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Research Article

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Comparison of Lymphocyte/Monocyte ratio (LMR) with Child-Pugh Score and MELD Score in the Determination of Hepatic Dysfunction Severity and Outcome in Cirrhotic Patient

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ABSTRACT

Background: Lymphocyte/monocyte ratio (LMR) is a simple and effective marker that has the potential to predict the severity of hepatic dysfunction in a cirrhotic patient, like the Model for End-Stage Liver Disease (MELD) score and the Child- Pugh (CP) score. However, the usefulness of this newer tool has not yet been tested.

Objectives: Comparison of Lymphocyte/Monocyte ratio with Child-Pugh Score and MELD Score in the determination of hepatic dysfunction severity in patients with cirrhosis was the objective of the study.

Materials and Methods: This cross-sectional analytical study was conducted on cases of cirrhotic patients in the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, dated from September 2018 to August 2019. A total of 40 compensated cases and 82 decompensated cases were included in the process of obtaining informed written consent. Information about clinical profile, laboratory parameters (complete blood count including ESR, serum total bilirubin, serum albumin, ALT, AST, serum creatinine, prothrombin time, INR, etc.) were collected. LMR, MELD score, and CP score were calculated both in compensated and decompensated cirrhotic patients to assess the relationship with the severity of hepatic dysfunction. The correlation between LMR and the CP/MELD score was established by the Pearson correlation test. The receiver operating characteristic (ROC) curve and cut-off values of LMR were obtained, and areas under the ROC (AUROC) curve were calculated to identify the best LMR and/or the MELD score or CPS for predicting hepatic decompensation. The Bland-Altman plot and the Heliey- MacNeil test were used for comparison of measurement techniques. The data were analyzed with the help of SPSS version 20.

Observation and Results: The mean age of the decompensated group was higher than that of the compensated group ($p<0.05$). The mean values for LMR and MELD and CP scores were 7.93±3.08, 5.25±0.43 & 7.10 ±1.19, respectively. Average LMR was significantly higher in compensated cirrhosis patients while CP and MELD Score was lower in that group ($p<0.001$). MELD and CP were positively correlated with each other ($p<0.001$). LMR was negatively correlated to both MELD and CP scores ($p<0.001$). Of all patients, only 4 died (3.3%) and rest 118 (96.7%) survived. The cut off value of LMR, CP and MELD were LMR ≤ 2.18 (sensitivity: 75%, specificity: 87.3%), CPS ≥13.5 (sensitivity: 75%, specificity: 98.3%) & MELD ≥30.5 (sensitivity: 75%, specificity: 94.9%) respectively. Pairwise comparison showed that the difference between the AUCs of MELD and LMR was not statistically significant (0.953 vs 0.887; $p=0.081$). Patients in the low LMR group showed decreased survival than those in the high LMR group ($p=0.000$). The no survived group had lower LMR and higher MELD and CP scores than those of the survived group ($p<0.001$).

Conclusion: In comparison with Child-Pugh Score and MELD Score in the determination of hepatic dysfunction severity in cirrhotic patients, Lymphocyte/ Monocyte ratio is a useful tool.

Keywords: Liver Cirrhosis, Lymphocyte Count, LMR, CP Score, Meld Score, Chronic Hepatitis C, ROC Analysis, Inflammation Mediators, Hepatic Dysfunction

Introduction

Liver cirrhosis has a high morbidity and mortality, which is the 14th common cause of death and it leads to 1.03 million deaths per year in the world [1]. In Bangladesh, incidence of liver diseases is increasing day by day. Study shows that in our country, among the patients with liver diseases, most are suffering from chronic liver diseases like cirrhosis [2,3]. Incidence of Chronic liver disease (CLD) in Dhaka division, 37% and figure is similar to that of Barisal (38%) and Khulna (39%) divisions, both located in the Southern part of Bangladesh. However, in Sylhet division

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only 22.8% patients had CLD, while the figures are extremely high and stand at 50 and 69% respectively in case of Chittagong and Rajshahi divisions [2].

Over the years, many clinical and biochemical parameters have been established to predict the prognosis of cirrhotic patients and correctly assess their short and medium term survival [4]. Currently, a few scoring systems, such as model for end- stage liver disease (MELD) score, Child-Turcotte-Pugh (CTP) score have been proposed for predicting prognosis and survival in liver cirrhosis. However, each scoring system has certain limitations [5,6].

The Child-Pugh score was formulated more than 30 years ago by Child and Turcotte but it is still considered as the cornerstone in prognostic evaluation of cirrhotic patients [7]. However, CTP score has some limitations such as a narrow score range of disease severity and inclusion of subjective criteria such as hepatic encephalopathy and ascites [5,8]. Model for end-stage liver disease score was initially created to predict the survival of patients undergoing trans-jugular intrahepatic porto-systemic shunts. The present version of MELD score incorporated only 3 objective variables, including total bilirubin, creatinine, and INR. MELD score is difficult to calculate without a personal digital assistant and inclusion of INR has certain drawbacks such as INR does not sufficiently reflect coagulopathy and there is an inter-laboratory variation in INR value. Currently, it has been used to rank the priority of liver transplantation candidates [9-11].

Numerous studies have been accomplished to elaborate the role of various inflammatory markers in determining of severity and survival of these patients. Among these markers, the ratio of neutrophils to monocytes, ratio of neutrophils to platelets, and distribution of red cell width (RDW) and its ratio with other blood cells are well studied [12,13].

During the last few years, the most studied inflammatory marker is reported to be the lymphocyte-to-monocyte ratio (LMR). This inflammatory marker has shown its valuable role in determining the survival of patients with various diseases, such as cancer, cardiovascular disease, gastrointestinal diseases (Crohn disease), and colorectal carcinoma [6]. LMR has been also shown to be a good prognostic marker for patients with hepatocellular carcinoma in many recent studies [14,15]. This marker is extensively studied because it is cost-effective, can provide a user-friendly interface and easy to calculate and interpret. The use of lymphocyte-to-monocyte ratio has compared favorably to the traditional staging systems for many critical diseases, and thus, it has been proposed as an alternative method or even as a new standard for assessing the severity and prognosis of patients with liver cirrhosis [5,6,16]. The aim of this study was to compare the lymphocyte-monocyte ratio with MELD and Child-Pugh scores in cirrhosis patients in determining the severity of liver disease and outcome.

Materials and Methods

This Cross sectional analytical study was conducted in Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University dated from September 2018 to August 2019. Before starting of the study ethical clearance was taken from institutional review board of BSMMU.

Patients of both gender aged >18 years who was diagnosed as compensated or decompensated liver cirrhosis were included in the study. Patients admitted because of other medical illness, such as diabetes mellitus, ischemic heart disease, or cerebrovascular accident, patients with superimposed hepatocellular carcinoma, patients with any other concurrent illness that could alter LMR, such as the presence of hematological malignancy, autoimmune disease, or chronic infection (tuberculosis), patients who were administered antibiotics in the last 14 days, pregnant women, severely ill patients or patients not willing to participate in this study were excluded.

