30 days. Elevated serum CRP level is an independent predictor of early mortality in patients with decompensated cirrhosis of liver. It was also observed that, high serum CRP level was associated with increased frequency of cirrhosis related complications.

Keywords: *Cirrhosis, decompensation, c-reactive protein (CRP), systemic inflammation.*

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INTRODUCTION

Cirrhosis, a final pathway for a wide variety of chronic liver diseases is a pathologic entity defined as diffuse hepatic fibrosis with replacement of normal liver architecture by nodules. The rate of progression of chronic liver disease to cirrhosis may be quite variable, from weeks in patients with complete biliary obstruction to decades in patients with chronic hepatitis C.[1] Cirrhosis is classified into two main prognostic stages: compensated and decompensated cirrhosis. Median survival in the compensated stage exceeds 12 years whereas it is only 2 years in patients who develop decompensation.[2] Currently, liver transplantation is the only curative remedy for end stage cirrhosis.

The serum C-reactive protein (CRP) is an acute phase protein found in the blood stream. Its level rises in response to inflammation. It has been extensively studied in rheumatologic conditions, coronary artery diseases, tissue necrosis and bacterial translocation.[3,4] Several studies have been performed on the association of CRP with the severity of inflammation in liver disease, such as fatty liver and chronic hepatitis C.[5,6] Furthermore recent studies demonstrated that systemic inflammatory

response was a major prognostic factor in patients with cirrhosis and serum CRP can be used to reflect this exacerbated inflammation that coexist during the course of cirrhosis.[7]

In cirrhotic patients, once decompensation occurs, early mortality risk increases sharply. Predicting the mortality in such patients is of utmost important as depending on their prognosis, proper organ allocation for liver transplantation can be prioritized. Another important role of prognostic markers is to foresee probable complications e.g. spontaneous bacterial peritonitis and hepatorenal syndrome. Child-Pugh score and model for end-stage liver disease (MELD) have been used for many years for assessing the prognosis of cirrhosis. However, Child-Pugh score has important limitations and it only tells us about 1, 5 and 10 years mortality. The MELD score has been being used as a marker of prognosis of cirrhosis since long, even though 10 to 20% of patients are still misclassified and it only tells us about 3 month mortality.[8] On the context of our country a cheap, efficient and readily available marker to predict early mortality in cirrhotic patients can prove to be a boon, considering our socio economic status. Furthermore currently there are no established marker that can predict 30 days mortality in patients with decompensated cirrhosis of liver. Recent study suggested that serum CRP was able to predict early mortality in HBV related decompensated cirrhotic patients.[9] So, we have investigated whether serum CRP level could predict 30 days mortality in hospitalized patients with decompensated cirrhosis of liver.

MATERIALS AND METHODS

It was a hospital based prospective observational study. The study was carried out in the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh between October 2017 to February 2019. Patients with decompensated cirrhosis attending at Hepatology department were selected as study population. A total of 89 decompensated cirrhotic patients were observed during this study period. Initial investigations were done to meet up inclusion and exclusion criteria including liver chemistry (serum bilirubin, serum albumin, prothrombin time), ascitic fluid analysis, AFP, serum creatinine, urine R/E, CXR, ECG, abdominal ultrasonography, endoscopy of upper gastrointestinal tract. Decompensated cirrhosis was diagnosed with a combination of physical, biochemical and radiological findings and defined by history or presence of one or more of clinical ascites, variceal bleeding, jaundice, or hepatic encephalopathy.[10] The inclusion criteria were age > 18 years with decompensated cirrhosis of liver (cirrhotic patients with presence or history of one or more of clinical ascites, jaundice, variceal bleeding or encephalopathy). The exclusion criteria were acute on chronic liver failure, acute hepatitis, hematologic disorder, malignancy, pregnancy, ischaemic heart disease, renal failure, clinical infections, rheumatological condition associated with elevated CRP. The patients were chosen according to purposive sampling. Blood sample for serum CRP levels was collected and was measured in the department of Biochemistry, using Immunoturbidimetry. The patients were divided into two groups, survival and nonsurvival group. The selected patients were longitudinally followed to observe mortality or appearance of cirrhosis related complications (variceal bleeding, hepatic encephalopathy,hepatorenal syndrome and spontaneous bacterial peritonitis) for a period of 30 days. Follow up was done either in person or over telephone. End of study was considered after death or 30 days whichever one was shorter. The statistical analysis was carried out using SPSS version 22.0. Qualitative data were analyzed by Chi-square test & quantitative data were analyzed by student's t-test. Mann Whitney-U test was used to analyze non-parametric data. The discriminative ability of serum CRP to predict the outcome was evaluated by using the area under receiver operating characteristic curve (AUC). $P< 0.05$ was considered statistically significant.

