

## Article

# Correlation between the Lymphocyte-To-Monocyte Ratio (LMR) and Child–Pugh and MELD/MELDNa Scores in Vietnamese Patients with Liver Cirrhosis

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**Abstract:** Objectives: This study aims to determine cirrhotic patients' clinical and laboratory characteristics, thereby examining the correlation between lymphocyte-to-monocyte ratio and Child–Pugh and MELD/MELDNa scores. Methods: A cross-sectional study with an analysis of 153 patients admitted to the Department of Gastroenterology–Clinical Hematology at Can Tho Central General Hospital. Data were collected via patient interviews and medical records. Results: The included patients were more likely to be male (66.7%) and were  $\geq 60$  years old (51.6%). Excessive alcohol consumption and hepatitis B were the dominant causes of cirrhosis (35.3% and 34.0%). The clinical and laboratory characteristics were similar to previous studies in cirrhotic patients. The mean Child score was  $9.3 \pm 2.1$ , including 9.8% of patients with Child A, 44.4% for Child B, and 45.8% for Child C. The mean MELD and MELDNa scores were  $16.9 \pm 7.1$  and  $19.4 \pm 8.1$ , respectively. The mean lymphocyte-to-monocyte ratio (LMR) is  $2.0 \pm 2.2$  (from 0.09 to 25.3), being negatively correlated with the other scores (Pearson correlation coefficients were  $-0.238$ ;  $-0.211$  and  $-0.245$ , respectively, all  $p$ -values  $< 0.01$ ). Patients with LMR below 3.31 were more likely to be classified as Child–Pugh B and C. Conclusion: The correlation between LMR with Child–Pugh, MELD, and MELDNa scores was weak and negative.

**Keywords:** liver cirrhosis; clinical; hematological; LMR; Child–Pugh; model for end-stage liver disease; MELDNa; Vietnamese



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## 1. Introduction

Liver cirrhosis is the most prevalent hepatobiliary disease in Vietnam and other countries. Important causes of cirrhosis involve hepatitis B virus, hepatitis C virus, alcohol, and diseases of the biliary tract, such as gallstones, sclerosing cholangitis, autoimmune hepatitis, etc. [1,2]. However, there is no accurate data on the percentage of patients with cirrhosis because this disease often manifests silently. In Vietnam, the mortality rate of cirrhotic patients has not been fully accounted for since the disease is usually detected when complications are present. The leading causes of death in patients with cirrhosis were encephalopathy, gastrointestinal bleeding, hepatorenal syndrome, cancer, infections, etc. [3].

Liver transplantation is a breakthrough method in the treatment of cirrhosis but is mainly done in developed countries. The number of patients waiting for liver transplantation is increasing, so it is necessary to have an early but straightforward prognosis to

identify patients who need transplantation. Over the past 40 years, the Child–Pugh classification has been widely used to predict mortality in patients with cirrhosis, and other scores were also referred to. For instance, the MELD (Model for End-Stage Liver Disease) index has been examined as a predictor of mortality in cirrhosis patients awaiting liver transplantation in Europe and America to replace the Child–Pugh score to classify patients on the waiting list for liver transplantation [4,5]. Further developed from the MELD index, the MELD-Na has recently been applied to cirrhotic patients with low serum sodium levels [6,7].

Alternatively, the lymphocyte-to-monocyte ratio is currently a prognostic marker in advanced cirrhosis given the integration of systemic inflammation and immune system dysregulation in its physiopathological pathway. This starts with a local injury in the liver, which, once over-compensated, leads to the diminished synthesis of immune proteins and recognition receptors and further reduces the bactericidal capacity of the innate immune system. Secondarily, the gut and its associated lymphoid tissue, which act as the barrier against intestinal pathogens, are affected, i.e., leaky and overwhelmed by an elevated enteric bacterial load. Such a long-lasting inflammation finally results in the exhaustion and reprogramming of various immune cell lines, including LMR alteration. Other clinical and biochemical parameters such as heart rate and respiration rate, body temperature, and portal blood pressure are also changed when cirrhosis advances [8]. Recent studies have shown that white blood cell count is an isolated factor of systemic inflammation and can be an independent predictor of the development of acute-on-chronic liver failure, its severity, and its associated mortality [9–12]. Additionally, the LMR has shown a role in predicting the survival of different patients such as cancer, cardiovascular disease, and Crohn's [13–17]. Given that the LMR is an easy to obtain, readily available, low-priced, and reproducible biomarker [16], it could be considered a prognostic marker in patients with cirrhosis but has not been studied adequately. Our study, therefore, aimed to determine the clinical and laboratory characteristics of cirrhotic patients and thereby examine the correlation between LMR and current prognostic tools in use, such as Child–Pugh and MELD/MELDNa scores.

