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Neutrophil to Lymphocyte Ratio (NLR) as a Predictor of Mortality in Critically Ill Cirrhotic Patients

AHMED RAMADAN, M.D.; KAUSAR ABUL KASHEM, M.Sc.; MAHMOUD ABOUEL KHAIR, M.D. and TAMER ELBAZ, M.D.

The Department of Endemic Medicine and Hepato-Gastroenterology, Faculty of Medicine, Cairo University

Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) is a novel inflammation score that has been shown to predict poor clinical outcomes.

Aim of Study: Is to explore the utility of NLR as a predictor of short-term mortality in critically ill cirrhotic patients.

Patients and Methods: This is a prospective observational cohort study in which fifty critically ill cirrhotic patients admitted in the intensive care unit without hepatocellular carcinoma were enrolled between December 2017 and June 2018. NLR in comparison with CTP, MELD, SOFA, APACHE II scores was assessed for the prediction of mortality.

Results: Patients were 32 males and 18 females with mean age of 57.8±11.3 years. The etiologies of liver cirrhosis included HCV infection (n=38), HBV (2), AIH (3), NASH (1), Wilson disease (1) and cryptogenic (5). The follow-up duration was 28 days, during which 28 patients died (56%). The median NLRs were 12.8 and 11 in non-surviving and surviving patients respectively (p-value=0.536). The lone factor that correlated with mortality was serum sodium level (p 0.049). NLR score was found significant in correlation with MELD score (p-value=0.002).

Conclusion: We found a higher NLR among non-survived patients but without statistical significance. Serum sodium played a clearer role in predictingmortality. A significant correlation was found between NLR and MELD to predict early mortality in critically ill cirrhotic patients and no single independent score effectively predicted mortality.

Key Words: *Neutrophil to lymphocyte ratio (NLR) – ICU – Cirrhosis – Mortality.*

Introduction

CIRRHOSIS is the end stage of liver disease caused by different hepatocellular insults. Once present, the natural course of cirrhosis from compensated disease to decompensated disease. This decompensation is commonly associated with ascites, disturbed mental condition, coagulopathy, jaundice and overall persistent worsening of liver functions [1]. Once deterioration of end-stage liver disease occurs, the 5-year survival markedly drops to lower than 20% and liver transplantation is largely recommended [2]. However, the limited number of available organs leads to a significant burden of the disease and results in a large number of intensive care unit (ICU) admissions [3].

Patients admitted to ICU have a poor prognosis. Septic shock is one of the leading causes of mortality in the ICU. Predicting mortality in patients hospitalized in ICU is crucial for assessing the severity of illness, interventions and health care policies. Several severity scores have been developed with the objective of predicting hospital mortality after ICU admission. The first scores that were proposed include APACHE 4 (Acute Physiology and Chronic Health Evaluation) and SAPS6 (Simplified Acute Physiology Score). These scores are known to discriminate survivors and non-survivors well [4]. However, several studies showed that they fail to accurately predict the actual probability of death [5]. A number of non-invasive and invasive clinical markers and systems have been proposed and some of them are clinically well established to assess prognosis in liver disease, in particular, cirrhosis.

The systemic inflammatory response (SIRS) is recently recognized as a main pathogenetic factor in circulatory dysfunction and immune dysregulation of advanced cirrhosis [6]. Neutrophil to lymphocyte ratio (NLR) is considered a marker of SIRS. It represents the relationship between the neutrophilic count (reflecting ongoing inflammation) and lymphocytic count (reflecting the immune regulatory pathway) [7]. Elevated NLR previously proved to be a useful predictor for overall survival in several cancerous conditions such as pancreatic cancer, lung cancer and colorectal cancer [8-10]. In addition, it predicted the overall survival for patients

Correspondence to: Dr. Ahmed Ramadan Mohamed
E-Mail: ramadan22ahmed@gmail.com

with hepatocellular carcinoma (HCC) and played a good prognostic factor post HCC management such as radiofrequency ablation and trans-arterial chemo-embolization (TACE) [11-13]. Moreover, NLR was an early indicator ofsevere acute pancreatitis [14] and predicted hepatitis B related liver cell failure [15,16].