Ethical consideration

Ethical clearance for the study was taken from the Institutional Review Board of BSMMU prior to commencement of this study. Approval paper was given by 146th Institutional Review Board, Bangabandhu Sheikh Mujib Medical University, meeting held on 07 October 2017 (No. BSMMU/2017/10935).

RESULTS

During the study period total 89 patients were enrolled. It was observed that 23 (25.84%) patients did not survive and 66 (74.16%) patients were found alive.

Table- I shows baseline characteristics of the patients, it was observed that mean age was found 48.63±13.23years. Male female ratio was 6.42:1. 56.2% patients had hepatitis B and 12.4% patients had Hepatitis C. Mean systolic BP was 103.65±8.18 mmHg, mean diastolic BP was 69.21±4.52 mmHg, mean Hb % was 9.87±1.81 g/dl, mean TC was 7.45±5.50x109/L, , mean platelet count was 111.94±83.65 x109/L, mean serum CRP was 23.67±25.11 g/L, mean serum creatinine 1.19±0.46 mg/dl, mean serum sodium was 132.01±6.36 mmol/L, mean serum potassium was 3.89±0.72 mmol/L, mean serum bilirubin 5.25±6.98 mg/dl, mean ALT was 59.53±41.79 U/L, mean prothrombin time was 19.52±7.10 sec, mean INR was 1.63±0.57, mean serum albumin was 2.51±0.56 g/dl, mean CP score 9.85±2.02 and mean MELD score 17.64±6.87.

Table I: Baseline characteristics of the study patients (n=89)

Baseline characteristics		Mean±SD	Min	Max
Age (Years)		48.63±13.23	22	80
Sex				
	Male	77		
	Female	12		
Cause of cirrhosis				
	Hepatitis B	50		
	Hepatitis C	11		
	Non-B non-C	28		
Systolic BP (mmHg)		103.65±8.18	90	130
Diastolic BP (mmHg)		69.21 ±4.52	60	80
Hb% (g/dl)		9.87±1.81	3.4	14.50
TC ($x10^9$/L)		7.45±5.50	1.50	34.00
Platelet count (x109/L)		111.94±83.65	15	450
CRP (mg/L)		23.67±25.11	0.32	98.05
S. Creatinine (mg/dl)		1.19±0.46	0.46	4.40
S. Sodium (mmol/L)		132.01±6.36	114	144
S. Potassium (mmol/L)		3.89±0.72	2.1	6.00
S. Bilirubin (mg/dl)		5.25±6.98	0.3	32.70
ALT (U/L)		59.53±41.79	13	233
Prothrombin time (Sec)		19.52±7.10	10.9	46.7
INR		1.63±0.57	0.91	4.00
Serum albumin (g/dl)		2.51±0.56	1.2	3.8
CP score		9.85±2.02	7	14
MELD score		17.64±6.87	7	38

