Platelet-Lymphocyte Ratio and Neutrophil-Lymphocyte Ratio as Early Mortality Predictors for Patients with End-Stage Chronic Liver Disease

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ABSTRACT

Background: *Chronic liver disease (CLD) often results in fatal complications. Child-Turcotte-Pugh (CTP) score is the earliest predictor of mortality but the model for end-stage liver disease (MELD) score is more objective. Studies showed platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) could become mortality predictors for chronic liver disease. We aimed to investigate NLR and PLR as early mortality predictors for CLD, in comparison with CTP and MELD scores.*

Method: *This was a retrospective observational cohort study. We recruited patients with CLD (liver cirrhosis and hepatocellular carcinoma/HCC), from Saiful Anwar Hospital, Indonesia. Data regarding PLR, NLR, CTP, and MELD scores were obtained from the medical records. Participants were followed for 30 days to determine survival.*

Results: *Ninety patients were recruited in the study. There were 31 deaths (34.4%) in 30 days. Mortality was higher in HCC patients than liver cirrhosis. Although NLR had similar sensitivity with CTP (51.6%), neither PLR (p 0.956) nor NLR (p 0.087) could significantly better predict mortality than CTP (p 0.001) or MELD scores (p 0.002). In opposite to PLR, NLR had a positive correlation with MELD and CTP scores.*

Conclusion: *On the contrary to the PLR, the NLR positively correlated with the severity of the disease, NLR had the potential as a predictor of early mortality for patients with end-stage CLD as compared to CTP and MELD scores. But either NLR or PLR still could not substitute both CTP and MELD scores.*

Keywords: *platelet-lymphocyte ratio, neutrophil-lymphocyte ratio, chronic liver disease, mortality*

ABSTRAK

Latar belakang: *Penyakit liver kronik seringkali menyebabkan komplikasi bersifat fatal. Skor Child-Turcotte-Pugh (CTP) merupakan skor paling awal sebagai prediktor mortalitas namun skor model for end-stage liver disease (MELD) merupakan skor paling obyektif. Penelitian menunjukkan platelet-lymphocyte ratio (PLR) dan neutrophil-lymphocyte ratio (NLR) dapat menjadi prediktor mortalitas untuk penyakit liver kronik. Penelitian ini bertujuan untuk membandingkan NLR dan PLR sebagai prediktor mortalitas dini untuk penyakit liver kronis dengan skor CTP dan MELD.*

Metode: *Studi ini bersifat kohort observasi retrospektif. Seluruh pasien dengan penyakit liver kronis (sirosis hati dan karsinoma hepatoseluler/KSH) dari RSUD Dr. Saiful Anwar direkrut dalam penelitian. Data mengenai PLR, NLR, skor CTP dan MELD diambil dari rekam medis. Partisipan diikuti selama 30 hari untuk menentukan kesintasan.*

Hasil: *Sembilan puluh pasien dianalisis dalam penelitian ini dan didapatkan 31 kematian (34.4%) dalam 30 hari. Tingkat mortalitas lebih tinggi pada pasien KSH dibandingkan sirosis hati. Meskipun NLR memiliki sensitivitas yang sama dengan skor CTP (51.6%), namun baik PLR (p = 0.956) maupun NLR (p = 0.087) masih belum dapat memprediksi mortalitas secara lebih baik dibandingkan skor CTP (p = 0.001) maupun MELD (p = 0.002). Berkebalikan dengan PLR, NLR menunjukkan korelasi positif terhadap skor MELD dan CTP.*

Simpulan: *Berkebalikan dengan PLR, NLR berkorelasi positif dengan tingkat keparahan penyakit dan NLR berpotensi sebagai prediktor mortalitas dini untuk pasien dengan penyakit liver kronis bila dibandingkan dengan skor CTP dan MELD. Namun NLR dan PLR masih belum dapat menggantikan skor CTP maupun MELD.*

Kata kunci: *platelet-lymphocyte ratio, neutrophil-lymphocyte ratio, penyakit liver kronis, mortalitas*