Following admission in Department of Gastroenterology patients who match the inclusion and exclusion criteria were approached for enrollment in the study. All of the participants were briefed regarding the nature of the study and also about the aim, objectives, and usefulness of the study. Written informed consent was collected from each patient and from their attendant in case of patients who are unable to provide consent. Information about demographic and clinical profile and laboratory parameters of all patients were collected on the predesigned data sheet. Data of complications of cirrhosis, including jaundice, ascites, variceal bleeding, hepatorenal syndrome and hepatic encephalopathy were recorded. For the convenience of the study, the study population was divided into two groups. Group A consists of the patients having of compensated cirrhosis and group B consists of the patients having decompensated corrhosis. Blood samples were collected for complete blood count, prothrombin time (PT), international normalized ratio (INR), serum albumin, serum electrolytes, and liver function tests. At the time of admission, LMR and CP and MELD scores were calculated for each patient. Lymphocyte and monocyte counts were obtained from complete blood count results and LMR was calculated by dividing the lymphocyte count with the monocyte count. MELD score were calculated using a standard formula available online, and CP score were calculated using five variables (hepatic encephalopathy, INR, ascites, bilirubin, and albumin). LMR and MELD and CP scores were compared between the compensated and decompensated CLD patients groups. In addition, the relationships between these variables were determined. Following investigations, the investigations report were recorded in a preformed case record form. Strict confidentiality was maintained regarding patient information throughout the study.

Operational Definitions

Cirrhosis: Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury that leads to portal hypertension and end stage liver disease. Four clinical stages of cirrhosis have been proposed, with stages 1 and 2 representing compensated cirrhosis; stages 3 and 4 representing decompensated cirrhosis [17].

- Stage 1: absence of both ascites and varices;
- Stage 2: presence of varices without bleeding and the absence of ascites;
- Stage 3: characterized by ascites with or without esophageal varices; and
- Stage 4: characterized by variceal bleeding with or without ascites.

Decompensated Cirrhosis: The presence of jaundice, ascites, variceal bleeding, hepatorenal syndrome or hepatic encephalopathy in patients with cirrhosis is defined as decompensated cirrhosis [18].

MELD Score: The Model for End-Stage Liver Disease, or MELD, is a scoring system for assessing the severity of chronic liver disease. It is calculated according to the following formula MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43 [19].

Child-Pugh's Classification: The Child-Pugh score (or the Child-Turcotte-Pugh score or Child Criteria) is used to assess the prognosis of chronic liver disease, mainly cirrhosis. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement [20].

Points	1	2	3
Encephalopathy	None	Minimal	Advanced (coma)
Ascites	Absent	Controlled	Refractory
Bilirubin (micromol/l)	<34	34-51	>51
Albumin (g/l)	>35	28-35	<28
Prothrombin (s)	<4	4-6	>6

Lymphocyte to monocyte ratio: Lymphocyte and monocyte counts are obtained from complete blood count results, and LMR is calculated by dividing the lymphocyte count with the monocyte count [6].

Statistical Analysis

Collected data were encoded and inputted into SPSS software 20 for windows 10. Continuous variables were expressed as mean ± standard deviation (SD), whereas qualitative or categorical variable were expressed by frequency and percentage. To determine the association between different categorical variable, chi-square test was considered. In case of normally distributed continuous variable, association determined by student-t test. In case of non-normally distributed data corresponding, non-parametric test was considered like Mann Whitney U test. Correlation between LMR and CP/MELD score were established by Pearson correlation test. The receiver operating characteristic (ROC) curve and cut-off values of LMR was obtained and areas under ROC (AUROC) curve were calculated to identify the best LMR and/or the MELD score or CPS for predicting hepatic decompensation and outome. Bland-Altman plot and Hanley MacNeil test were used for comparison of measurement techniques. Data analysis was done with 95% confidence interval. A $p<.05$ was considered as a value of significance.

Results

Table 1: Age distribution of patients with compensated and decompensated cirrhosis (n=122)

Age (years)	Group A (Compensated cirrhosis) (n=40) n (%)	Group B (Decompensated cirrhosis) (n=82) n (%)	Total (n=122) n (%)	P value
18 - 30	9 (22.5)	4 (4.9)	13 (10.7)	0.043
31 - 40	8 (20.0)	12 (14.6)	20 (16.4)	
41 - 50	13 (32.5)	29 (35.4)	42 (34.4)	
51 - 60	7 (17.5)	22 (26.8)	29 (23.8)	
61 - 70	2 (5.0)	10 (12.2)	12 (9.8)	
≥70				
Mean±SD	43.12±12.88	51.19±11.98	48.54±12.81	0.001

P value determined by χ^2 test and independent sample t test as appropriate

Total 122 patients (95 male and 25 female) of cirrhosis were taken for the study and divided them into two groups. Among them, Group A consisted 40 patients with compensated cirrhosis and Group B consisted 82 patients with decompensated cirrhosis. Table I shows, average age of patients was 48.54±12.81 years. Age of compensated group was 43.12±12.88 years and of decompensated group 51.19±11.98 years. The Group B patients was of significantly higher age than that of Group A ($p<0.001$). Majority of patients (34.4%) belonged to age group 41 - 50 years.

Table 2: Demographic characteristics of patients with compensated and decompensated cirrhosis

Characteristics		Group A (Compensated cirrhosis) (n=40) n(%)	Group B (Decompensated cirrhosis) (n=82) n(%)	Total (n=122)	P value
Sex Distribution	Male	28 (70)	67 (81.7)	95 (77.9)	1.44
	Female	12 (30)	15 (18.3)	27 (22.1)	

Residence	Rural	33 (82.5)	58 (70.7)	91 (74.6)	0.161
	Urban	7 (17.5)	24 (29.3)	31 (25.4)	
Marital Status	Unmarried	3 (7.5)	3 (3.7)	6 (4.9)	0.357
	Married	37 (92.5)	79 (96.3)	116 (95.1)	
Education	Illiterate	6 (15.0)	19 (23.2)	25 (20.5)	0.461
	Below SSC	15 (37.5)	26 (31.7)	41 (33.6)	
	SSC	9 (22.5)	10 (12.2)	19 (15.6)	
	HSC	5 (12.5)	15 (18.3)	20 (16.4)	
	Graduate & above	5 (12.5)	12 (14.6)	17 (13.9)	
Occupation	Goverment	1 (2.5)	6 (7.3)	7 (5.7)	0.126
	Non-goverment	6 (15.0)	12 (14.6)	18 (14.8)	
	Business	20 (50.0)	37 (45.1)	57 (46.7)	
	House Wife	10 (25.0)	13 (15.9)	23 (18.9)	
	Farmer	0	11 (13.4)	11 (9.0)	
	Unemployed	3 (7.5)	3 (3.7)	6 (4.9)	
Monthly Income	<10000	23 (57.5)	36 (43.6)	59 (48.4)	0.519
	10000 to 20000	13 (32.5)	32 (39.0)	45 (36.9)	
	20000 to 40000	3 (7.5)	10 (12.2)	13 (10.7)	
	>40000	1 (2.5)	4 (4.9)	5 (4.1)	
Physical activity	Mild	12 (30.0)	22 (26.8)	34 (27.9)	0.168
	Moderate	24 (60.0)	40 (48.8)	64 (52.5)	
	Severe	4 (10.0)	20 (24.4)	24 (19.7)	