In our study, we aimed to prospectively evaluate the efficacy of the NLR in comparison with other liver-specific scoring systems like Child-Turcutt-Pough and Model of End-Stage Liver Disease (CTP and MELD) and ICU related scoring systems of predicting mortality (SOFA and APACHE II) in predicting the short-term outcome of critically ill liver cirrhotic patients who are admitted in ICU. Thus, it could help to preserve the resources of ICU for high-risk patients and improve the outcome of such patients through prioritizing their admissions in ICU.

Patients and Methods

This is a prospective observational cohort study to evaluate the efficacy of the neutrophil to lymphocyte ratio (NLR) in comparison with liver-specific scoring systems (CTP and MELD) and ICU related scoring systems of predicting mortality (SOFA and APACHE II) in predicting the outcome of critically ill liver cirrhotic patients admitted in ICU, so we can improve their outcome through prioritizing their admissions in ICU.

We enrolled fifty patients; between December 2017 to June 2018, This study enrolled fifty critically ill cirrhotic ICU admitted patients in the Endemic Hepatology and Gastroenterology Department, Faculty of Medicine, Cairo University, Egypt; during the period of December 2017 to June 2018. We excluded cirrhotic patients with the following criteria: Presence of hepatocellular carcinoma, haematological disorders, cardiac cirrhosis, concurrent autoimmune disease, Human Immunodeficiency Virus seropositivity, primary renal diseases and pregnancy. Local ethical committee approval was taken before starting the study. All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

All included patients were thoroughly assessed, investigated and managed during their ICU admission. Laboratory assessment included liver biochemical profile (serum bilirubin, albumin, liver enzymes and INR), complete blood count with differential counts, C Reactive Protein (CRP), serum creatinine and electrolytes (sodium and potassium). Ultrasonographic examination, ascetic fluid analysis and arterial blood gases are performed to studied patients. Several scores were calculated: Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, Sequential Organ Failure Assessment (SOFA) score and Acute Physiology And Chronic Health Evaluation II (APACHE II) score. Neutrophil to lymphocyte (NLR) score is measured by dividing the neutrophil value to the lymphocyte value in complete blood count. The primary outcome was defined as death from any cause after admission to the ICU unit.

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 21) as follows: Classification variables were expressed as frequency and percentage and continuous variables were expressed as mean ± standard deviation. The differences among categorical variables were evaluated by Chi-square test and Fisher for sure Chi-square test. Mann-Whitney U test was applied for comparison of median values of two groups. Correlation analysis was done by Spearman correlation analysis test. Multiple linear regression was used to find the significant predictors for the NLR scores. $p<0.05$ was accepted as statistically significant.

Results

In our study, fifty consecutive critically ill cirrhotic patients were ICU admitted. Their mean age was 57.8±11.3 years with a male predominance (64%). Chronic hepatitis C represented the commonest aetiology of liver disease (76%). Other aetiologies included autoimmune hepatitis, HBV, NASH, Wilson's disease while cryptogenic cirrhosis was documented in 10% of cases. The primary cause of ICU admission was hepatic encephalopathy (66%) followed by gastrointestinal bleeding (22%), renal impairment (14%), dyspnea (10%) and persistent vomiting that led to dehydration (6%). The majority of patients had decompensated cirrhosis (82% were CTP class C) while CTP class B was present in 16% of patient and a single patient was CTP class A (Table 1). Concerning the baseline laboratory data and the different scores at time of ICU admission, patients had low platelet count (127.6±85.6 10^3/cmm), hyperbilirubinemia (5.48± 6.78mg/dl), hypoalbuminemia (2.3±0.52 g/dl) and high INR (1.77±0.46). The mean leucocytic count was 10.69±6.55 10^3/cmm. Serum creatinine level was high (2.04±1.7mg/dl) while normal electrolyte levels (sodium and potassium). High CRP level (79.36±72.04) was documented. Concerning the different scores, mean MELD score, SOFA score

and APACHE II score were 21.9±7.8, 6.9±2.8 and 19±6 respectively. NLR score was 16.37±15.57 (Table 2). During the 28-days follow up period, 30 patients died while 15 patients remained alive and we missed data for 5 patients. The main causeof death was sepsis and metabolic acidosis (61%) while other causes were hematemesis and hepatic encephalopathy.

Table (1): Demographic and baseline features of studied patients.