## 2. Methods

### 2.1. Settings and Study Population

A cross-sectional study was conducted, including patients over 15 years old who were diagnosed with cirrhosis and hospitalized at the Department of Gastroenterology–Clinical Hematology at Can Tho Central General Hospital between March 2019 and March 2020. Patients who did not have hematological and biochemical tests had other severe medical conditions that affected the assessment of liver function and did not consent to participate in the study were excluded. Patients diagnosed with hepatic carcinoma (based on the standards by the Ministry of Health of Vietnam [18]) were transferred to a specialized center, namely Can Tho Oncology Hospital, thus not being included in our study population. In total, 153 patients were selected and interviewed by trained medical research assistants, and their medical records were also retrieved.

### 2.2. Data Analysis

Based on their clinical and laboratory values, patients were classified according to the Child–Pugh Scale A (5–6 points), B (7–9 points), and C (10–15 points) and according to their MELD and MELDNa values, using the following formulas:

$$\text{MELD} = 3.78 \times \ln [\text{blood bilirubin (mg/dL)}] + 11.2 \times \ln [\text{INR}] + 9.57 \times \ln [\text{blood creatinine (mg/dL)}] + 6.43 \quad (1)$$

$$\text{MELDNa} = \text{MELD} - \text{Na} - [0.025 \times \text{MELD} \times (140 - \text{Na})] + 140 \quad (2)$$

$$\text{Lymphocyte/monocyte ratio} = \text{Lymphocyte/monocyte} \quad (3)$$

Data were analyzed using SPSS 16.0 software. Qualitative variables are commented by frequency and percentage, and quantitative variables were commented as mean  $\pm$  standard

deviation or median (min–max). Pearson’s correlation coefficients were used to evaluate the correlation between LMR and Child–Pugh and MELD/MELDNa scores.

### 2.3. Ethical Issues

This study was conducted in compliance with ethical principles of medical research, i.e., affecting the health and spirit of the patient. It was approved by the Scientific Research Council of Can Tho University of Medicine and Pharmacy on 14 May 2021, according to Decision No: 1003/QD-CYDCT. The patients and/or their families were explained the purpose of the study and the personal and medical information that would be collected. All included cases gave consent to participate in the study.

## 3. Results

### 3.1. Characteristics of the Included Subjects

A total of 153 patients who met the inclusion criteria were included in the study. The majority of patients were over 60 years old (51.6%), were male (66.7%), were farmers, or had retired (36.6% and 43.8%). Table 1 shows that alcohol abuse and hepatitis B virus infection were the most common causes of cirrhosis (35.3% and 34.0%). Since being diagnosed with cirrhosis  $\leq 5$  years, the time accounted for the most significant percentage (62.1%).

**Table 1.** Patient characteristics at admission.

Patient Characteristics ( <i>n</i> = 153)	Percentage
Age at admission	
<40	8.5
40–59	39.9
60	51.6
Male	66.7
Job	
Farmer	36.6
Worker	6.5
Purchase	4.6
Officials	3.3
Housewife	5.2
Retired	43.8
Causes of cirrhosis	
Alcohol abuse <sup>a</sup>	35.3
Hepatitis B virus	34.0
Hepatitis C virus	11.1
Steatosis	3.3
Time from being diagnosed with cirrhosis	
First diagnosis	24.8
5 years	62.1
6–10 years	9.1
>10 years	4.0

<sup>a</sup> Consumption of more than 2 units per day (1 unit is equal to 354 mL of beer, 150 mL of wine, or 45 mL of strong liquors).

### 3.2. Clinical and Subclinical Characteristics

Table 2 shows that fatigue is the most common symptom with a rate of 90.2%, followed by anorexia at 82.4%, insomnia, and abdominal pain, which are also present at a high level of 56.9% and 49.7%; symptoms of nausea, loose stools, and constipation were found in <20%; and menstrual disorders were only 1.9% (Table 3). Vital signs with temperature <38 °C (88.9%), blood pressure 100–140 mmHg (79.1%), and pulse <100 beats/minute (69.3%) are the group of vital signs accounting for the majority of patients’ component grouping. Examination of physical symptoms with jaundice accounted for a high percentage (68.5%), followed by varicose veins (41.8%), cleft hands (39.2%), limb edema (55.6%), and mucosal bleeding, while gynecomastia in men accounts for a low rate (8.5%; 7.77%). Symptoms

of abdominal examination included no ascites (30.1%), little ascites (23.5%), and much ascites (46.4%).