* P value determined by Chi-square test

Table 2 shows, male patients were 77.9% of the study patient's and 22.1% were female. Patients from rural area were 74.6% and married population was 95.1%. Among all, 20.5% were illiterate and majority (33.6%) has educational qualification below SSC (33.6%). Most patients were businessman (46.7%).

Majority patients (48.4%) had monthly family income <10000 taka. Among all, 52.5% did moderate heavy physical activity. Proportion of genders, distribution of residence, marital status, educational qualification, occupation, monthly income between two groups were statistically similar (p>0.05). There was also no statistically significant different in relation to physical activity (p>0.05).

Figure 1 shows, most of the patients had hepatis B virus infection (82.79%),8.2% had hepatitis C and 4.92% had Wilson disease.

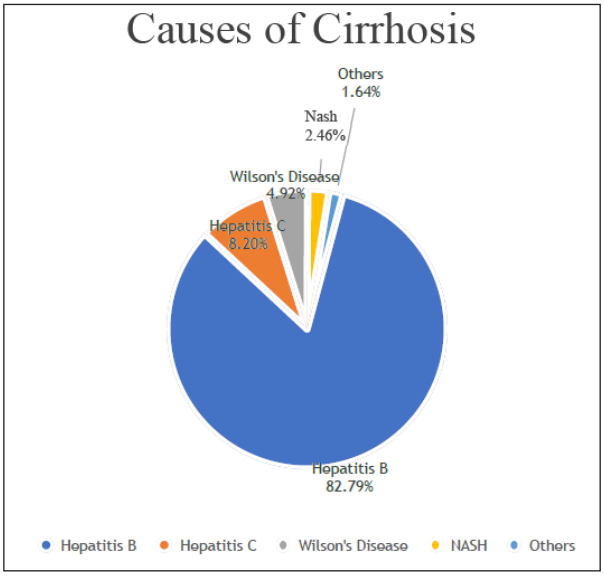


Figure 1: Causes of cirrhosis (n=122)

Table 3: Clinical features of the patients (n=122)

Clinical features	Group A (Compensated cirrhosis) (n=40) n (%)	Group B (Decompensated cirrhosis) (n=82) n (%)	Total (n=122) n (%)	P value
Anemia	11 (27.5)	59 (72.0)	70 (57.5)	<0.001
Jaundice	0	41 (50.0)	41 (33.6)	<0.001
Hyperpigmentation	0	20 (24.4)	20 (16.4)	0.001

Wasting	0	28 (34.1)	28 (23.0)	<0.001
Palmar erythema	0	1 (1.2)	1 (0.8)	0.483
Clubbing	0	10 (12.2)	10 (8.2)	0.021
Leuchonychia	4 (10.0)	61 (74.4)	65 (53.3)	<0.001
Edema	1 (2.5)	29 (35.4)	30 (24.6)	<0.001
Caput medusa	4 (10.0)	22 (26.8)	26 (21.3)	0.033
Splenomegaly	36 (90)	82 (100)	118 (96.7)	0.004
Testicular atrophy	9 (22.5)	59 (72.0)	68 (55.7)	<0.001
Flapping tremor	0	28 (34.1)	28 (23.0)	<0.001
GCS (mean±SD)	14	13±1.60	13.33±1.39	<0.001
Hepatic encephalopathy	0	28 (34.1)	28 (23.0)	<0.001
Ascites	0	73 (89.0)	73 (59.8)	<0.001

P value determined by $\chi 2$ test and independents samples t test as appropriate

Table 3 shows, the more common presenting feature of decompensated cirrhosis patients were jaundice, flapping tremor, ascites and hepatic encephalopathy ($p<0.05$).

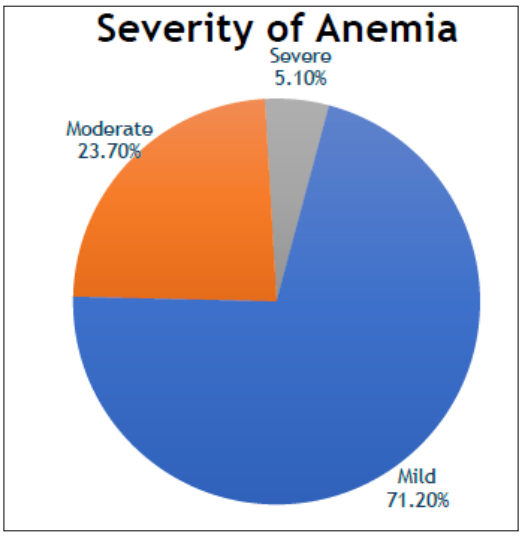


Figure 2: Severity of anemia among decompensated cirrhosis patients (n=59)

The Figure 2 shows, only 5.1 % had severe anemia in decompensated cirrhosis patients and majority had mild anaemia (71%).

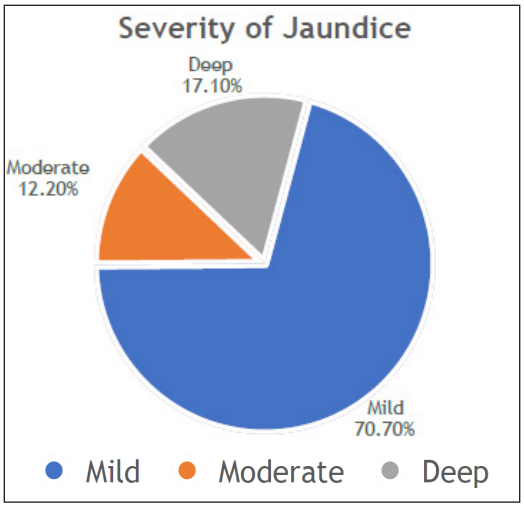


Figure 3: Severity of jaundice among decompensated cirrhosis patients (n=41)

Figure 3 shows, of the decompensated cirrhosis patient majority (70.7%) had mild jaundice, 17.1% had moderate jaundice and 12.2% had severe jaundice.