INTRODUCTION

Liver cirrhosis, as the progression of chronic liver disease (CLD), often result in fatal complications, especially in the decompensated state.[1] The Global Burden of Disease reported 10.6 million cases of decompensated cirrhosis in 2017 worldwide with more than 1.32 million deaths. Cirrhosis-related deaths were estimated to be 2-4% of all deaths in 2017.[2] Chronic liver disease could also develop into hepatocellular carcinoma (HCC). More than half of patients with HCC had evidence of cirrhosis. Hepatocellular carcinoma is the 5th most common cancer in 2012, which causes 9.1% of cancer-related death of all cancer in the world. East Asia, South East Asia, and North Africa have the highest rate of mortality.[3] Mortality in decompensated chronic liver disease was commonly caused by gastrointestinal bleeding, peritonitis, sepsis, hepato-renal syndrome, and trauma.[1] According to Lancet Gastroenterology and Hepatology Commission and WHO data, end-stage liver disease related mortality still become a particular burden in Indonesia. Adult mortality rate due to liver cirrhosis in Indonesia was as high as 51.1 per 100,000 per year for men and 27.1 per 100,000 per year for women in 2016. Hepatitis B was found in 37% of all mortality related to cirrhosis and 29.1% of all mortality related to HCC in 2015. Meanwhile Hepatitis C was discovered in 35.8% of all mortality due to cirrhosis and 35.2% of all mortality related to HCC. About 17.4% of all mortality in cirrhosis and 20.9% of all mortality in HCC were caused by NAFLD and other causes.[4] There are some barriers in applying comprehensive management for end-stage liver disease in Indonesia, including mortality prevention due to cirrhosis and HCC. Those barriers are related to low disease surveillance, geographical barriers, and the limitations of health care facilities and infrastructures.[4] Advance management such as TIPS and liver transplantation are not available in almost all hospitals in Indonesia. Therefore, studies about simple and easy mortality predictor parameters will be beneficial in preventing mortality due to end-stage liver disease in Indonesia.

The earliest scoring system for predicting mortality in cirrhosis was Child-Turcotte-Pugh (CTP) score, which classify patients into 3 groups (A, B, and C). CTP score mainly predicts post-operative mortality but it could also predict mortality risk and complications due to liver dysfunction. CTP score also helps stratify priority for liver transplantation.[5,6] Meanwhile model for end-stage liver disease (MELD) score was established in 2001 by United Nation for Organ Sharing to determine liver allocation. MELD score is more objective than CTP score and clinically has more benefit in characterizing disease severity because it includes some parameters such as creatinine, total bilirubin, International normalized ratio (INR), and etiology of cirrhosis.[7] MELD score was modified to increase its precision as a mortality predictor for compensated and decompensated chronic liver disease. Some modifications include the addition of sodium as a parameter (MELD-Na) and the addition of serum sodium ratio index as a parameter (MESO).[7,8] Easier parameters for predicting mortality of patients with liver cirrhosis and hepatocellular carcinoma were platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR), which gained increasing interest recently. Studies showed NLR could be independently used as an early mortality predictor in patients with

decompensated hepatitis B-related cirrhosis, could estimate fibrosis level and long term mortality rate, and could become predictor for decompensated state and urgency of liver transplantation.[9,10,11] NLR also predicted mortality for patients with HCC after therapy.[12] Meanwhile PLR could serve as a marker for significant fibrosis in patients with hepatitis C infection, and independent predictor for prognosis of the patient with HCC after treatment.[13,14,15] Separately, some authors had studied NLR, PLR, CTP and MELD score in association with end-stage liver disease in Indonesia. Some studies indicated a conformity between NLR and CTP score in assessing the severity of chronic liver disease.[16,17] Those studies were confirmed by another study by Sungkar et al, which indicated a significant correlation between NLR and CTP score as marker of disease severity of liver cirrhosis.[18] Thus, NLR could potentially serve as marker of prognosis. In a study, Arsana et al, compared the performance of NLR, type IV collagen, and fibrosis score such as APRI score and FIB-4, as screening parameters for liver fibrosis in chronic hepatitis B infection.[19] Another study by Siregar and Irwansyah compared between PLR and degree of HCC according to BCLC, which pointed out a significant difference between PLR level and degree of HCC.[20] Study by Nasir et al, showed a negative correlation between plasma fibrinogen and MELD score as a marker for disease severity in cirrhosis.[21] MELD score also had significant correlation with plasma Cystatin C as studied by Gunadi et al.[22]