Data of studied patients	N (%)
Age:	
30-50 years	11 (22%)
51-70 years	34 (68%)
>70 years	5 (10%)
Gender:	
Male	32 (64%)
Female	18 (36%)
Aetiologyof liver cirrhosis:	
HCV	38 (76%)
Cryptogenic	5 (10%)
AIH	3 (6%)
HBV	2 (4%)
NASH	1 (2%)
Wilson disease	1 (2%)
Indications for ICU admission:	
Hepatic encephalopathy	33 (66%)
Hematemesis & melena	11 (22%)
Renal impairment	7 (14%)
Dyspnea	5 (10%)
Persistent vomiting/Dehydration	3 (6%)
Child Pugh score:	
Child A	1 (2%)
Child B	8 (16%)
Child C	41 (82%)

Table (2): Laboratory data and different scores of studied patients.

	Mean ± SD
TLC (10^3/cmm)	10.69±6.55
Neutrophil count (%)	80.6±11.6
Lymphocyte count (%)	10±8.6
Platelet (10^3/cmm)	127.6±85.6
Total Bilirubin (mg/dl)	5.48±6.78
Albumin (g/dl)	2.3±0.52
Creatinine (mg/dl)	2.04±1.7
Sodium (mg/dl)	132.9±8.8
Potassium (mg/dl)	4.5±1.2
CRP	79.36±72.04
INR	1.77±0.46
CTP Score	11±2
MELD Score	21.9±7.8
SOFA Score	6.9±2.8
APACHEII Score	19±6
NLR Score	16.37±15.57

Deceased patients had higher NLR values than survived patients but without statistically significant difference. We looked for a potential correlation between NLR and other laboratory values. High serum creatinine and hypoalbuminemia showed a significant correlation with NLR. No similar correlation was found with platelet count, serum bilirubin, CRP, electrolytes and haemoglobin levels. Among scores, MELD score significantly correlated with NLR values while the other scores (CTP, SOFA and APACHE II scores) did not correlate with NLR (Table 3). In addition, we assessed the different variables including patients' age, laboratory values and the different scores if they correlated with survival outcomes. The lone factor that correlated with survival was serum sodium level (p 0.049). No significant differences were found between died and survived patients as regards the other parameters (Table 4).

Table (3): Correlation between NLR and Laboratory values and different scores.

	NLR Score	
	r	p-value
Platelet (x10^3cmm)	0.27	0.058
INR	–0.168	0.243
Total Bilirubin (mg/dl)	0.272	0.056
Albumin (g/dl)	–0.305	0.031
Creatinine (mg/dl)	0.495	<0.001
Hemoglobin (g/dl)	0.142	0.324
Sodium (mmol/L)	–0.135	0.350
Potassium (mmol/L)	0.254	0.075
CRP	0.232	0.209
CTP Score	0.102	0.479
MELD Score	0.425	0.002
SOFA Score	0.244	0.088
APACHEII Score	0.23	0.108

Table (4): Correlation between survival and different quantitative variables.

	Died (n=30)	Alive (n=15)	p-value
Age (years) Mean±SD	58.6±12.21	57±10.51	0.555
TLC (10^3/cmm) Mean±SD	11.93±6.38	9.51±7.34	0.139
Neutrophil count (%) Mean±SD	83.3±11.3	76.6±12.71	0.055
Lymphocyte count (%) Mean±SD	8.5±7.14	11.4±11.12	0.966
Platelet (10^3/cmm) Mean ±SD	126.9±66.86	141.7±120.91	0.613
INR Mean ±SD	1.8±0.46	1.68±0.41	0.366
ALT (IU/L) Median (IQR)	62.5(37-132)	58(26-102)	0.329
Bilirubin (mg/dl) Median (IQR)	2.4(1.4-10)	2(1.33-3.32)	0.448
Albumin (g/dl) Mean ±SD	2.25±0.58	2.38±0.35	0.227
Creatinine (mg/dl) Mean±SD	2.26±1.73	1.87±1.84	0.202
Sodium (mg/dl) Mean±SD	130.7±9.79	136.6±6.22	0.049
Potassium (mg/dl) Mean±SD	4.7±1.11	4.3±1.48	0.096
CRP Mean ±SD	84.01±63.98	76.25±95.01	0.344
CTP Score Mean±SD	12±1.83	11±2.29	0.169
MELD Score Mean±SD	23.6±8.27	19.4±5.99	0.117
SOFA Score Mean±SD	7.2±2.78	6.8±3	0.846
APACHE II Score Mean±SD	20±5.24	17±4.98	0.098
NLR Score Median (range)	12.8 (8.4-21.5)	11 (4.3-34)	0.536

Finally, we performed regression analysis for NLR with other calculated scores. MELD score was the only significant predictor of mortality while the rest of scores revealed no significance. NLR and MELD showed a significant positive correlation (Table 5 and Fig. 1).