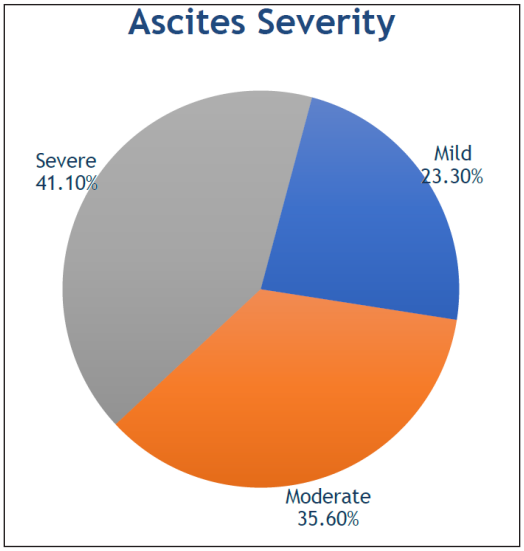


Figure 4: Severity of ascites among decompensated cirrhosis patients (n=73)

Figure 4 shows, of decompensated cirrhosis patients 41.1, 35.6 and 23.3 % had mild, moderate and severe ascites respectively.

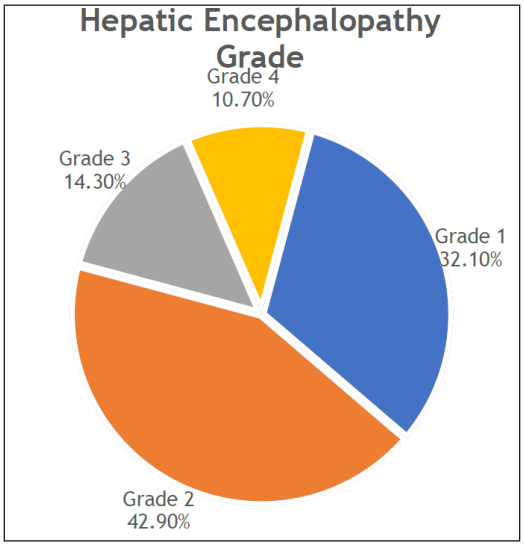


Figure 5: Grade of hepatic encephalopathy among decompensated cirrhosis patients (n=28)

Figure 5 shows, 32.10% had grade 1, 42.9% had grade 2, 14.3% had grade 3 and 10.7% had grade 4 hepatic encephalopathy.

Table 4: Investigation profile of patients (n=122)

Investigations Profile	Group A (Compensated cirrhosis) (n=40)	Group B (Decompensated cirrhosis) (n=82)	Total (n=122)	P value
Hematological				
Hemoglobin (g/dl)	11.71±2.23	10.40±2.01	10.83±2.17	0.001
ESR (mm)	23 (7 - 80)	38.5 (2 - 120)	30 30 (2 - 120)	0.012
WBC (/mm^3)	6000 (1500 -12300)	6000 (1000 - 16500)	6000 (1000 - 16500)	0.913
Lymphocyte (%)	31.70 ±6.14	21.91 ±8.16	25.12 ±8.83	<0.001
Monocyte (%)	4.50 ±1.52	6.87 ±2.67	6.09 ±2.60	<0.001
Platelet (/mm^3)	160000 (50000 - 550000)	106500 (20000 - 450000)	135000 (20000 - 550000)	0.007
LFTs				
Serum bilirubin (mg/dl)	0.95 (0.30 - 1.20)	2.5 (0.29 - 49.30)	1.5 (0.29 - 49.30)	<0.001
ALT (IU/L)	47.5 (10 - 170)	46 (8 - 261)	46.5 (8 - 261)	0.911
AST (IU/L)	38.5 (10 - 147)	40.5 (10 - 345)	40 (10 - 345)	0.481
Serum albumin (mg/dl)	38.86 ±6.00	25.10 ±5.89	29.61 ±8.77	<0.001
PT (s)	12.92 ±1.45	17.83 ±4.89	16.22 ±4.69	<0.001
INR	1.06 ±0.12	1.53 ±0.40	1.37 ±0.40	<0.001
RFT				
Serum creatinine (mg/dl)	0.84 ±0.21	1.51 ±2.19	1.29 ±1.82	0.058
Sodium (mmol/l)	138.53 ±3.69	130.71 ±6.38	133.27 ±6.73	<0.001
Potassium (mmol/l)	4.01 ±0.35	3.92 ±0.76	3.95 ±0.66	0.374
Chloride (mmol/l)	104.18 ±4.38	99.70 ±6.52	101.16 ±6.26	<0.001

Data is expressed as mean±SD or median (range) as appropriate P value determined by independent samples t test or Mann-Whitney U test as appropriate Table 4 shows, decompensated cirrhosis patients had significantly lower hemoglobin, lymphocyte percentage, platelet count, albumin, sodium, chloride levels and significantly higher ESR, monocyte percentage, bilirubin, and PT than compensated cirrhosis patients ($p<0.05$). WBC count, ALT, AST, serum creatinine and potassium levels were statistically similar between two groups.

Table 5: Severity scores among patients (n=122)

Severity scores	Group A (Compensated cirrhosis) (n=40)		Group B (Decompensated cirrhosis) (n=82)		Total (n=122)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
LMR	7.93	±3.08	3.50	±1.52	4.95	±2.99	<0.001
CPS	5.25	±0.43	10.02	±1.94	8.45	±2.76	<0.001
MELD	7.10	±1.19	20.59	±8.56	16.17	±9.49	<0.001

LMR: Lymphocyte-monocyte ratio; CPS: Child-Pugh Score; MELD: Model for End-Stage Liver Disease; P value determined by independent samples t test

Table 5 shows, lymphocyte-monocyte ratio (LMR), Child-Pugh Score (CPS) and Model for End-stage Liver Disease (MELD) score were compared and contrasted for characterization of severity in cirrhosis patients in this study. Average LMR was significantly higher in compensated cirrhosis patients than that of decompensated ones ($p<0.001$). CPS and MELD score was significantly lower in group A than that of decompensated group ($p<0.001$).

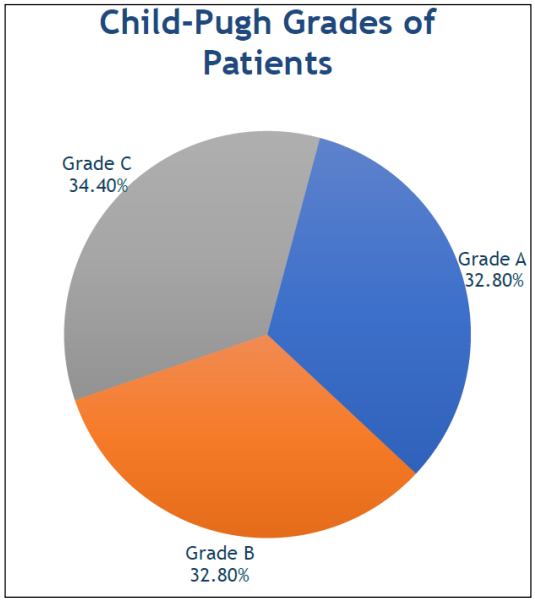


Figure 6: Child-Pugh severity grades of patients (n=122)

Figure 6 shows, among the patients, 34.4, 32.8 and 32.8 % had Child-Pugh Grade C, B and A grading respectively. All the compensated cirrhosis patients had grade A disease (n=40), 40 decompensated cirrhosis patients had grade B disease and 42 decompensated cirrhosis patients had grade C disease.

