# 0NEUTROPHIL TO LYMPHOCYTE RATIO AND HIGH SENSITIVITY C - REACTIVE PROTEIN AS PREDICTORS OF SHORT TERM MORTALITY IN HOSPITALIZED PATIENTS WITH LIVER CIRRHOSIS

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**Abstract**

**Background and aim:** Cirrhotic patients have increased mortality and longer hospital stay due to increased susceptibility to develop bacterial infection. Herein, we aimed to evaluate the role of neutrophil to lymphocytes ratio(NLR) and high sensitivity C-reactive protein(Hs-CRP) in diagnosis of infection and prediction of short term mortality in hospitalized cirrhotic patients.

**Patients and methods:** The study included 50 cirrhotic patients hospitalized in ICU of a central Liver hospital. The presence of overt infection was evaluated. The NLR was calculated as the ratio of the neutrophils to lymphocytes in the peripheral blood. Hs-CRP concentration was measured by Immunoturbidimetric assay. Model for End-Stage Liver Disease(MELD) score, Child-Pugh score and the presence of systemic inflammatory response syndrome(SIRS) were assessed.

**Results:** The main cause of admission was refractory ascites(50%), followed by hematemesis(24%), spontaneous bacterial peritonitis(18%) and hepatic encephalopathy(8%). Development of SIRS occurred in 24(48%) patients and death occurred in 15(30%) patients. NLR and Hs-CRP were significantly higher in patients who developed SIRS(0.03and *P*= 0.01) respectively. For predicting short-term survival, MELD score, NLR and Hs-CRP were significant factors(*P* = 0.03, 0.01 and 0.01 respectively).

**Conclusion:** NLR and Hs-CRP are helpful diagnostic markers of infection and development of SIRS in hospitalized cirrhotic patients. In addition to the classical MELD score, NLR may be a useful predictor of the short-term mortality in hospitalized cirrhotic patients particularly in Child–Pugh class C.

**Keywords*:*** high sensitivity C-reactive protein, Neutrophil-to-lymphocyte ratio, Liver cirrhosis, SIRS, short-term Survival

## Introduction

Cirrhosis is a late stage of scarring(fibrosis) of the liver caused by many forms of liver diseases and conditions, such as hepatitis and chronic

alcoholism(1-4).The concept of systemic inflammatory response syndrome(SIRS) has been strongly suggestive of complex pathophysiologic response to an insult such as infection(5). SIRS can be found in up to 67% of cirrhotic patients with bacterial infections compared to 37% of patients without, making sepsis a common complication of advanced cirrhosis(6).

Cirrhotic patients with increased risk for bacterial infection during hospitalization have increased mortality four times and have a poor prognosis.(7-9) Recognition of bacterial infections in patients with liver cirrhosis has become a great challenging from both the clinical and the laboratory point of view.(10)

Studies increasingly focused on the importance of neutrophil-to-lymphocyte ratio(NLR) as an independent prognostic factor of morbidity and mortality in several conditions, such as cancers and cardiovascular diseases.(12, 13)

C-reactive protein(CRP) is a useful inflammatory marker synthesized in the liver, used to identify the presence of acute or chronic inflammation and infections. Also, it's a good factor in predicting short-term mortality in patients with hepatocellular carcinoma(HCC), and outcomes after liver transplantation.(14-16)

## Patients and Methods

### ***Design:***

Prospective observational study was performed at ICU of a Central Liver Hospital between July 2017 and July 2018**.**

### ***Ethical Consideration:***

The study was approved by the University Ethical Committee and Review Board. All the patients who participated in the study provided written informed consents.

***Patients:***

The study included 50 cirrhotic patients with range of age between 44 and 67 years admitted secondary to various causes including uncontrolled ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis(SBP) and hepatorenal syndrome. Patients below 18 years, previously diagnosed as HCC or patients with extrahepatic malignancy were excluded from the study. Because of financial issues and policy of hospital admission we could not include compensated cirrhotics as a control group.

***Methods:***

**All patients were subjected to the following**:

Full history taking and clinical examination.