Table-II shows distribution of the study patients by lab parameters, mean TC of WBC was found (6.76±5.42) x 109/L in survival group and (9.43±5.31) x 109/L in non-survival group, mean CRP was 13.65±14.40 in survival group and 52.40±27.32 in non-survival group, mean serum sodium was 133.13±5.45 mmol/L in survival group and 128.64±7.77 mmol/L in non-survival group, mean serum bilirubin was 5.23±7.79 mg/dL in survival group and 5.31±4.11 mg/dL in non-survival group, mean CTP score was 9.50±2.05 survival group and 10.81±1.66 in non-survival group, mean MELD score was 16.64±6.98 in survival group and 20.74±6.25 in non-survival group. 22.73% patients developed cirrhosis related complications in survival group and 82.61% in non-survival group.

Table II: Distribution of the study patients by lab parameters (n=89

Lab parameters	Survival Group (n=66) Mean ±SD	Nonsurvival Group (n=23) Mean±SD	P value
Hb% (g/dl)	9.76±1.98	10.15±1.18	0.271ns
TC (x109/L)	6.76±5.42	9.43±5.31	0.044s
Platelet count (x109/L)	98.49±64.29	151.68±117.67	0.054ns
S. CRP (mg/L)*	13.65±14.40	52.40±27.32	0.000s
S. Creatinine (mg/dl)	1.21±0.51	1.15±0.26	0.614ns
S. Sodium (mmol/L)	133.13±5.45	128.64±7.77	0.005s
S. Potassium (mmol/L)	3.84±0.67	4.05±0.84	0.250ns
S. Bilirubin (mg/dl)*	5.23±7.79	5.31±4.11	0.045s
ALT (U/L)	63.97±63.64	75.50±51.41	0.447ns
Prothrombin time(Sec)	18.66±6.28	21.91±8.72	0.059ns
INR	1.55±0.48	1.86±0.74	0.071ns
Serum albumin (g/dl)	2.57±0.55	2.31±0.57	0.057ns
CP score	9.50±2.05	10.81±1.66	0.011s
MELD score	16.64±6.98	20.74±6.25	0.016s

s= significant, ns=non-significant
P value reached from unpaired t-test
* P value reached from Mann Whitney-U test

Table-III shows the type of the cirrhosis related complications of the patients. It was observed that variceal bleeding developed in 6(9.1%) case in survival group and 3(13.04%) in non-survival group. Hepatic encephalopathy developed in 8(12.12%) cases in survival group and 14(60.87%) cases in non-survival group. HRS developed in 1(1.15%) case in survival group and (8.69%) in non-survival group. Total 15(22.73%) patients developed complications in survival group and 19(82.61%) in non-survival group which were statistically significant ($p<0.05$) between the groups.

Table III: Cirrhosis related complications in study patients within 30 days (n=89)

Name of the complication	Survival Group (n=66)		Non-Survival Group (n=23)		P value
	N	%	N	%	
Variceal bleeding	6	9.1	3	13.04	
HRS	1	1.51	2	8.69	0.000[s]
Hepatic encephalopathy	8	12.12	14	60.87	
Total complication	15	22.73	19	82.61	

s= significant, ns=non-significant

Table-IV shows high leukocyte count, low serum sodium, high serum bilirubin, high serum CRP level, high CTP and MELD score were independent risk factors for 30-day mortality in univariate logistic regression analysis.

Table IV : Univariate analysis for predictor of mortality within 30 days (n=89)