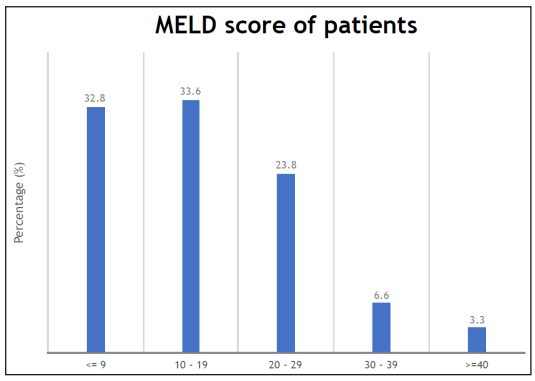


Figure 7: MELD score levels of patients (n=122)

Figure 7 shows, majority of patients had MELD score between 10 - 19 (33.6%), followed by ≤ 9 (32.8%), 20 - 29 (23.8%), 30 - 39 (6.6%) and ≥ 40 (3.3%).

Table 6: Pair-wise correlation table among different scoring systems (N=122)

Correlation pairs	Correlation coefficient (r)	p-value
LMR & CPS	-0.737	<0.001
LMR & MELD	-0.688	<0.001
CPS & MELD	0.891	<0.001

LMR: Lymphocyte-monocyte ratio; CPS: Child-Pugh Score; MELD: Model for End-Stage Liver Disease; Pearson's bivariate correlation was performed to compare between two groups

Table 6 showed that LMR had significantly strong negative correlation with CPS and MELD scores (r= -0.737& -0.688respectively, p<0.001 for both) but CPS and MELD had significantly strong positive correlation (r= 0.891, p<0.001).

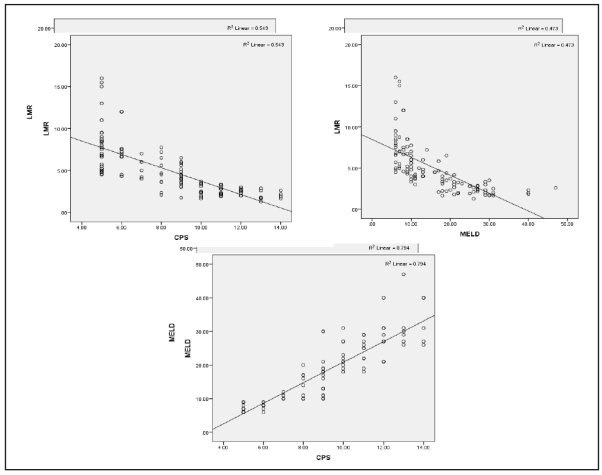


Figure 8: Pearson correlation showing correlation between LMR & CPS, LMR & MELD and CPS & MELD.

Figure 8 shows pearson correlation, the scatter diagrams of pair wise correlation among LMR, CPS, MELD Score.

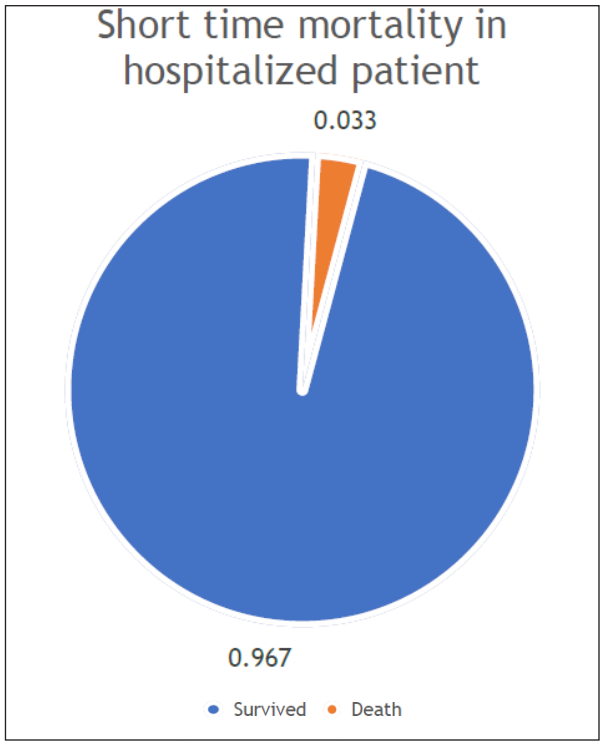
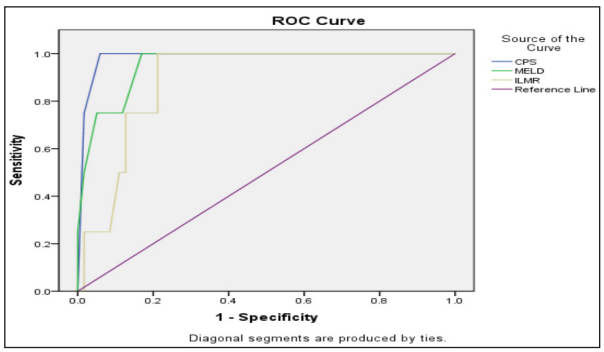


Figure 9: Short term mortality in hospitalized patients (n=122)

Figure 9 shows, among all patients only 4 died (3.3%) and rest 118 (96.7%) survived during hospital stay.



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CPS	.984	.012	.001	.961	1.000
MELD	.953	.032	.002	.890	1.000
ILMR	.887	.043	.009	.803	.970

The test result variable(s): CPS, MELD, ILMR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 10: ROC curve analysis 1/LMR, CPS and MELD in the prediction of death among patients

Figure 10 shows, a negative correlation of LMR with CPS and MELD, an inverse of LMR was taken for ROC analysis. The ROC analysis of different score in the prediction of death among cirrhosis patients found significant AUC 0.887, 0.984 and 0.953 respectively for 1/LMR, CPS and MELD scores ($p<0.05$ for all).