Laboratory investigations including:

1- Complete blood count(CBC) was done using cell counters(CELL DYN 3500, CELL DYN 1700 & Ruby CELL DYN).
2- Random blood glucose, Liver function tests and Kidney function tests which were done using *Dimension* RxL *Max* Integrated Chemistry System and *Hitachi Modular* P800 chemistry analyzer.
3- NLR was calculated by dividing the neutrophil count by the lymphocyte count.
4- Measurement of Hs-CRP was done by immunoturbidimetric assay using BT-1500 System(Biotecnica Instruments, Italy)

according to manufacturer's instructions. Turbidity is caused by the formation of antigen- antibody(polyclonal goat anti-h CRP antibody) insoluble complexes. CRP Calibrator High was used to generate a calibration curve. The reaction is nonlinear, endpoint with wavelength at 340 nm, assay temperature between 18-37 °C and measuring range from 0.0 to 22 mg/dl. The assay Sensitivity was 0.6 mg/dl with no known cross-reactivity.

5- Other specific investigations to detect infection including blood, urine, sputum, wound secretions and ascitic fluid sampling and culture.
6- Other laboratory investigations to detect etiology of cirrhosis as hepatitis markers, anti-smooth muscle Ab, anti-mitochondrial Ab, serum copper and serum iron.

Radiological assessment with abdominal U/S and/or MSCT Abdomen.

Upper endoscopy: Screening or therapeutic

Patients were considered to have SIRS if they have two or more of the following criteria:

(a)Core temperature of >38 °C or<36 °C.

(b)Heart rate of >90 beats/min.

(c)Respiratory rate of >20 breaths/min; partial carbon dioxide pressure(PaCO2)≤ 32 mmHg or the need of mechanical ventilation.

(d)White blood cell(WBC) count of >12,000/mm3 or <4000/mm3, or differential count showing >10 % immature polymorphonuclear neutrophil cells(PMNCs).

Assessment of the severity of liver cirrhosis using Child-Turcotte-Pugh(CTP) score and Model for End Stage Liver Disease(MELD) score.

**Statistical Analysis:**

Data was collected and analyzed those using SPSS(Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data was expressed in form of mean±SD or median(range) while nominal data was expressed in form of frequency (percentage). Student t-test was used to compare mean of different two groups. Multivariate regression analysis was used to determine the independent risk factors for prediction of SIRS and death(within three months) in hospitalized cirrhotic patients. A receiver operating characteristic(ROC) curve was constructed and the area under the curve(AUC) was calculated to evaluate the discriminatory capacity of each. The cut off value for the maximum sensitivity and specificity of the NLR and Hs-CRP was calculated. A Kaplan–Meier survival analysis was performed to compare the OS of the patients in different groups. Pvalue was significant if< 0.05.

**Results**

**Demographic Data of Studied Patients:** are shown in table1. Mean age of enrolled patients was 54.32±5.28 years. 37patients (74%) were males, 30(60%) patients came from rural areas and 16(32%) patients were smokers. 15(30%), 6(12%), 3(6%) and 5(10%) patients had diabetes mellitus, hypertension, chronic kidney disease and ischemic heart disease respectively. Majority(42%) of patients had no comorbidities.

Mean duration of cirrhosis was 4.13±1.12 years. In majority of cases(64%) hepatitis C virus infection was the etiology of liver cirrhosis.

The main cause of admission was refractory ascites in 50% of patients. Based on abdominal U/S, 26(52%) patients had moderate ascites, 12(24%) of them had mild ascites and also 12(24%) patients had marked ascites.

**Table1:Demographic data and disease characterization of the enrolled patients.**

| Variables | N=50 |
|---|---|
| **Age(years)** | 54.32±5.28 |
| Range | 44-67 |
| **Sex** | |
| Male | 37(74%) |
| Female | 13(26%) |
| **Residence** | |
| Rural | 30(60%) |
| Urban | 20(40%) |
| **Comorbidities** | |
| Nothing | 21(42%) |
| Diabetes mellitus | 15(30%) |
| Hypertension | 6(12%) |
| Renal disease | 3(6%) |
| Ishaemic heart disease | 5(10%) |
| **Smoking** | 16(32%) |
| **Disease characterization** | |
| **Duration of disease(years)** | 4.13±1.12 |
| Range | 3-7 |
| **Aetiology of liver cirrhosis** | |
| Hepatitis C viruses | 32(64%) |
| Hepatitis B virus | 10(20%) |
| Both infection | 4(8%) |
| Alcoholic hepatitis | 1(2%) |
| Cryptogenic cirrhosis | 3(6%) |
| **Causes of admission** | |
| Refractory ascites | 25(50%) |
| Spontaneous bacterial peritonitis | 9(18%) |
| Hematemesis | 12(24%) |
| Hepatic encephalopathy | 4(8%) |
| **Degree of ascites based on U/S** | |
| Mild | 12(24%) |
| Moderate | 26(52%) |
| Marked | 12(24%) |

**Baseline Laboratory Data of Studied Patients:**are summarized in table2. The mean level of NLR was 7.04±2.45; C-reactive protein was

45.09±10.56 mg/dl and HsCRP was 103.45±23.45 mg/dl. Additionally, 60% of patients were Child Pugh class B.