**Table 2.** Clinical and laboratory characteristics of patients participating in the study.

Clinical Features ( <i>n</i> = 153)	Percentage
Physical symptoms	
Fatigue	90.2
Anorexia	82.4
Insomnia	56.9
Stomachache	49.7
Nausea	11.1
Loose stools	19.6
Constipation	16.3
Sign of life	
Temperature (°C)	
<38	88.9
38–<39	5.9
39	5.2
Blood pressure (mmHg)	
<100	8.5
100–140	79.1
>140	12.4
Pulse (times/minute bpm)	
<100	69.3
100–120	26.8
>120	3.9
Symptoms of abdominal examination	
No ascites	30.1
Little ascites	23.5
Much ascites	46.4
Physical symptoms	
Perceptual disturbances	24.8
Nevus araneus	41.8
Palmar erythema	39.2
Leg edema	55.6
Gynecomastia	7.7 (8/103 male pts)
Mucosal bleeding	8.5
Jaundice	68.5
Subclinical Features	Mean (SD)
Peripheral blood cell analysis	
Platelets/mm <sup>3</sup>	115730 ± 88122
Prothrombin rate (%)	57.09 ± 20.44
INR	1.64 ± 0.64
APTT (seconds)	38.60 ± 9.70
Indicators of red blood cells	
Red blood cell count/mm <sup>3</sup>	3.42 ± 0.87
Hematocrit (%)	31.49 ± 7.10
Hemoglobin (g/dL)	10.37 ± 2.48
MCV (fL)	93.42 ± 12.08
MCH (g)	30.70 ± 4.61
Indicators of white blood cells	
WBC/mm <sup>3</sup>	8.567 ± 6.040.50
Neutrophil/mm <sup>3</sup>	6.173.20 ± 5.423.30
Lymphocyte/mm <sup>3</sup>	1.295.50 ± 826.28
Monocyte/mm <sup>3</sup>	821.14 ± 535.15
Acidophilic/mm <sup>3</sup>	245.43 ± 350.27
Preferred Base/mm <sup>3</sup>	42.77 ± 57.79

**Table 2.** *Cont.*

Subclinical Features	Mean (SD)
Blood chemistry	
Albumin (g/L)	27.03 ± 6.15
Protein (g/L)	67.75 ± 9.11
Total bilirubin (μmol/L)	89.42 ± 109.07
Direct bilirubin (μmol/L)	59.29 ± 81.50
SGOT (U/L)	123.90 ± 247.86
SGPT (U/L)	76.61 ± 182.59
Glucose (mmol/L)	7.27 ± 5.06
Urea (mmol/L)	5.95 ± 3.90
Creatinine (μmol/L)	95.74 ± 63.17
Sodium (mmol/L)	131.76 ± 4.75
Potassium (mmol/L)	3.65 ± 0.68
Chlorine (mmol/L)	96.12 ± 5.16
Calcium (mmol/L)	2.03 ± 0.17

**Table 3.** Child–Pugh Scale.

Assessment Scale	Child–Pugh Scale			
	All	Group A	Group B	Group C
Number of patients, <i>n</i> (%)	153 (100)	15 (9.8)	68 (44.4)	70 (45.8)
Classification based on rating scales, median (min–max)				
MELD	16 (6–40)	9 (6–15)	13 (6–23)	22 (9–40)
MELDNa	19 (6–40)	9 (6–19)	15.5 (6–30)	25.5 (9–40)
Lymphocyte/monocyte	1.76 (0.09–25.34)	2.07 (1.07–4.32)	2.01 (0.36–25.34)	1.23 (0.09–5.05)

In addition, Table 2 also details the hematological and biochemical paraclinical characteristics. Platelets, red blood cells, APTT(s), and INR changed according to the patients' pathology. The leukocyte values, prothrombin, and bilirubin ratios reflect increased liver fibrosis. Albumin and protein index were within normal limits ( $27.0261 \pm 6.15047$  g/L;  $67.75 \pm 9.10516$  g/L). However, the average glucose value was slightly high ( $7.268 \pm 5.06297$  mmol/L). Electrolyte parameters indicate that sodium, chloride, calcium, and potassium may be affected in cirrhotic patients.

### 3.3. Correlation between LMR and the Child–Pugh and the MELD/MELD-Na Scores

Most patients belonged to Child B and Child C classifications (44.4% and 45.8%). The mean MELD score is  $16.9 \pm 7.1$ . The mean MELDNa score is  $19.5 \pm 8.1$ . The mean LMR was  $2.0 \pm 2.2$ . Details of LMR, MELD, and MELD-Na values per Child–Pugh classification are shown in Table 3.