Table 7: Cut-off value, sensitivity and specificity of difference scores in predicting death among patients

Score	Cut-off value	Sensitivity (%)	Specificity (%)
LMR	≤ 2.18	75%	87.3%
CPS	≥ 13.5	75%	98.3%
MELD	≥ 30.5	75%	94.9%

Table 7 shows that at a Cut-off value ≤2.18 of LMR had a sensitivity and specificity of 75% and 87.3% respectively. MELD score at a cut-off value ≥30.5 showed 75% sensitivity and 94.9% specificity in prediction of death among patients with cirrhosis. At a cut-off value of CPS score ≥13.5 was also 75% sensitive but was more specific (98.3%) than LMR and MELD scores.

Table 8: Pair wise comparison of ROC curves* for different scoring methods

Pair	Difference between areas	95% CI		P value
		Lower	Upper	
1/LMR~CPS	0.098	0.027	0.171	0.171
1/LMR~MELD	0.068	-0.008	0.144	0.081
CPS~MELD	0.031	-0.017	0.078	0.211

*Hanley & McNeil, 1982

Table 8 shows, pair wise comparison of ROC curves which was done using Hanley & McNeil method. This shows that 1/LMR had significantly lower AUC than that of CPS score ($p<0.05$), but statistically similar AUC with that of MELD score ($p>0.05$). CPS and MELD score showed statistically similar AUC ($p>0.05$).

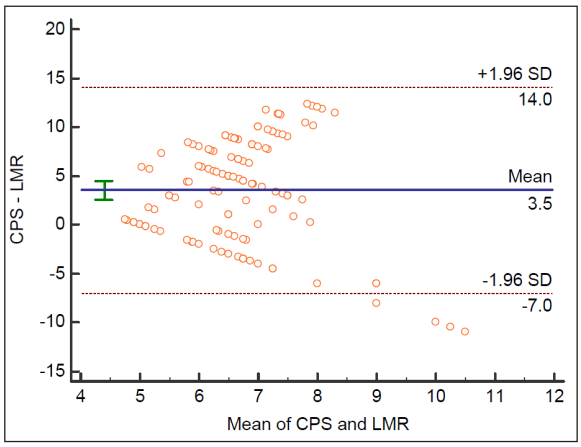


Figure 11: Bland-Altman Plot between CPS and LMR

Figure 11 shows, a Bland-Altman plot which was constructed between CPS and LMR scores. Score clusters around the mean and within 2 standard deviation of the mean when the differences plotted against the averages of the two measurements. This shows that both tests had good agreement in the evaluation of cirrhosis severity.

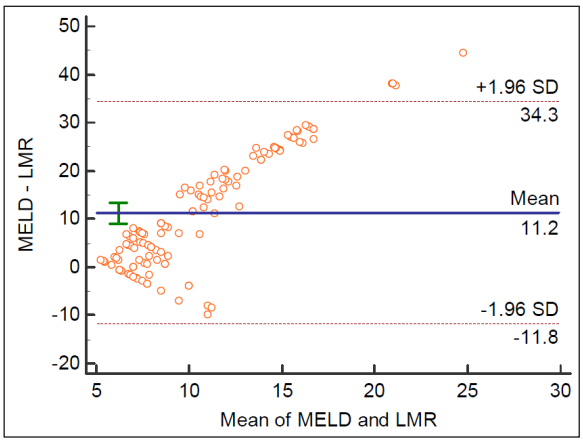


Figure 12: Bland-Altman Plot between MELD and LMR

Figure 12 shows, another Bland-Altman plot was constructed between MELD and LMR scores. Score clusters around the mean and within 2 standard deviation of the mean when the differences plotted against the averages of the two measurements. This shows that both tests had good agreement in the evaluation of cirrhosis severity.

Table 9: Distribution of LMR values in relation to CPS grades (n=122)

CPS Grades	N	LMR (Mean±SD)
Grade A*	40	7.92±3.07
Grade B*	40	4.61±1.38
Grade C*	42	2.43±0.59

*P value <0.001 obtained by ANOVA with post hoc analysis by Bonferroni method

Table 9 shows, the CPS grade A, B and C patients had 7.92±3.07, 4.61±1.38 and 2.43±0.59 LMR respectively. The scores were significantly different from each other in relation to CPS groups ($p<0.001$).

Table 10: Characteristics of variables of the two groups (low LMR vs. high LMR) (n=122)

Variables	Low LMR (≤2.18) (n=18)	High LMR (>2.18) (n=104)	P value
Age (years)	51.94	47.96	0.225
Hemoglobin (g/dl)	9.87	10.99	0.042
WBC (x 10^9 cells /L)	7.33	3.91	0.300
Platelet (x 10^3 cells /L)	108.05	156.62	0.042
Bilirubin (mg/dl)	6.85	3.11	0.071
ALT (U/L)	43.77	60.17	0.127
AST (U/L)	49.44	49.23	0.986
PT (sec)	19.74	15.60	<0.001
INR	1.71	1.31	<0.001
Albumin (g/dl)	22.67	30.81	<0.001
Na (mmol/l)	125.94	134.53	<0.001
Ka (mmol/l)	3.79	3.98	0.383
Cl (mmol/l)	97.39	101.82	0.005
MELD	27.50	14.21	<0.001
CPS	11.77	7.88	<0.001
Survived	15 (83.3)	103 (99)	<0.001
Not survived	3 (16.7)	1 (1)	

Data was expressed as mean and n (%). LMR: Lymphocyte-monocyte ratio; CPS: Child-Pugh Score; MELD: Model for End-Stage Liver Disease; P value determined by independent samples t test and Chi-squared test.

Table 10 shows, significant low hemoglobin, platelet, albumin, sodium and chloride level in low LMR group (p<0.001).PT, INR CPS and MELD score were significantly high in low LMR group than that of high LMR group (p<0.001).In low LMR group 16.7% died and in high LMR group only 1% died. The difference was statistically significant (p<0.001).

Table 11: Association of LMR with CP class of patients with liver cirrhosis (n=122)

CP class	Low LMR (≤2.18) (n=18) (n%)	High LMR (>2.18) (n=104) (n%)	P value
A	0	40 (38.5)	<0.001
B	2 (11.1)	38 (36.5)	
C	16 (88.9)	26 (25.0)	

Data was expressed as n (%). CPS: Child-Pugh Score; P value determined by Chi-squared test

Among low LMR patients, 88.9% had CP C and 11.1% had CP B disease. Whereas in high LMR group respectively 25, 36.5 and 38.5% patients had CP C, B and A disease. Low LMR group had significantly more patients with higher CP class than high LMR group.