**Table2:Baseline laboratory data of studied patients.**

| Variables | Mean±SD |
|---|---|
| **Complete blood picture** | |
| Total leucocytic count(x$10^3$/ml) | 4.7±1.5 |
| Neutrophil | 3.2±3.6 |
| Lymphocyte | 1.7±1.1 |
| Monocytes | 0.4±0.04 |
| Eosinophil | 0.09±0.02 |
| Basophils | 0.1±0.04 |
| Hemoglobin(mg/dl) | 10.6±1.34 |
| Platelets(x$10^3$/ml) | 142±77 |
| **Kidney function tests** | |
| Creatinine(mg/dl) | 68.1±24.7 |
| Urea(mg/dl) | 5.7±1.1 |
| **Random blood sugar(µmol/l)** | 5.6±1.5 |
| **Liver function tests** | |
| Aspartate transaminase(U/L) | 78.3±10.3 |
| Alanine transaminase(U/L) | 67.5±12.7 |
| Alkaline phosphatase(U/L) | 114±45.34 |
| Bilirubin(µmol/l) | 54.3±11.7 |
| Protein(mg/dl) | 66.9±7.2 |
| Albumin(mg/dl) | 25.4±4.9 |
| **Neutrophil to lymphocytes ratio(NLR)** | 7.04±2.45 |
| **C- reactive protein(CRP)(mg/dl)** | 45.09±10.56 |
| **High sensitive C-reactive protein(mg/dl)** | 103.45±23.45 |
| **Child Pugh Class** | |
| B | 30(60%) |
| C | 20(40%) |
| **MELD score** | 12.01±1.11 |

**Outcome of Studied Patients:** and development of SIRS are shown in Figure1. Mean duration of hospital stay was 7.67±2.04 days. Development of SIRS occurred in 24 patients(48%) and death occurred in 15(30%) patients.

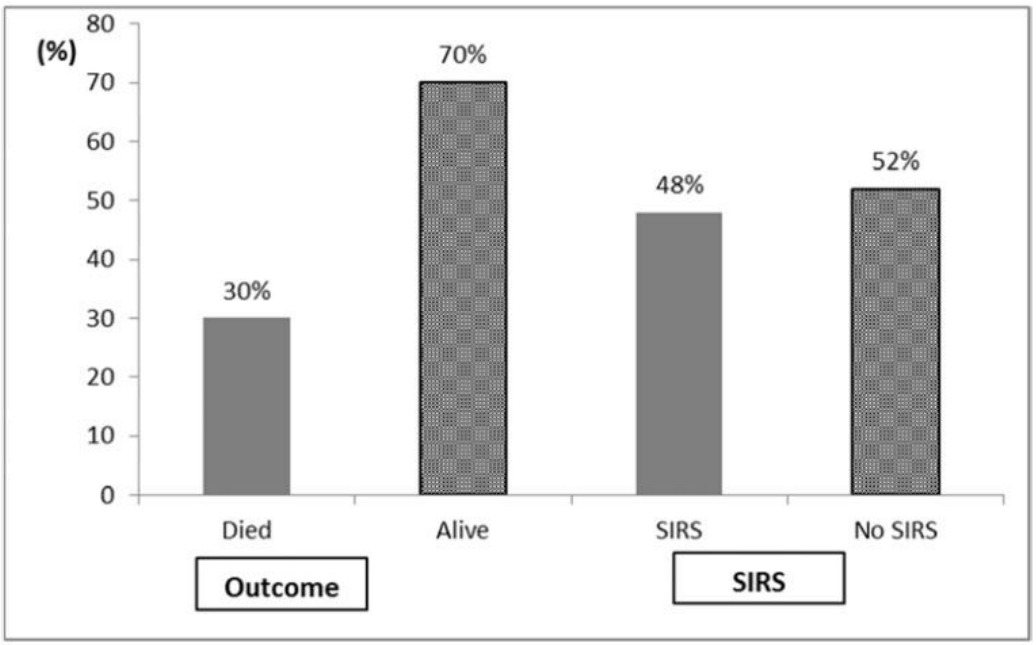


**Figure (1) Outcome and development of SIRS in the current study**

**Level of NLR, CRP and HsCRP based on the patients' Outcome:**

The levels of NLR, CRP and HsCRP were significantly higher in dead(9.11±1.89, 47.98±11.56 and 110.34±27.89 respectively) in comparison to alive patients(5.01±2.12, 39.04±9.87 and 93.03±17.98 respectively) with *P*= 0.01, 0.03 and 0.01 respectively as shown in table3.