Lab parameters	Survive (n=66) Mean±SD	Not-survive (n=23) Mean±SD	P value
Age	49.02±13.90	47.52±11.30	0.644[ns]
Systolic BP (mmHg)	103.18±7.92	105.00±8.92	0.362[ns]
Diastolic BP (mmHg)	68.94±3.56	70.00±6.57	0.467[ns]
Hb% (g/dl)	9.76±1.98	10.15±1.18	0.271[ns]
TC (x10^9/L)	6.76±5.42	9.43±5.31	0.044[s]
Platelet count (x10^9/L)	98.49±64.29	151.68±117.67	0.164[ns]
S. CRP (mg/L)*	13.65±14.40	52.40±27.32	0.000[s]
S. Creatinine (mg/dl)	1.21±0.51	1.15±0.26	0.614 [ns]
S. Sodium (mmol/L)	133.13±5.45	128.64±7.77	0.005[s]
S. Potassium (mmol/L)	3.84±0.67	4.05±0.84	0.250[ns]
S. Bilirubin (mg/dl)*	5.23±7.79	5.31±4.11	0.045[s]
ALT (U/L)	63.97±63.64	75.50±51.41	0.447[ns]
Prothrombin time(Sec)	18.66±6.28	21.91±8.72	0.059[ns]
INR	1.55±0.48	1.86±0.74	0.071[ns]
Serum albumin (g/dl)	2.57±0.55	2.31±0.57	0.057 [ns]
CP score	9.50±2.05	10.81±1.66	0.011[s]
MELD score	16.64±6.98	20.74±6.25	0.016[s]

s= significant, ns=non-significant
P value reached from unpaired t-test
* P value reached from Mann Whitney-U test

Table-V shows in multivariate analysis only high serum CRP level (OR 1.075, 95% CI 1.027-1.122%, p=0.001) was significantly associated with mortality within 30 days.

Table V: Multivariable logistic regression analysis as predictor of mortality within 30 days (n=89).

Variables	Adjusted OR	95% CI		P Value
		Lower bound	Upper bound	
TC (x10^9/L)	0.999	0.880	1.191	0.557 [ns]
S. Sodium (mmol/L)	0.914	0.822	1.035	0.258[ns]
S. Bilirubin (mg/dl)	0.798	0.643	0.991	0.077 [ns]
CTP score	1.178	0.695	2.533	0.835 [ns]
MELD score	0.987	0.929	1.474	0.224[ns]
CRP	1.075	1.027	1.122	0.001s

OR=odds ratio, CI-Confidence interval, s=significant; ns=non-significant

Figure 1: Receiver-operator characteristic (ROC) curve of serum CRP level for prediction of mortality within 30 days:

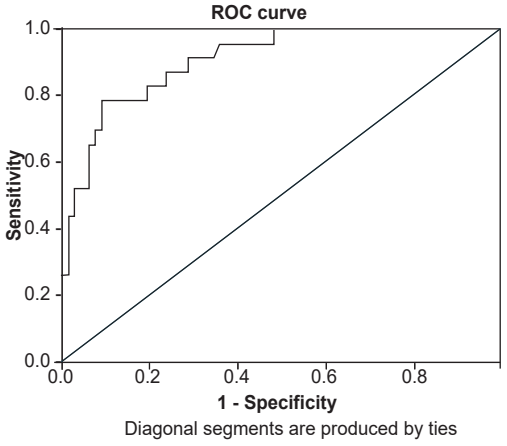

Fig.-1: Receiver-operator characteristic curves of Serum CRP level

Figure-1 shows based on the receiver-operator characteristic (ROC) curve, serum CRP level had an area under curve 0.907. Receiver operator characteristic (ROC) was constructed by using serum CRP level, which gave a cut off value 31, with 78% sensitivity and 90% specificity for prediction of mortality.

Table-VI shows mortality within 30 days is 4(6.06%) in serum CRP < 31 group but 17(73.91%) in serum CRP > 31 group and presence of complications is 14 (21.21%) in serum CRP <31 group but 16(69.56%) in serum CRP > 31 group.

Table- VI: Outcome of the study patients by CRP level within 30 days (n=89).