Table 12: Characteristics of variables of the two groups (survived and non- survived) (n=122)

Variables	Survived (n=118)	Not survived (n=4)	P value
Age (years)	48.72	43.25	0.403
Hemoglobin (g/dl)	10.81	11.12	0.782
WBC (x 10^9 cells /L)	6.44	3.02	0.694
Platelet (x 10^3 cells /L)	151.34	120.00	0.522
Bilirubin (mg/dl)	3.15	18.72	0.224
ALT (U/L)	56.88	83.25	0.508
AST (U/L)	49.22	50.25	0.964
PT (sec)	15.86	26.50	0.125
INR	1.34	2.26	0.117
Albumin (g/dl)	29.82	23.50	0.018
Na (mmol/l)	133.57	124.25	<0.001
K(mmol/l)	3.94	4.10	0.783
Cl (mmol/l)	101.27	97.75	0.403
MELD	15.49	36.25	0.017
CPS	8.27	13.75	<0.001
LMR	5.04	2.10	<0.001

Data was expressed as mean and n (%). LMR: Lymphocyte-monocyte ratio; CPS: Child-Pugh Score; MELD: Model for End-Stage Liver Disease; P value determined by independent samples t test and Chi-squared test.

Table 12 shows, serum sodium level is significantly low in non-survived group than survived group (p<0.05). CPS is high and LMR is low in non-survived group than that of survived group which is statistically significant (p<0.05).

Though MELD Score is also higher in non-survived group, it's not statistically significant (p>0.05).

Discussion

Hepatic cirrhosis is frequently associated with systemic inflammation [21]. Numerous complications develop in patients of cirrhosis with systemic inflammation which adversely influences the survival of patients [22,23]. Therefore, easy, reproducible and readily-available markers are needed in order to optimize prognosis and lengthen survival. Thus, surrogate serum markers and clinical parameters of systemic inflammation have been sought to improve disease follow-up and management [23]. This study was aimed to assess the role of LMR in assessing the severity in comparison to Child-Turcotte-Pugh score and Model for End-stage Liver Disease (MELD).

Total 122 patients were taken for the study and among them 40 had compensated cirrhosis and 82 patients had decompensated cirrhosis. Decompensated cirrhosis patients had significantly lower lymphocyte count, platelet count, albumin, sodium and chloride levels and significantly higher ESR, monocyte count, bilirubin and PT than compensated cirrhosis patients (p<0.05). ALT, AST and creatinine levels were statistically similar in both groups. Nearly similar findings were reported in other studies [24,25].

Mean LMR was 4.95±2.99 which is significantly lower in cirrhotic patients. Previously Jamil and Durrani as well as Zhang et al found that LMR was significantly lower in cirrhotic patients in comparison to chronic hepatitis patients and healthy controls [6,10]. This study adds to the findings that average LMR was significantly lower in decompensated cirrhosis patients than that of compensated group. Mean CPS and MELD scores were 8.45±2.76 and 16.17±9.49 respectively and both were positively correlated and significantly higher in decompensated group. This is evident that both of these scores were increase with progression of disease. Many studies have suggested that the increasing scores predict severe hepatic dysfunction as well as worse outcomes in patients with liver cirrhosis [11,26].

CPS and MELD score were negativity correlated with LMR and the correlation was strong. These findings were similar to those of Jamil & Durrani and Zhang et al. [6,10]. As the disease progresses, CPS and MELD Score were increases and disruption of LMR ensued and causes decrease in ratio.

The predictive values of the three variables for determining the disease severity and mortality in the cirrhotic patients were assessed using ROC curve analysis. The predictive value was highest for CP score followed by MELD score and LMR (CP=0.984, MELD=0.953 & LMR-1=0.887). In comparison, Jamil and Durrani found that the predictive value was higher for MELD score than for LMR and CP (MELD=0.958; LMR=0.807; CP=0.760) [6]. Zhang et al. also found the similar AUC for MELD score, which was approximately 0.9 and for LMR was 0.8 [10]. This slightly higher predictive value of CP Score may be explained by presence of more hepatic encephalopathy and ascites and absence of significant renal impairment which plays a vital role in MELD Score.

Pairwise comparison of AUCs by using Hanley & McNeil's method showed that there was no statistically significant difference between the AUCs of MELD score and LMR ($p>0.05$) but those between CP and LMR scores were significant ($p<0.05$). Approximately similar AUCs without significant difference showed that both MELD score and LMR can be used with the same efficacy to determine the outcome in these patients during hospital stay.

At a cut-off value of CP Score ≥13.5, sensitivity was 75% and specificity was 98.3% and of MELD score ≥30.5, sensitivity was 75% and specificity was 94.9%. In contrast, Jamil & Durrani found a cut-off value for CP and MELD score respectively >9 (sensitivity: 94.29%, specificity: 56.46%) and >15 (sensitivity: 77.14%, specificity: 88.44%) [6]. In comparison to their study as well as the study of Zhang et al, the present study found a higher sensitivity and specificity for all scores in predicting severity and mortality in hospital [10]. CP was the most sensitive and specific score followed by MELD and LMR. Jamil & Durrani noted that higher sensitivity of CP score indicates that its predictive value in identifying patients with poor outcomes is higher than that of MELD score, whereas the higher specificity of MELD score indicates its predictive value in identifying patients with good outcomes is higher than that of CP score [6]. In contrast to this, all of these score were accurate in predicting poor outcome of cirrhotic patient [6].

At a cut-off value of LMR in this study ≤2.18, sensitivity was 75% and specificity was 87.3%. Study by Jamil and Durrani, the cut-off value for LMR was ≤3.31 (sensitivity and specificity 80 and 74.83% respectively) [6]. Whereas Zhang et al. found a lower cut-off value (2.1) with sensitivity and specificity similar to that of Jamil and Durrani et al. [10].

Among all patients, only 4 patients died (3.3%) and rest 118 patients survived during inpatient hospital treatment. The patients were grouped according to low and high LMR (≤2.18 and >2.18). It was found that patients with low LMR had high MELD and CP scores than those with high LMR. These results are consistent with that of Jamil & Durrani and Zhang et al. [6,10]. Comparing survived group with the non-survived group, MELD and CP scores were significantly higher in the non-survived group than in the survived group and LMR was significantly lower in non-survived group.

Many recent studies have shown that LMR can be used as an independent predictor for survival of patients with liver cirrhosis. Cai et al. proposed a nomogram to predict the survival of patients with decompensated chronic liver disease. The nomogram, based on neutrophil-to-lymphocyte ratio and LMR, was found to be an accurate model in predicting the survival of these patients [5].

In this study patients with cirrhosis groups were further subdivided in to three groups based on their CPS class. Group A, B and C correspond CPS A, B and C classes respectively. Bivariate analysis showed that the mean LMR of these three groups were 7.92±3.07, 4.61±1.38 and 2.43±0.59 respectively which indicate that a distinct value of LMR for each CPS classes can be found. Therefore, LMR has the potential of using as a surrogate for CPS for prognostic grading of cirrhosis patients in places where the CPS can't be obtained. But further well-designed studies are recommended for validation of this idea. Though LMR in predicting the survival of patients with hepatocellular carcinoma has been extensively studied but data on predicting the survival of patients with liver cirrhosis are very limited [27,28]. More studies are required to further emphasize the importance of LMR in predicting the survival of patients with liver cirrhosis because it is simple, easy to calculate and interpret, relatively cheap.