**Table3:Level of CRP, HsCRP and NLR based on the Outcome**

| | **NLR** | **CRP** | **HsCRP** |
|---|---|---|---|
| **Dead** | 9.11±1.89 | 47.98±11.56 | 110.34±27.89 |
| **Alive** | 5.01±2.12 | 39.04±9.87 | 93.03±17.98 |
| ***P*value** | **0.01** | **0.03** | **0.01** |

**Level of NLR, CRP and HsCRP based on development of SIRS:**

Neutrophil, NLR, CRP and HsCRP were significantly higher in patients who developed SIRS(3.54±1.45, 8.55±2.01, 45.92±9.45 and 105.51±29.98 respectively) in comparison to those who didn't

(2.21±0.78, 6.38±1.87, 41.22±10.36 and 97.94±20.45 respectively) with P=0.01, 0.03, 0.04 and 0.01 respectively. There was no significant difference in TLC and lymphocytes between both groups as shown in table4.

**Table4:TLC, lymphocytes, neutrophils and NLR in those who developed SIRS**

| **Variables** | **SIRS** | **No SIRS** | ***P*value** |
|---|---|---|---|
| Total leucocytic count($x10^3$/ml) | 4.11±0.99 | 3.99±1.01 | 0.22 |
| Neutrophil($x10^3$/ml) | 3.54±1.45 | 2.21±0.78 | 0.01 |
| Lymphocyte($x10^3$/ml) | 1.65±1.01 | 1.74±0.34 | 0.07 |
| **NLR** | 8.55±2.01 | 6.38±1.87 | 0.03 |
| **CRP** | 45.92±9.45 | 41.22±10.36 | **0.04** |
| **HsCRP** | 105.51±29.98 | 97.94±20.45 | **0.01** |

**Multivariate Regression Analysis for Prediction of SIRS and Mortality in Hospitalized Patients with Liver Cirrhosis:**

Predictors for development of SIRS in hospitalized cirrhotic patients were low albumin level, CRP, and HsCRP. It was also, noticed that predictors of short-term death in such patients was Child class C, high MELD score, NLR, HsCRP and development of SIRS as shown in table5.

**Table5:Multivariate Regression Analysis for prediction of SIRS and death in hospitalized patients with liver cirrhosis**

| | **Prediction of SIRS in hospitalized patients with liver cirrhosis** | | | **Prediction of death in hospitalized patients with liver cirrhosis** | | |
|---|---|---|---|---|---|---|
| | **Odd's ratio** | **95% confidence interval** | ***P* value** | **Odd's ratio** | **95% confidence interval** | ***P* value** |
| Age | 0.34 | 0.91-1.23 | 0.56 | 0.34 | 1.11-2.05 | 0.51 |
| Sex | 1.22 | 1.34-2.01 | 0.11 | 1.22 | 0.34-1.01 | 0.09 |
| Cause of admission | 2.98 | 0.65-1.91 | 0.45 | 0.56 | 1.65-1.98 | 0.31 |
| Low albumin level | **1.24** | **1.56-2.13** | **0.04** | 2.14 | 0.34-1.34 | 0.34 |
| Child Class | 2.67 | 1.03-2.12 | 0.16 | **1.56** | **1.98-2.60** | **0.02** |
| MELD score | 1.09 | 2.09-3.11 | 0.51 | **1.11** | **2.19-3.01** | **0.03** |
| NLR | 1.47 | 1.11-1.43 | 0.47 | 2.01 | 2.11-3.05 | **0.01** |
| CRP | 1.56 | 0.34-0.99 | 0.01 | 0.98 | 0.34-0.99 | 0.30 |
| Hs CRP | 2.51 | 1.04-2.87 | 0.01 | **1.99** | **1.11-1.77** | **0.01** |
| SIRS | - | - | - | **2.13** | **0.32-0.99** | **0.02** |

**Diagnostic Accuracy of NLR, CRP and HsCRP for Prediction of SIRS:**

For prediction of SIRS in hospitalized cirrhotic patients, NLR had 71% sensitivity and 50% specificity at a cutoff point > 5.1 with AUC was 0.57. CRP had 92% sensitivity and 73% specificity at a cutoff point> 43 mg/dl with AUC was 0.88 while HsCRP had 100% sensitivity and 80% specificity at a cutoff point> 94 mg/dl with AUC was 0.95 as shown in figure2.