Table (5): Regression analysis NLR with other scores.

	B	*p*-value	95.0% Confidence Interval for B	
			Lower Bound	Upper Bound
(Constant)	16.064	0.226	–10.272	42.401
CTP Score	–1.712	0.19	–4.304	0.88
MELD Score	1.042	0.009	0.273	1.811
SOFA Score	0.556	0.649	–1.889	3.001
APACHE II Score	–0.375	0.414	–1.292	0.542

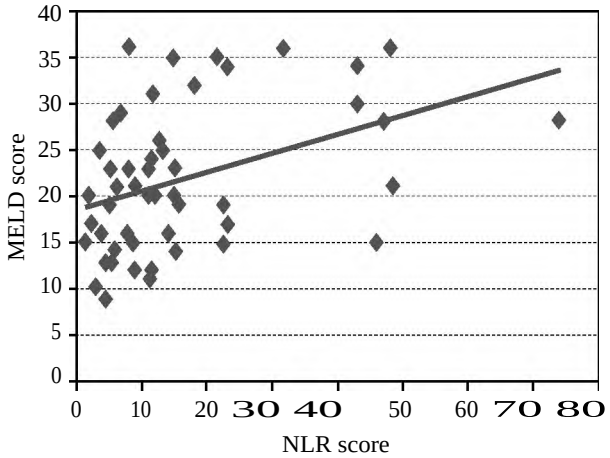

Fig. (1): Correlation between NLR and MELD score.

Discussion

Liver cirrhotic patients are functionally immunosuppressed and they are more liable to infection [17]. Infection is a common triggering factor for various organ dysfunctions, including hepatic encephalopathy, renal derangement and shock. Many studies previously described the need forclassifying these patients, to determine who is going to benefit from ICU admission [18]. Researchers have been persistently looking for scoring systems that are actually capable of providing accurate information on both disease severity and short-term prognosis [19]. Standard hepatic prognostic scores, such as CTP and MELD scores, are insufficient as they focus on the liver without considering other systems [20].Different scoring systems developed to anticipate the fate of critically ill patients admitted to the ICU. These models performed well to predict the mortality of the general ICU patient population but they under/overestimated mortality in selected patient sub-groups [21].

NLR can be easily calculated using differential complete blood count and is a fast-growing parameter that is currently widely studied. Numerous studies reported that NLR can be used as a prognostic marker of mortality [22]. Our median NLR value of non-surviving patients was higher than that for surviving patients but without statistically significant difference (*p*-value 0.536). This result was actually different from many other studies. However, the type of study, the nature of patients, the aim for NLR and the primary outcomes of these studies were not comparable to our study. While we did a prospective study for short term survival of critically ill cirrhotic patients upon their ICU admission, Biyik et al., performed a retrospective study and enrolled 145 stable cirrhotic patients without overt infection and followed them for more than two years. They showed a good prognostic role for NLR [23]. Leithhead et al., studied NLR in patients listed for liver transplantation and in the absence of overt infection [6]. In other studies, NLR was used to predict hospital acquired bacterial infections in decompensated cirrhosis [24] and to early detect antibiotic resistance in patients with infected cirrhotic ascites [25]. Rice et al., investigated the long-term survival (one year follow-up) in hospitalized patients with cirrhosis and awaiting liver transplantation. They concluded that the risk of death associated with acute immune dysregulation (and so NLR) even persisted long after their initial hospitalization [26]. While our patients predominantly developed decompensated liver cirrhosis post-viral hepatitis (76%), Khoury et al., studied NLR association with inflammatory activity and fibrosis grade in patients with non-alcoholic fatty liver disease (NAFLD) [27]. This was further clarified in a systematic review for the role of NLR to assess liver fibrosis and cirrhosis [28].