Overall, particular study in Indonesia about comparison between PLR and NLR with CTP and MELD score as mortality predictors in end-stage chronic liver disease is still lacking. In a study, Hasan et al, exhibited Systemic Immune-Inflammation Index (SII) as better predictor of one year survival than NLR in untreated advanced HCC patients.[23] A study by Utami, indicated a significant correlation between NLR and CTP score as long term survival predictors in HCC.[24] Sindhughosa et al showed association between ALBI, PALBI, and FIB-4 score with MELD score as mortality predictors in liver cirrhosis.[25] Meanwhile, Nababan et al developed two new scores which serve as better predictor than MELD and CLIF-C OF scores in predicting in-hospital mortality of acutely decompensated liver cirrhosis.[26] To the best of our knowledge, there has not any studies which directly compare between 2 simple predictors, NLR and PLR, with CTP and MELD scores as short term mortality predictor (30 days) in end-stage chronic liver disease patients in Indonesia. NLR and PLR as mortality predictors, has their advantages as simple predictors which might be easily applied in all regions of Indonesia with healthcare facility limitations. Therefore, this study aimed to investigate NLR and PLR as early (30 days) mortality predictors in patients with end-stage CLD, which comprised of liver cirrhosis and HCC patients, in comparison with CTP score and MELD score.

METHOD

This was a retrospective observational cohort study using data from medical records. We recruited purposively all patients ≥ 18 years old from the inpatient ward of Saiful Anwar General Hospital with chronic liver disease of all causes (comprised of liver cirrhosis and HCC) from December 2018 and August 2019. Diagnosis of liver cirrhosis and HCC was established by the laboratory, imaging, or biopsy examination. The exclusion criteria were chronic liver disease with incomplete examination or incomplete data, chronic liver disease with hematological malignancy (leukemia, immune thrombocytopenia, myelodysplastic syndrome), chronic liver disease due to malignancy/metastases from extra-liver malignancy, chronic liver disease with ongoing chemotherapy or anticoagulant therapy, chronic liver disease with autoimmune disease, pregnancy, and chronic infection. Because this study used medical records, written informed consent was waived. All patients' data were recorded anonymously to ensure confidentiality. Protocol of the study had been ethically accepted by Health Research Ethic Committee of Faculty of Medicine, Universitas Brawijaya (No. 73/EC/KEPK/03/2022).

CTP and MELD scores are reference predictor scores for clinical outcomes in patients with chronic liver disease. CTP score incorporates variables of ascites, hepatic encephalopathy, total bilirubin, albumin, and INR. MELD score incorporates variables of dialysis, creatinine, bilirubin, and INR. Platelet-lymphocyte ratio is the ratio between platelets and lymphocytes in peripheral blood. The neutrophil-lymphocyte ratio is the ratio between neutrophils and lymphocytes in peripheral blood. Both ratios and both scores were calculated on day 1, in the same time, when the patients first arrived at the hospital. The survival of the subjects was determined 30 days after the subjects were recruited.

Baseline characteristics of the subjects were presented categorically in numbers (%). Continuous

variables were screened for normality using the Kolmogorov-Smirnov tests and for homogeneity using the Levene tests. Continuous variables were presented as the median and interquartile range (IQR). Chi-square tests were performed to analyze categorical variables between two outcome groups. Analysis of continuous variables in the outcome groups was performed using Mann-Whitney U tests. The prognostic tests were carried out using the receiver operating characteristic (ROC) curve. Cut off for every predictor was chosen using the Youden Index. Correlation analysis were carried out using Spearman test. The results of the analysis were presented as ROC curve, AUC, cut-off value, sensitivity, specificity, and correlation coefficient. P value < 0.05 was considered statistically significant. All statistical analyses were performed using statistical package for social sciences (SPSS) version 26.0 (IBM Corp).