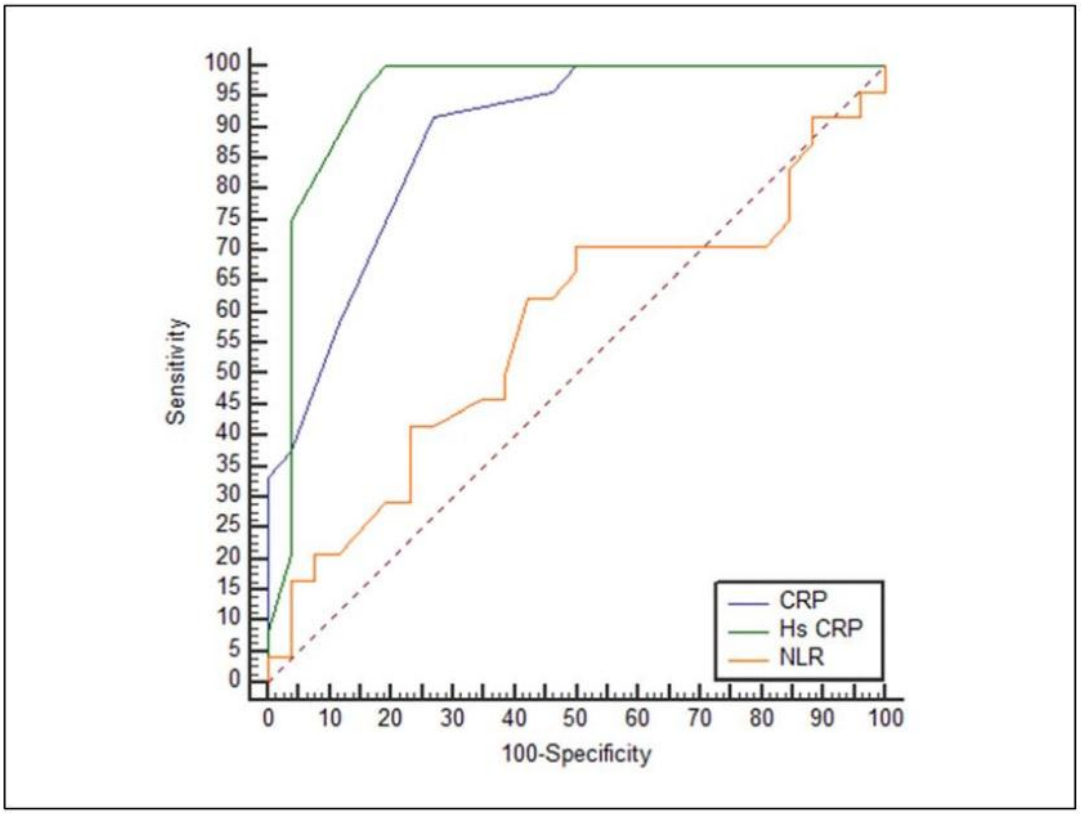


**Figure (2) Receiver operating characteristic (ROC) curve for NLR, CRP and Hs-CRP as predictors for SIRS**

## Diagnostic Accuracy of NLR, CRP and HsCRP for Prediction of Short-Term Mortality:

For prediction of short-term mortality in hospitalized cirrhotic patients, NLR had 100% sensitivity and 90% specificity at a cutoff point>7.8 with AUC 0.95. CRP had 53% sensitivity and 64% specificity at a cutoff point< 43 mg/dl with AUC 0.65 while HsCRP had 100% sensitivity and 60% specificity at a cutoff point> 94 mg/dl with AUC 0.94 as shown in figure3.