Different pathophysiologic explanations were proposed to explain the role of NLR in prediction of mortality in cirrhotic patients. A raised NLR could be due to high neutrophilic count, low lymphocytic count or both. Kalra et al highlighted the role of low-doseendotoxaemia induced by the chronic liver disease with a subsequent deleterious SIRS. This will be associated with abundant neutrophils with a possible qualitative functional defect [29]. Concerning the reduced number of lymphocytes, Zhang et al., proposed that a large number of lymphocytes could be recruited to the liver to play a role in necroinflammation [16]. This was proved by Zou et al., who found that the intrahepatic CD8+ T-cell number was nearly 50-fold higher in patients with acute on chronic liver cell failure as compared to normal individuals [30]. Finally, Kwon et al., presumed that features of decompensated

liver cirrhosis, such as hepatic encephalopathy, hepatorenal syndrome, hypersplenism and hyperventilation, may mask the presence of overt infection and SIRS in cirrhotic patients **[7]**.

In our study, NLR strongly correlated with MELD score in prediction of mortality of studied patients. Deng et al., declared that adding NLR to other conventional predictive systems provided added values without extra economic costs **[31]**. As NLR correlates with hepatic decompensation, it is clearly expected that NLR will be related to higher values of MELD score. Lin et al., proposed a nomogram that incorporated NLR with MELD and albumin for prediction of 30-day mortality in decompensated liver cirrhosis **[32]**. Certain studies found that NLR could even predict mortality in low MELD score patients **[23,29]**.

In our study, the mean serum sodium level in surviving and non-surviving patients were 136.6 ±6.22 and 130.7±9.79 respectively. This proved to be statistically significant (p-value=0.049). A negative correlation between NLR and serum sodium was previously demonstrated in a study that focused on patients listed for liver transplantation **[6]**. Another study concluded that low sodium levels were associated with high complications in critically ill cirrhotic patients. It was also associated with in-hospital mortality and poor short-term prognosis **[33]**. Even more, Bossen et al., studied 1112 patients of whom 302 developed hepatic encephalopathy. They concluded that the hazard rate to develop encephalopathy increased by 8% for every one mmol/L reduction in serum sodium **[34]**. Although being within normal ranges, serum sodium below 139mEq/L predicted mortality in cirrhotic patients **[35]**. Sodium incorporated with MELD score (MELD-Na) well predicted mortality of patients with decompensated liver cirrhosis **[36]**.

In conclusion, we found a higher NLR level among non-survived patients but without statistical significance. Serum sodium played a clearer role in the prediction of mortality. In addition, a significant correlation was found between NLR and MELD to predict early mortality in critically ill cirrhotic patients. No single independent score effectively predicted mortality in our studied patients.

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النسبة بين خلايا العدلة والخلايا الليمفاوية كمؤشر للوفاة فى مرضى التليف الكبدى فى الحالات الحرجة

لقد لوحظ ارتفاع فى نسبة الوفيات لمرضى التليف الكبدى المتواجدين بوحدات الرعاية الحرجة وذلك يعود لخلل فى جهاز المناعة الخاص هؤلاء المرضى.

وللتنبؤ باحتمالية الوفاة لهؤلاء المرضى تم دراسة عدة معايير لتقييم المرضى للمساعدة فى هذا الأمر ومنها قياس النسبة بين خلايا النيتروفيل واللمف فى الدم.

ولقد تم دراسة هذه العلاقة على عدد خمسين مريضاً من مرضى التليف الكبدى المتواجدين برعاية قسم الأمراض المتوطنة بالقصر العينى فى الفترة من ديسمبر ٢٠١٧ إلى يونيو ٢٠١٨ كان متوسط مدة المتابعة ٢٨ يوماً بالنسبة لـ٤٥ مريضاً (تم فقدان متابعة ٥ مرضى)، توفى خلالها ٢٨ مريضاً.

وأظهرت النتائج وجود علاقة بين هذه النسبة وبين ارتفاع نسبة الوفاة بين مرضى الرعاية حيث وجد أن انخفاض هذه النسبة مرتبط بارتفاع معدل الوفاة ووجود أيضاً علاقة بين انخفاض هذه النسبة وارتفاع معيار الميلد المستخدم أيضاً فى تقييم مرضى التليف الكبدى وارتفاع نسبة الوفاة.

لذلك لابد من إجراء المزيد من الابحاث فى هذا المجال باستخدام أعداد أكبر من المشاركين لإثبات وجود علاقة بين هذه النسبة والتنبؤ بمعدل الوفاة لمرضى التليف الكبد عند الحجز بوحدات الرعاية الحرجة ومقارنتها بالمعايير المستخدمة الأخرى فى هذا المجال.