RESULTS

Among 164 subjects with chronic liver disease in this study period, 90 subjects fulfilled the inclusion criteria and were recruited in the study. Table 1 described the baseline characteristics of study participants in both outcome groups. Comorbidities (diabetes mellitus, hypertension, and heart failure) were found in 19 patients (21.1%). There were 31 deaths in 30 days (34.4%). Table 1 revealed 58.1% (n = 18) of all deaths were male. About 67.7% (n = 21) of deceased participants were < 60 years old. Mortality occurred in 15 participants (48.4%) with chronic hepatitis B infection and 3 participants (9.7%) with chronic hepatitis C infection. The percentage of mortality was higher in hepatocellular carcinoma patients than liver cirrhosis group.

But overall, there were not any significant differences in both outcome groups regarding gender, age, etiology of chronic liver disease, comorbidities, and sub-group of chronic liver disease. Significant differences were obtained in CTP and MELD scores between surviving and deceased groups (p = 0.001 and 0.002, respectively). Both scores were significantly higher in the deceased group (Table 1). Laboratory parameters did not show any statistically significant differences between the two outcome groups including PLR and NLR. The median value of PLR was higher in the surviving group than in the deceased group. But the median of NLR in the deceased group was higher than the median NLR in the surviving group (Table 1).

Sub-group analysis of the subjects with liver cirrhosis indicated higher median value of parameters in the deceased group (Table 2). The medians of NLR, MELD, and CTP scores were higher in deceased group with significant differences for CTP and MELD scores. Meanwhile, PLR had similar medians between survive and deceased groups. Subjects with HCC in the deceased group also showed higher medians of PLR, NLR, MELD, and CTP scores (Table 2). But, the differences were only significant also for MELD and CTP scores (p 0.044 and 0.003, respectively).

When they were analyzed for overall subjects, the MELD and CTP scores had nearly similar AUC for predicting early mortality (AUC 0.704 vs. 0.722, respectively; Figure 1a), and both were statistically significant (p = 0.002; 95% CI: 0.587-0.820 vs. p 0.001; 95% CI: 0.612-0.832, respectively). But, this study observed neither PLR (p 0.956) nor NLR (p 0.087) could significantly better predict mortality for all subjects in 30 days than CTP and MELD scores. Analysis for the area under the curve (AUC) in the ROC curve exhibited a significantly lower area for PLR and NLR than either CTP score or MELD score (Figure 1b and 1c). Sensitivity and specificity of MELD and CTP scores, PLR, and NLR in predicting early mortality were presented in Table 3. The highest sensitivity was yielded by the MELD score and the highest specificity was elicited by the CTP score. NLR and CTP scores had similar sensitivity (51.6%) for predicting early mortality. But PLR had the lowest sensitivity (45.2%) and specificity (64.4%).

The ROC analysis in the sub-group analysis (Table 3) also showed MELD and CTP scores as significant predictors of early mortality (p = 0.000 and 0.011, respectively) in subjects with liver cirrhosis. On the other hand, either NLR or PLR did not exhibit significant roles in predicting early mortality (p = 0.243 and 0.713, respectively). Sub-group analysis also yielded same sensitivity for NLR and CTP score for predicting early mortality in the liver cirrhosis group. ROC analysis indicated CTP score as the only significant predictor of early mortality in subjects with HCC (p = 0.000). Neither NLR (p 0.235) nor PLR (p = 0.532) could replace the role of CTP and MELD scores in predicting early mortality, even though NLR showed a quite high specificity for subjects with HCC.

Although PLR and NLR did not significantly predict early mortality, correlation analysis indicated a significant positive correlation between NLR and MELD score (r 0.212; p = 0.044). The positive