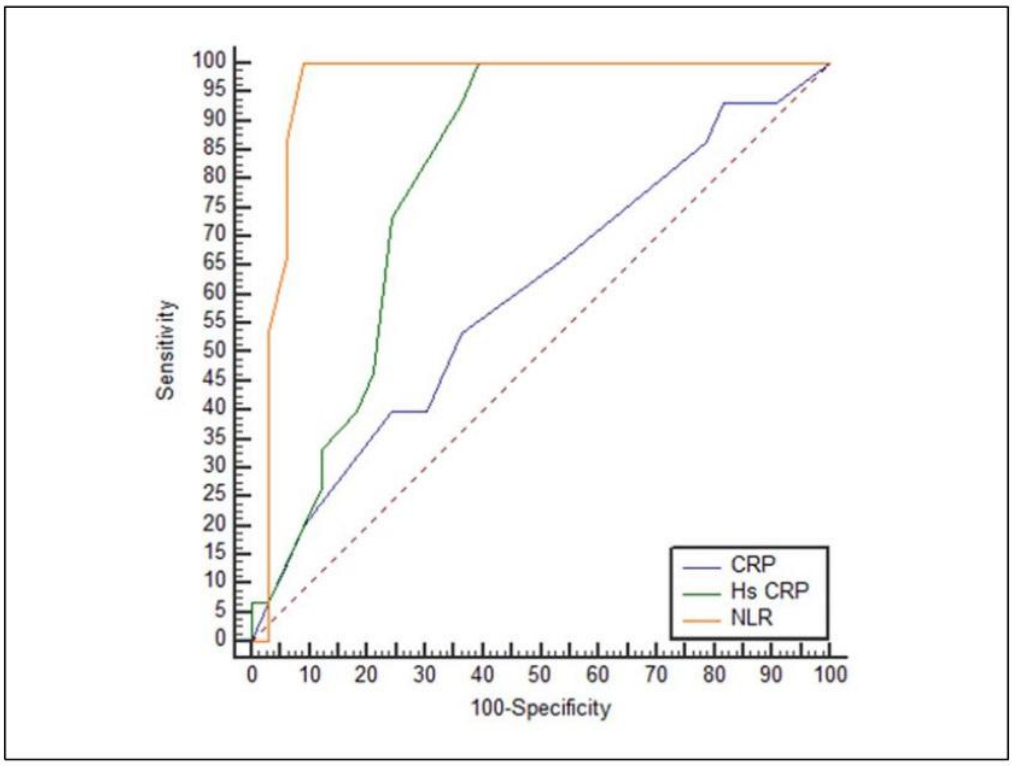


**Figure (3) Receiver operating characteristic (ROC) curve for NLR, CRP and Hs- CRP as predictors for short term mortality**

## Levels of CRP, HsCRP and NLR based on CTP Score:

It was noticed that CRP, HsCRP and NLR were significantly higher in patients with Child C(46.22±9.34, 105.44±19.36 and 9.08±1.99 respectively) in comparison to those with Child B(38.11±8.05, 98.01±21.87 and 5.11±1.11 respectively) with $P< 0.05$ as shown in table6, figure4.

**Table6: Level of CRP, HsCRP and NLR based on CTP Score**

| | CRP | Hs CRP | NLR |
|---|---|---|---|
| **Child B** | 38.11±8.05 | 98.01±21.87 | 5.11±1.11 |
| **Child C** | 46.22±9.34 | 105.44±19.36 | 9.08±1.99 |
| ***P*value** | **0.01** | **0.01** | **0.01** |