Parameters	Serum CRP <31 (n=66) N(%)	Serum CRP >31 (n=23) N(%)	P value
Mortality within 30 days	4(6.06%)	17(73.91%)	0.000s
Appearance of complications	14(21.21%)	16(69.56%)	0.000s

s= significant, ns=non-significant

P value reached from unpaired t-test and chi- square test

DISCUSSION

This prospective observational study was carried out with the aim to evaluate serum CRP level as a predictor of early mortality in patients with decompensated cirrhosis of liver. CRP is classically considered an important regulator of the innate immune system and a paramount mediator of the acute-phase response.[11] C-reactive protein is predominantly synthesized in the liver in response to proinflammatory cytokines and IL-6 appears to be the main regulator.[12] In cirrhotic patients, immune and inflammatory systems are activated and inflammatory markers, such as interleukin-6 and tumor necrosis factor-alfa, have been found to be elevated.[13] Inflammatory response activation may be caused by occult infections associated with bacterial translocation that complicates the increase of intestinal permeability in these patients.[14] Systemic inflammation has been shown to favor serious complications (variceal bleeding, encephalopathy and acute-on-chronic liver failure) and death in cirrhotic patients.[15,7]

In this study it was observed that majority of patients in surviving group 29(44%) and nonsurviving group, 13(56.50%) were within age 31-50 years. It was also observed that majority of patients both in survival and nonsurvival group were male which were 56(84%) and 21(91%) in survival and nonsurvival group respectively. Mean CRP was found 13.65±14.40 in survival group and 52.40±27.32 in non-survival group, mean CTP score was 9.50±2.05 survival group and 10.81±1.66 in non-survival group, mean MELD score was 16.64±6.98 in survival group and 20.74±6.25 in non-survival group. In this study it was observed that majority of study population both in survival and non-survival group had hepatitis B, which was 38(57.57%) and 12(52.17%) in survival and non-survival group respectively.

Univariate logistic regression analysis showed that high leukocyte count, low serum sodium, high serum bilirubin, high serum CRP level, high CTP and MELD score were independent risk factors for 30-day mortality.

In multivariate analysis, only high serum CRP level (OR 1.075, 95% CI 1.027-1.122%, p=0.001) was significantly associated with mortality within 30 days. Zhu et al. (2017) found that serum high CRP level at base line and MELD score were independent risk factor for 1-month mortality in HBV decompensated cirrhotic patients.[9] Martino et al. (2015) also found high serum CRP level at base line and at day 15 and MELD score predicted 3 month mortality independently in decompensated cirrhotic patients.[16] Cervoni et al. (2016) also found high serum CRP level at base line and at day 15 and MELD score predicted 6 month mortality in decompensated cirrhotic patients.[17]

In this study it was observed that based on the receiver-operator characteristic (ROC) curve, serum CRP level had an area under curve (AUC) at 0.907 and the best cut off value of CRP was 31 mg/L. Cervoni et al. (2016) found the best predictive value of CRP was 29 mg/L.[17] Martino et al. (2015) found the best cut off value of CRP was 32 mg/L.[16] Zhu et al. (2017) found that the median value of CRP was 29 mg/L[9] Cirrhosis related complications e.g. variceal bleeding, hepatic encephalopathy and HRS developed more frequently in higher CRP (>31) group. But previous studies, e.g. Zhu et al. (2017) and Martino et al. (2015) did not show any significant correlation between CRP and cirrhosis related complications.[9,16]

CONCLUSIONS

In this prospective study, we observed that CRP was able to predict short-term mortality in patients with decompensated cirrhosis of liver. It was also observed that, high CRP levels was associated with increased frequency of cirrhosis related complications. The prognostic value of CRP was independent of the usual prognostic criteria such as MELD and CTP scores. Hence, we assume that

measuring CRP is a simple and accurate way of diagnosing systemic inflammation and has a relevant impact on prognosis in cirrhotic patients.

Limitations

We did not investigate the relevance of serial measurements of CRP. Only one cross-sectional value of CRP was monitored. We were not able to determine whether CRP variation over time would perform better in predicting outcomes of decompensated cirrhotic patients. It was beyond of our scope to exclude all extra hepatic causes that could influence serum CRP level like subclinical infection.

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