Table 1. Baseline characteristics of study participants

Variables	Outcome		p*
	Survive	Deceased	
Sex			
Male	43 (72.9%)	18 (58.1%)	0.153
Female	16 (27.1%)	13 (41.9%)	
Age (year old)			
< 60	43 (72.9%)	21 (67.7%)	0.609
≥ 60	16 (27.1%)	10 (32.3%)	
Etiology			
Hepatitis B	36 (61%)	15 (48.4%)	0.503
Hepatitis C	5 (8.5%)	3 (9.7%)	
Others	18 (30.5%)	13 (41.9%)	
Chronic liver disease			
HCC	34 (57.6%)	21 (67.7%)	0.350
Liver cirrhosis	25 (42.4%)	10 (32.3%)	
CTP score			
CTP-A	18 (30.5%)	1 (3.2%)	**0.000**
CTP-B	27 (45.8%)	11 (35.5%)	
CTP-C	14 (23.7%)	19 (61.3%)	
Comorbidities			
DM	6 (6.7%)	0 (0.0%)	0.066
HT	6 (6.7%)	2 (2.2%)	0.556
HF	3 (3.3%)	1 (1.1%)	0.684
Scores			
CTP score	8.00 (6-10)	11.00 (8-12)	**0.001**
MELD score	14.00 (10-21)	21.00 (15-28)	**0.002**
Laboratory parameters			
Platelet count	222000 (92000-336000)	198000 (87000-304000)	0.604
Lymphocyte count	1030.9 (767.3-1593.8)	1048.6 (781.9-1592.8)	0.963
Neutrophil count	7957.5 (5319.3-11505)	9549.5 (6415.2-17365)	0.064
PLR	165.4 (94.8-361.5)	161.4 (83.7-369.8)	0.956
NLR	6.75 (4.4-9.99)	10.8 (4.71-15.9)	0.087

*p significant <0.05. Categorical variables were presented as numbers (%). Continuous variables were presented as median (IQR). HCC: hepatocellular carcinoma; CTP: Child-Turcotte-Pugh; MELD: Model for End-Stage Liver Disease; DM: diabetes mellitus, HT: hypertension, HF: heart failure; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio.

Table 2. Median differences in sub-group analysis of liver cirrhosis and HCC subjects

Variables	Outcome		p*
	Survive	Deceased	
Liver cirrhosis group	n = 25	n = 10	
MELD score	13.0 (9.5-18.0)	22.0 (17.75-32.25)	**0.007**
CTP score	9.0 (7.5-11.0)	11.0 (9.5-13.0)	**0.025**
NLR	6.25 (3.63-11.5)	9.43 (3.85-16.3)	0.250
PLR	114.7 (64.6-187.1)	114.1 (84.2-242.5)	0.715
HCC group	n = 34	n = 21	
MELD score	14.5 (11-21.25)	20 (13.5-27)	**0.044**
CTP score	8.0 (5.75-9.0)	9.0 (7.5-12)	**0.003**
NLR	7.34 (5.01-9.65)	10.63 (4.71-13.48)	0.215
PLR	227.31 (133.9-389.4)	246.71 (91.46-372.26)	0.533

*p significant < 0.05. Categorical variables were presented as numbers (%). Continuous variables were presented as median (IQR). HCC: hepatocellular carcinoma; CTP: Child-Turcotte-Pugh; MELD: model for end-stage liver disease; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio.

Table 3. Comparison of ROC analysis between MELD score, CTP score, NLR and PLR in sub-group analysis of liver cirrhosis and HCC subjects

Variables	AUC	Cut-Off	p*	Sensitivity	Specificity
Liver cirrhosis group					
MELD score	0.808	17.5	**0.000**	80%	76%
CTP score	0.742	10.5	**0.011**	70%	68%
NLR	0.626	7.02	0.243	70%	64%
PLR	0.540	89.29	0.713	80%	36%
HCC group					
MELD score	0.651	19.5	0.055	61.9%	70.6%
CTP score	0.741	10.5	**0.000**	42.9%	94.1%
NLR	0.600	10.6	0.235	52.4%	85.3%
PLR	0.450	231.1	0.532	57.1%	52.9%

*p was significant if <0.05; AUC: area under the curve; 95% CI: 95% confidence interval. HCC: hepatocellular carcinoma; CTP: Child-Turcotte-Pugh; MELD: Model for End-Stage Liver Disease; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio