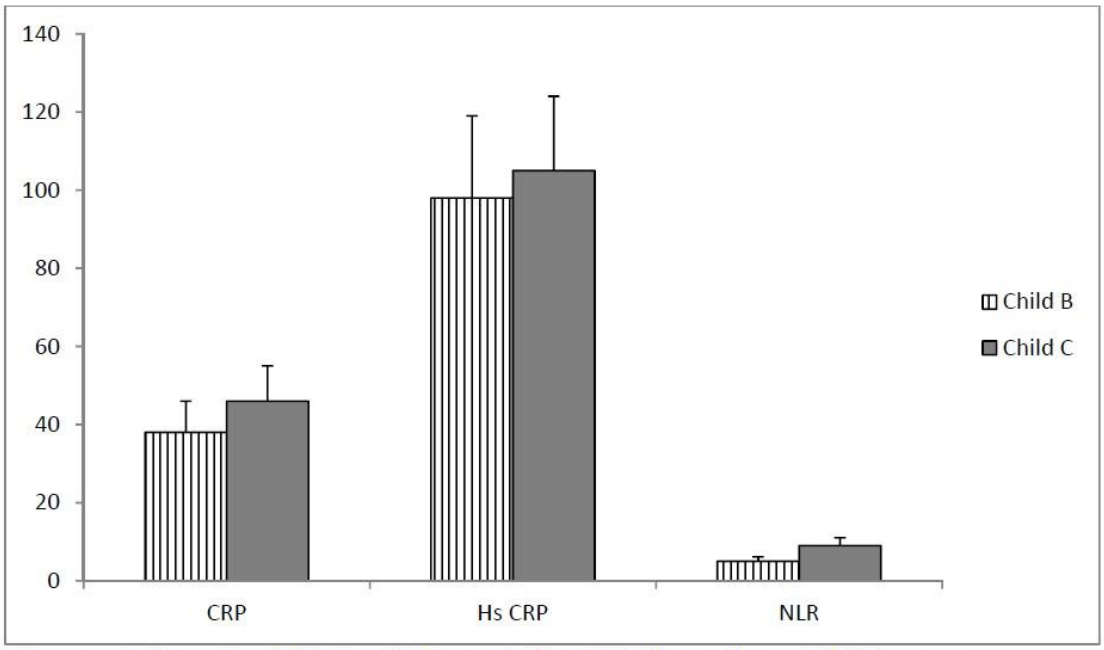


**Figure 4: Level of NLR, CRP and Hs CRP based on Child score**

## Discussion

Cirrhosis is a condition in which the liver does not perform its functions properly due to long term damage so that cirrhosis is one of the leader causes of morbidity and mortality in more developed countries. In Egypt, almost one-fifth(18.1%) of all deaths in males 45 to 54 years old were due to liver cirrhosis(17).

Regarding the demographic characteristic of the sample the mean age of cases in this study was 54.32 years old which was close to the mean of age in other studies(18, 19). Also we found that the majority of the cases included in the study were males(74%) which is consistent with similar studies(20).

Etiologically; the commonest causes of cirrhosis in our study were HCV infection(64%), HBV infection(20%), combined HBV and HCV infection(8%), cryptogenic cirrhosis(6%) and alcoholic cirrhosis was only (2%) which can be explained by low prevalence of alcoholism in Egypt due to religious prohibition and this is consistent with the finding of Darwish et al,.2001(21) and other worldwide studies(22-27).

In our study, SIRS occurred in 24 patients(48%) which can be explained by the immune-compromising state due to imbalance between proinflammatory (enhanced) and anti-inflammatory (inhibited) signaling pathways in immune cells(28-30).

In our study, we found that that patients who developed SIRS had significantly higher neutrophils levels and NLR compared to those who didn't.WBC had insignificant difference between both groups because cirrhotic patients show high WBC count even without infection. NLR reflects the interrelationship between the lymphomononuclear and neutrophilic arms of the process of inflammation. The neutrophilia occurred in the setting of chronic inflammation while lymphopenia is associated with malnutrition and bacterial infection(31, 32). Previously it was reported that higher NLR is associated with cancer and cardiac disease. MELD scoring system has successfully reduced liver transplantation(LT) wait-list registration but its accuracy in predicting mortality has been decreased in cirrhotic patients with MELD≤20 (35). Recently, NLR has come out as a useful predictor of mortality independent of MELD scores in patients with cirrhosis and with HCC, as well as in candidates on the LT waiting list(36, 37).

Our study revealed that CRP and HsCRP levels were significantly higher in patients who developed SIRS compared to those who didn't. Also, we noticed that low albumin level, CRP, and HsCRP were good predictors for development of SIRS in hospitalized cirrhotic patients

which is consistent with previous studies(8, 15, 38). Moreover, it was documented that cirrhotic patients had higher concentrations of CRP than those patients without cirrhosis(39, 40). Also, it was found that CRP is strongly associated with mortality in different populations of patients without cirrhosis in intensive care(41-43).

In our study predictors for development of SIRS in hospitalized cirrhotic patients were low albumin level, CRP, and HsCRP. It was also, noticed that predictors of short term death (within three months) in such patients were Child class C, high MELD score, NLR, HsCRP and development of SIRS.

## Conclusion:

NLR, CRP and HsCRP are helpful diagnostic markers of infection and development of SIRS in hospitalized cirrhotic patients and can be used as predictors of the short-term mortality in hospitalized cirrhotic patients in addition to the classical MELD and CTP score.

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