Our study showed that LMR had a weak, negative correlation with Child, MELD, and MELD-Na scores, with *r* being 0.238, 0.211, and 0.245, respectively (Table 4).

Additionally, when we stratified the patients by their LMR, i.e.,  $\leq 3.31$  and  $> 3.31$  (Table 5), patients in the  $\leq 3.31$  level were more likely to be classified as Child–Pugh B and C ( $p < 0.05$ ).

**Table 4.** Correlation between LMR and Child–Pugh, MELD, and MELD-Na scores.

<i>n</i> = 153 Patients		Lymphocyte/Monocyte	Child	MELD	MELD-Na
Lymphocyte/monocyte	Pearson correlation	1	−0.238	−0.211	−0.245
	Sig. (2-tailed)		0.003	0.009	0.002
Child	Pearson correlation	−0.238	1	0.749	0.744
	Sig. (2-tailed)	0.003		0.000	0.000
MELD	Pearson correlation	−0.211	0.749	1	0.947
	Sig. (2-tailed)	0.009	<0.001		0.000
MELDNa	Pearson correlation	−0.245	0.744	0.947	1
	Sig. (2-tailed)	0.002	<0.001	<0.001	

**Table 5.** Combination of LMR with Child–Pugh classification in cirrhotic patients.

The Child-Pugh Classifications	Lymphocyte/Monocyte $\leq 3.31$ , <i>n</i>	Lymphocyte/Monocyte $> 3.31$ , <i>n</i>
A	13	2
B	56	12
C	67	3

Contingency Coefficient *C* = 0.199 and *p* = 0.042.

## 4. Discussion

### 4.1. General Patient Characteristics

In our study, there were 153 patients, in which the number of male patients was double that of female patients (66.7%; 33.3%). This finding is consistent with the previous studies in Vietnam [19,20] and others worldwide [21–24]. Thus, the male predominance is apparent, especially in developing countries. The mean age of our study population was 60 years (ranging from 22 to 88 years), being higher than previous literature, i.e.,  $55.0 \pm 11.1$  by Vo et al. [20],  $54.8 \pm 8$  by Hassan et al. [25], and  $53.1 \pm 12.0$  by Jamil et al. [11]. Thus, our patients were a bit older. This could be explained by studies' differences in life expectancy and health care. We also found that the proportion of patients with cirrhosis was highest in retired people (43.8%) and farmers (36.6%). This could be explained by the fact that older patients were more likely to have other chronic diseases, increasing their severity of cirrhosis. The farming group accounted for the major working class in Vietnam. The leading causes of cirrhosis in our study, i.e., alcohol consumption (35.3%), hepatitis B (34.0%), and hepatitis C (11.1%), were consistent with another study in Vietnam by Vo et al. [26]. Meanwhile, studies in other parts of the world showed a markedly increased proportion of hepatitis B (76.4% in Abidjan) [21] and alcohol (63.9% in India and 81.4% in Portugal) [26–28]. Most patients in our study were recently diagnosed with cirrhosis (24.8%), and 62.1% had the disease for  $\leq 5$  years. This could be accounted for by the fatal complications in patients with prolonged cirrhosis that decreased the number of patients in the upper stratum, i.e., having the disease for  $\geq 6$  years.

### 4.2. Clinical and Laboratory Characteristics

In our study, fatigue (90.2%) and anorexia (82.4%) accounted for a very high proportion of functional symptoms. Other symptoms, i.e., insomnia, abdominal pain, nausea, diarrhea, and constipation, also accounted for a relative proportion. These findings were consistent with previous studies on patients with cirrhosis [29]. Only 5.2% of patients had a high fever in our study, and 79.1% had normal blood pressure. Regarding pulse status, the pulse rate is  $<100$  beats/min, accounting for 69.3%. Physical symptoms indicating jaundice were common in 68.5% of patients with cirrhosis, varicose veins (41.8%), crimson hands (39.2%), limb edema (55.6%), and perceptual disturbances (24.8%), which appeared at quite different rates. Notably, mucosal bleeding appeared, and male gynecomastia had a low frequency of only 8.5% and 7.77% of the patients studied, respectively. These symptoms



vary with the severity of the disease. In the symptoms of abdominal examination, ascites are a symptom that may indicate the decompensated stage of cirrhosis. The study by Bathaix et al. identified 61% ascites [21]; in the study of Charif I, the rate of ascites was 96% [30]. In the research by Mahassadi et al., 74.2% had ascites [31].