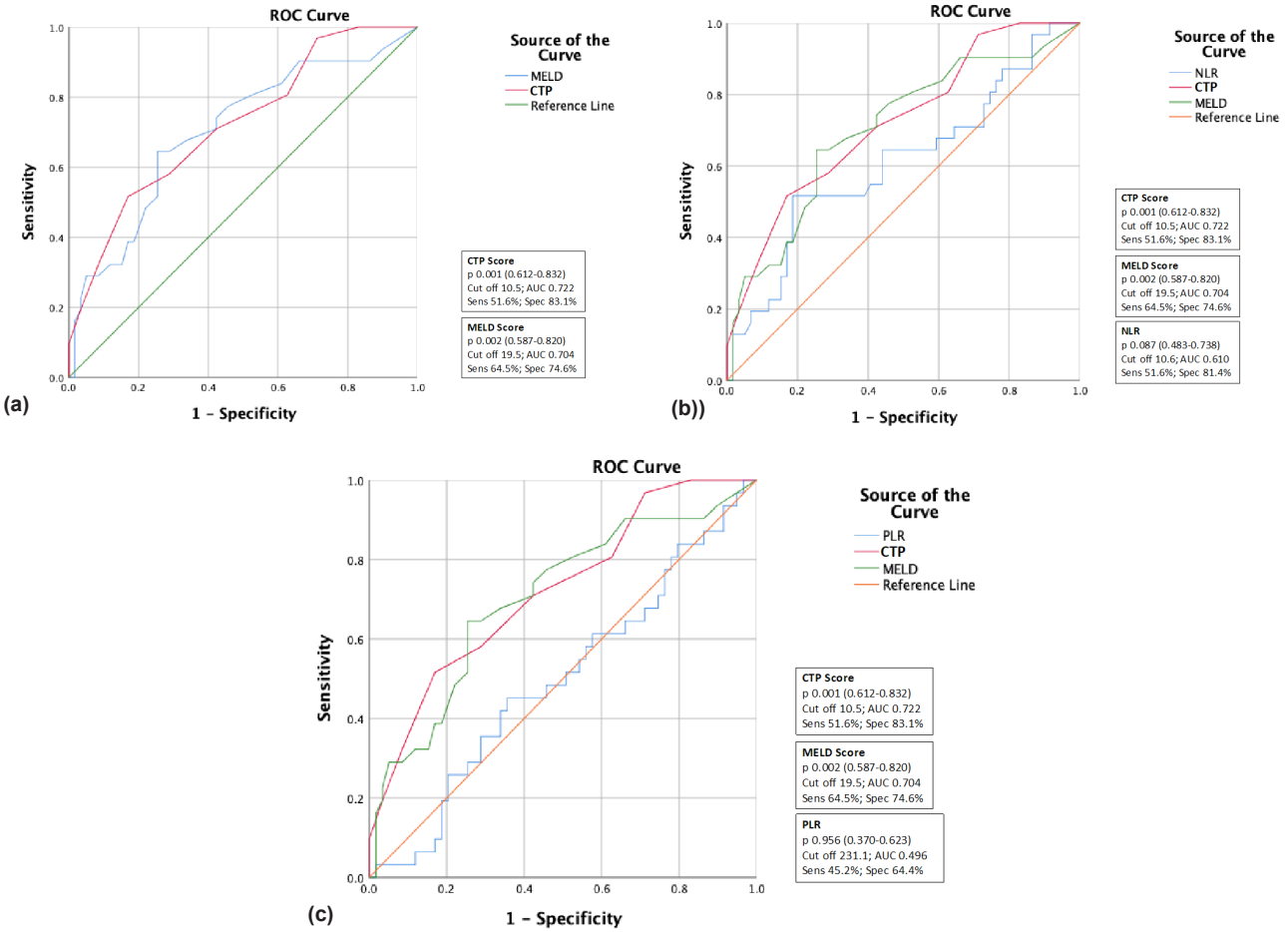

Figure 1. (a) ROC Curve comparing MELD and CTP scores. (b) ROC curves comparing NLR with MELD and CTP scores. (c) ROC curves comparing PLR with MELD and CTP scores. CTP: Child-Turcotte-Pugh; MELD: Model for End-Stage Liver Disease; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio

Table 4. Correlation between NLR and PLR and MELD and CTP scores

Variables	Correlation with MELD score		Variables	Correlation with CTP score	
	r	p		r	p
Overall subjects					
NLR	0.212	**0.044**	NLR	0.116	0.277
PLR	-0.080	0.451	PLR	-0.204	0.054
Liver cirrhosis group					
NLR	0.446	**0.007**	NLR	0.101	0.564
PLR	0.073	0.677	PLR	-0.071	0.685
HCC group					
NLR	0.130	0.345	NLR	0.174	0.204
PLR	-0.155	0.259	PLR	-0.199	0.145