Limitations

This was a single-center study and conducted on hospital admitted cirrhotic patients only; so the result may not be generalized for the all cirrhotic patients. Long term follow up was not done in this study.

Conclusions

In conclusion, this study showed that in comparison to Child-Pugh Score and MELD Score, Lymphocyte/Monocyte ratio (LMR) may be a useful tool for which further long term study is recommended in the determination of hepatic dysfunction severity and prognostic value in cirrhotic patients.

References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012. 380: 2095-2128.
2. Rahman S, Ahmed M, Alam M, Debnath C, Hoque M. Distribution of Liver Disease in Bangladesh: A Cross-country Study. J Hepato-Gastroenterol. 2014. 4: 25-30.
3. Mahtab M. Epidemiology of Viral Hepatitis and Liver Diseases in Bangladesh. J Hepato-Gastroenterol. 2015. 5: 26-29.
4. Botta F, Giannini E, Romagnoli P, Fasoli A, Malfatti F, et al. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: A European study. Gut. 2003. 52: 134-139.
5. Cai YJ, Dong JJ, Dong JZ, Chen Y, Lin Z, et al. A nomogram for predicting prognostic value of inflammatory response biomarkers in decompensated cirrhotic patients without acute-on-chronic liver failure. Alimentary Pharmacology and Therapeutics. 2017. 45: 1413-1426.
6. Jamil Z, Durrani AA. Assessing the outcome of patients with liver cirrhosis during hospital stay: A comparison of lymphocyte/ monocyte ratio with MELD and Child-Pugh scores. Turkish Journal of Gastroenterology. 2018. 29: 308-315.
7. Benedeto-Stojanov D, Nagorni A, Bjelaković G, Stojanov D, Mladenović B, et al. The Model for the End-Stage Liver Disease and Child-Pugh score in predicting prognosis in patients with liver cirrhosis and esophageal variceal bleeding. Vojnosanitetski Pregled. 2009. 66: 724-728.
8. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology. 2004. 40: 802-810.
9. Trotter JF, Olson J, Lefkowitz J, Smith AD, Arjal R, et al. Changes in international normalized ratio (INR) and Model for Endstage Liver Disease (MELD) based on selection of clinical laboratory. American Journal of Transplantation. 2007. 7: 1624-1628.
10. Zhang Jie, Feng G, Zhao Y, Zhang Juanwen, Feng L, et al. Association between lymphocyte-tomonocyte ratio (LMR) and the mortality of HBV-related liver cirrhosis: A retrospective cohort study. BMJ Open. 2015. 5: 1-8.
11. Peng Ying, Qi X, Guo X. Child-pugh versus MELD score for the assessment of prognosis in liver cirrhosis a systematic review and meta-analysis of observational studies. Medicine (United States). 2016. 95: 1-29.
12. Lou Y, Wang M, Mao W. Clinical Usefulness of Measuring Red Blood Cell Distribution Width in Patients with Hepatitis B. PLoS ONE. 2012. 7: 1-6.
13. Karagoz E, Ulcay A, Tanoglu A, Kara M, Turhan V, et al. 2014. Clinical usefulness of mean platelet volume and red blood cell distribution width to platelet ratio for predicting the severity of hepatic fibrosis in chronic hepatitis B virus patients. European Journal of Gastroenterology and Hepatology. 2012. 26: 1320-1324.
14. Hong YF, Chen ZH, Wei L, Ma XK, Li X, et al. Identification of the prognostic value of lymphocyte-to-monocyte ratio in patients with HBV-associated advanced hepatocellular carcinoma. Oncology Letters. 2017. 14: 2089- 2096.
15. Li GJ, Ji JJ, Yang F, Xu HW, Bai Y. Preoperative lymphocyte-to- monocyte ratio predicts survival in primary hepatitis B virus-positive hepatocellular carcinoma after curative resection. OncoTargets and Therapy. 2017. 10: 1181-1189.
16. Jehi L, Yardi R, Chagin K, Tassi L, Russo G Lo, et al. Development and validation of nomograms to provide individualised predictions of seizure outcomes after epilepsy surgery: A retrospective analysis. The Lancet Neurology. Elsevier Ltd. 2015. 14: 283-290.
17. Schuppan D, Afdhal N. Liver Cirrhosis. Lancet. 2008. 371: 838-851.
18. Harrison PM. Management of patients with decompensated cirrhosis. Clinical Medicine, Journal of the Royal College of Physicians of London. 2015. 15: 201-203.
19. Kamath Patrick S, Kim WR. The Model for End-stage Liver Disease (MELD). Hepatology. 2007. 45: 797-805.
20. Olongitas ECH, Eodoridis GVP, Vangeli M, Terreni N, Patch D. Systematic review: the model for end-stage liver disease - should it replace Child- Pugh' s classification for assessing prognosis in cirrhosis? Aliment Pharmacol Ther. 2005. 22: 1079-1089.
21. Behroozian R, Bayazidchi M, Rasooli J. Systemic Inflammatory Response Syndrome and MELD Score in Hospital Outcome of Patients with Liver Cirrhosis. Middle East journal of digestive diseases. 2012. 4: 168-172.
22. Abdel-Khalek EE, El-Fakhry A, Helaly M, Hamed M, Elbaz O. Systemic inflammatory response syndrome in patients with liver cirrhosis. Arab Journal of Gastroenterology. Arab Journal of Gastroenterology. 2011. 12: 173-177.
23. Dirchwolf M, Ruf AE. Role of systemic inflammation in cirrhosis: From pathogenesis to prognosis. World Journal of Hepatology. 2015. 7: 1974- 1981.
24. Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, et al. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. Liver International. 2012. 32: 1407-1414.
25. Hussain M, Khan A, Ali U Bin. Comparison of Serum Sodium Levels in Compensated and Decompensated Cirrhosis Secondary to Chronic Viral Hepatitis C. Pak Armed Forces Med J. 2016. 66: 752-55.
26. Said A, Williams J, Holden J, Remington P, Gangnon R, et al. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. Journal of Hepatology. 2004. 40: 897-903.
27. Song W, Tian C, Wang K, Zhang RJ, Zou SB. The pretreatment lymphocyte to monocyte ratio predicts clinical outcome for patients with hepatocellular carcinoma: A meta-analysis', Scientific Reports. Nature Publishing Group. 2017. 7: 1-7.
28. Yang T, Zhu J, Zhao L, Mai K, Ye J, et al. Lymphocyte to monocyte ratio and neutrophil to lymphocyte ratio are superior inflammation-based predictors of recurrence in patients with hepatocellular carcinoma after hepatic resection. Journal of Surgical Oncology. 2017. 115: 718-728.