The subclinical characteristics of platelet values, prothrombin ratio, INR, and APTT(s) were studied with similar properties to the study of the authors Alsaad AA et al. [32], Bathaix FM et al. [21], Liu X et al. [33], Biyik M et al. [34], and Marroni PC et al. [35]. These values changed with the severity of the disease. For instance, the prothrombin ratio is reduced in cirrhotic patients. Red blood cell indices, including the erythrocyte count, MCV, and MCH, also varied with the disease severity: most cirrhotic patients had macrocytosis. Meanwhile, some were noticed with microcytic anemia due to underlying disease or long-term blood loss. Regarding leukocytes, in our study, the white blood cell count and white blood cell composition varied according to the medical conditions, indicating that leukocytosis cirrhotic patients were at high risk. Regarding blood biochemical characteristics, the albumin value in our study was lower than in the Alsaad's study (29 g/L) [32] but higher than in the Bahaix's study (25.4 g/L) [21]. The mean protein level in the decanter was normal, and the glucose level was high. The bilirubin level was also high, with free bilirubin accounting for the major percentage. The values of hepatic enzymes (ALT and AST) and other biochemical results also varied with the disease severity.

#### 4.3. Correlation between LMR and the Child–Pugh and the MELD/MELD-Na Scores

In this study, the distribution of Child–Pugh scores was Child A (9.8%), Child B (44.4%), and Child C (45.8%). Meanwhile, these proportions in Charif's study were Child A (19.2%), Child B (54.6%), and Child C (26.1%) [30] and, in Fayad's study, were Child A (12.2%), Child B (35.8%), and Child C (52%) [24]. This shows a marked difference in the distribution across Child classifications, especially for Child B and C. The mean values of MELD and MELDNa scores and LMR in our study were similar to the findings by other authors [19,25,36].

A recent study on the pediatric population showed that LMR had a strong negative correlation with MELD but a weak negative correlation with Child–Pugh scores [37]. Meanwhile, in our study with most patients over 40 years, LMR showed a weak correlation with both. Whether the difference in age distribution and/or the comorbidities in the older population could play a role in the correlation with LMR is unknown.

Other studies on the prognosis potential of the LMR also had similar results for liver cancer, liver resection due to cancer, and hepatitis B infection, which mean that as this ratio decreased, these scores increased; that is, liver failure became more severe. [11,14–17,37–40].

A previous study by Jamil et al. [11] in 182 cirrhotic patients (mean LMR being 6.23) showed that the cut-off value of LMR at 3.31 could be used to determine the outcome of treatment during the hospital stay. These authors also noted that the LMR was easy to calculate and had a potential prognosis nearly equal to those of Child–Pugh and MELD scores [11]. Supporting, our additional analysis (Table 5) showed that patients with the  $LMR \leq 3.31$  were more likely to be classified with Child–Pugh B and C ( $p = 0.042$ ).

#### 4.4. Limitations and Implications

The current study had a cross-sectional design performed in a single center, and the number of included patients was also small. Therefore, we could not perform post hoc analyses to examine the correlation with the LMR in smaller cut-off strata, which could have varied with the patients' demographic, clinical, and subclinical parameters. For instance, the correlation between LMR and MELD could be stronger in the younger population, as discussed previously [37].

Given these limitations, we could only find a weak correlation between available scoring systems (i.e., Child–Pugh and MELD/MELDNa) and the LMR. Should the sample size be larger with more parameters included, this model could be improved with stronger

correlation in specific strata, as suggested in Table 5 with the LMR  $\leq 3.31$ . This small study population thus also limited the generalization of our findings.

Few studies evaluate the role of LMR as a prognostic tool in patients with liver cirrhosis, which is our study's main strength. Based on the current findings, we believe that a follow-up study with larger sample size is necessary to consolidate its clinical application versus other scoring systems such as Child–Pugh and MELD/MELD–Na.

## 5. Conclusions

Most patients in our study were over 60 years old and had 7 points or more of a Child–Pugh classification. Compared with popular prognostic rating scales for cirrhosis, such as Child–Pugh, MELD, and MELDNa, the LMR showed a weak negative correlation, with  $r$  being around 0.2. In addition, when we classified the LMR between the two levels as  $\leq 3.31$  and  $>3.31$ , the lower level included significantly more patients at Child–Pugh B and C, suggesting that the LMR can be used as a simple tool to predict the outcomes of cirrhotic patients in clinics with limited resources. Since the number of patients in our study was small, larger studies must corroborate our findings.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Not applicable.

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