*p significant if < 0.05; r: correlation coefficient. HCC: hepatocellular carcinoma; CTP: Child-Turcotte-Pugh; MELD: model for end-stage liver disease; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio.

correlation between NLR and MELD score was also obtained in the sub-group analysis of liver cirrhosis subjects (r 0.446; p = 0.007). Meanwhile, PLR had inverse correlations with both MELD and CTP scores even though they were not significant (Table 4). The negative correlations between PLR and both MELD and CTP scores were also elicited in the sub-group analysis of subjects with HCC (r -0.155; p = 0.259 and r -0.199; p = 0.145, respectively), although both correlations were not significant.

DISCUSSION

Chronic liver disease was commonly caused by hepatitis virus infection which induced chronic and persistent inflammatory response. Platelet-lymphocyte ratio and neutrophil-lymphocyte ratios had been commonly exerted as inflammatory markers. Both ratios could predict prognosis and disease progression in some conditions.[27,28] Perioperative PLR and NLR are associated with prognosis in some tumors. Some

studies also confirmed the association between both or one of the ratios with disease progression and prognosis in cardiovascular disease, deafness, vestibular neuritis, and thrombotic disease.[29,30] Either PLR or NLR had been studied as predictors for clinical outcome and prognosis in patients with HCC.[27,31] Studies suggested PLR and NLR corresponded with progression and prognosis of hepatitis virus-related HCC.[31,32] Studies by Chen et al and Liu et al indicated NLR when patient first came to the hospital could serve as an independent predictor of mortality in 3 months in patients with acute on chronic liver failure.[33,34] Biyik et al revealed that high NLR was related to a high risk of long-term mortality in subjects with early-stage cirrhosis (MELD score 10 and CTP score 7).[35]

Child-Turcotte-Pugh and MELD scores have been widely used to predict mortality in patients with end-stage liver disease. Our study used CTP and MELD scores as standard scores for predicting mortality in patients with chronic liver disease. The current study yielded higher specificity for MELD score in predicting early mortality in patients with chronic liver disease than previous studies but with lower sensitivity.[36,37] The AUC was higher for CTP score than MELD score in our study. It corresponded with some previous studies which also yielded higher AUSROC for CTP score than MELD score.[38-41] But other studies stated otherwise regarding AUC for CTP and MELD score.[42-44] Overall, CTP and MELD had overlapped 95% CI. High specificity for CTP and MELD scores suggested that both scores might have better discriminative ability to predict mortality.

But, our study did not yield significant results for NLR and PLR as predictors of mortality in 30 days as compared to CTP and MELD scores. In ROC curve analysis, both PLR and NLR had lower AUC than CTP and MELD scores. But NLR had potential as a predictor of early mortality because it had similar sensitivity and comparable specificity as the CTP score in this current study. The result was similar to the study by Li et al which also suggested although NLR could become a mortality predictor, NLR had a lower AUC than MELD score.[45] A study by Zhang et al indicated that NLR could serve as an independent predictor of 30-day mortality in patients with decompensated cirrhosis, but the predictive power of NLR was lower than the MELD score. Mortality risk increased proportionally to an increase of NLR.[9]

Our study indicated a positive correlation between NLR and the MELD score; so that higher NLR correlated with more severe disease. NLR also positively correlated with the CTP score although it was not statistically significant. A study by Zhang et al also indicated a positive correlation between NLR and MELD score and complications in patients with decompensated cirrhosis.[9] Whereas Li et al described a positive correlation between MELD score and NLR in hepatitis B-related decompensated cirrhosis. The current study also showed an inverse correlation between PLR and CTP and MELD scores, although they were not statistically significant.[45] A similar result was obtained in a study by Zhao et al which depicted a decrease of PLR in patients with hepatitis B-related chronic liver disease.[27] Other studies by Alsebaey et al and Meng et al also suggested a significant decrease in PLR in patients with hepatitis C-related cirrhosis and hepatocellular carcinoma.[13,29]

Sub-group analysis of liver cirrhosis and HCC subjects yielded unconvincing results of NLR and PLR as predicting parameters. Although NLR and PLR were higher in deceased subjects but the differences were not significant either in liver cirrhosis or HCC group. ROC analysis of both sub-groups also did not indicate significant roles of NLR and PLR as predictors of early mortality. These results might be related to relatively small number of samples in both sub-groups. But, there are other studies with conflicting results. A study by Kheder et al which mentioned although NLR and PLR were significantly associated with MELD score and mortality, but ROC analysis only showed MELD score as discriminative factor for mortality in subjects with decompensated cirrhosis.[46] Other study by Hasan et al, revealed higher NLR median value in deceased group of untreated advanced HCC, but NLR had inferior AUSROC than other predictor (SII) for predicting mortality.[23]

Many conditions affect lymphocyte, platelet, and neutrophil counts such as infections and other clinical conditions that eventually induce fluctuations in the value of platelet-lymphocyte and neutrophil-lymphocyte ratio.[29] In a normal situation, NLR and PLR have dynamic equilibrium. An increase of NLR in decompensated cirrhosis represents the increase of neutrophil and decrease of lymphocytes. Decompensation, which was induced by acute injury, would intensify liver inflammation and in turn, would trigger an increase in neutrophil count. Lymphocytes would be recruited to the liver in part of the necro-inflammation process that would decrease lymphocyte count in peripheral blood.[27,47] The disequilibrium was provoked by the production of pro-inflammatory mediators by inflammation cells such as cell growth

factor (CXCL-8), matrix metalloproteinase 8, and anti-apoptotic factors such as NFκβ. Cytokines and mediators would in turn induce production and activation of inflammatory cells.[33]

Activated platelet secreted a large amount of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which served as markers for angiogenesis, cell proliferation, and tumor metastasis.[48,49] Meanwhile lymphocyte decreases in patients with chronic inflammation including patients with chronic liver disease. Lymphocyte has a role in the anti-tumor response. Low lymphocyte infiltration could become a worse predictor of prognosis in patients with hepatocellular carcinoma.[50] Overall, an increase in the ratio of neutrophil-lymphocyte and platelet-lymphocyte reflects disequilibrium of immune response in which patient had high state of inflammation in chronic condition.

But, there were some important things to be considered. Platelet and lymphocyte each have a different lifespan and in the condition of abnormal hematopoiesis, PLR could decline because platelet was destroyed faster than lymphocyte. Chronic liver disease escalates platelet destruction due to hypersplenism and a decrease in thrombopoietin production. Homeostasis abnormalities also change neutrophil count by increasing neutrophil recruitment in which the increase of NLR reflects the severity of the disease.[51,52] These homeostasis alterations might correspond with the results of our study in which NLR was significantly correlated with CTP score and MELD score and PLR was inversely correlated with both scores.

Our study has some limitations, in which our study only includes one center retrospectively with relatively small number of samples and the statistical analysis did not include the impact of therapy and comparison with healthy control.

CONCLUSION

In this study, the increase of NLR was correlated with the progressivity of chronic liver disease as NLR indicated positive correlation with MELD and CTP score, and NLR had potential as a predictor of early mortality in comparison with CTP and MELD scores as standard predictors of early mortality. As NLR showed comparable sensitivity and specificity to CTP score in predicting early mortality, NLR could potentially be applied as predictor of early mortality of patient with end-stage CLD in the conditions of laboratory and healthcare facilities limitations. Whereas PLR still had to be further studied to confirm contradictive results with other studies, including the inverse correlation with CTP and MELD score. Current study indicated that either NLR or PLR still could not substitute CTP and MELD scores as predictors of early mortality in patients with end-stage CLD.

Current study highlighted the capability of simple laboratory examinations as predictors of prognosis which might be applicable for implementation in countries with healthcare facilities shortages. But of course, comprehensive management of patients with end-stage CLD, with complete laboratory and radiology examination and advanced therapy, would always be preferable. Overall, further study is still needed to confirm our study result with larger size of sample and to investigate factors that might be influenced early mortality in subjects with CLD. Future study should also involve subjects from different centers in order to generalize the study results.

Disclosure of Conflict of Interest

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Authors' Contribution:

Conception and Design: SM, AKW
Analysis and Interpretation of Data: SM, AKW
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Final Approval of the Article: SM, AKW

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