Platelet to White Blood Cell Ratio (PWR) to Predict Mortality in Acute on Chronic Liver Failure of Cirrhosis Patient: A Systematic Review

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ABSTRACT

Background: *Liver cirrhosis (LC) is still being important public health concern, due to the rising of global incidence and mortality. There is risk progression in LC patients to acute-on-chronic liver failure (ACLF) patients with high incidence of complication and high short-term mortality rate. It needs rapid and simpler predictor to immediate and accurate triage of the patient. The aim of this study is to review systematically the role of PWR to predict the mortality in ACLF cirrhosis patient.*

Method: *This systematic review study was identified by searching Pub-Med, Cochrane library, and EMBASE database (2016-2022). Only observational studies were included. ACLF patient was selected as the main subject in each study, and PWR was added as short-term mortality predictor. The Cochran seven step model was used to perform the review.*

Results: *Six cohort retrospective studies met inclusion criteria, including total 1,348 patient ACLF. Half of studies included had high level of evidence. The non-survivor ACLF patient had significantly lower PWR values than survivor. The range of HR of PWR to predict mortality in ACLF was 0.665-0.995, with p value < 0.0001. Whereas the cutoff range of PWR value to predict non survivor in ACLF patient was 7.83-14.2.*

Conclusion: *PWR had a predictive efficacy, similar to CLIF-SOFA and MELD score in terms of predicting short-term mortality in ACLF patients. PWR showed significantly independent risk factor of short term mortality in ACLF cirrhotic patient.*

Keywords: *acute-on-chronic liver failure (ACLF), liver cirrhosis, platelet to white blood cell ratio (PWR), CLIF-SOFA, MELD*

ABSTRAK

Latar belakang: *Sirosis hati masih menjadi masalah kesehatan publik yang penting. Terdapat risiko progresi pasien sirosis menjadi acute-on-chronic liver failure (ACLF), dengan tingkat komplikasi dan tingkat mortalitas jangka pendek yang tinggi. Oleh karena itu dibutuhkan alat prediktor yang lebih cepat, mudah dan akurat untuk menentukan kegawatan pasien. Tujuan studi ini adalah untuk menelaah secara sistematik peran PWR dalam memprediksi mortalitas pada pasien ACLF.*

Metode: *Studi telaah sistematik ini dilakukan dengan mengidentifikasi studi dari basis data Pub-Med, Cochrane library, dan EMBASE (2016-2022). Hanya studi observasional yang diinklusi. Pasien ACLF dipilih*

sebagai subjek utama pada tiap studi, dan PWR ditambahkan sebagai prediktor mortalitas jangka pendek. Tujuh tahap Cochrane model digunakan sebagai panduan untuk melakukan telaah.

Hasil: *Sebanyak 6 studi kohort retrospektif memenuhi kriteria inklusi dan eksklusi, dengan total 1348 pasien ACLF. Sebanyak 3 studi memiliki kualitas metode yang sangat baik. Pasien ACLF yang meninggal memiliki nilai PWR yang lebih rendah signifikan dibanding yang hidup. Rentang nilai HR dari PWR untuk memprediksi mortalitas ACLF adalah 0,665-0,995, dengan nilai p < 0,0001. Sementara nilai ambang batas dari PWR untuk memprediksi kematian ACLF adalah 7,83-14,2.*

Simpulan: *Skor PWR memiliki efikasi prediktif yang serupa dengan CLIF-SOFA and MELD score untuk prediksi mortalitas jangka pendek pada pasien ACLF. PWR menjadi faktor risiko independent yang signifikan dari mortalitas jangka pendek pasien sirosis dengan ACLF.*

Kata kunci: *acute-on-chronic liver failure (ACLF), sirosis hati, platelet to white blood cell ratio (PWR), CLIF-SOFA, MELD*

INTRODUCTION

Liver cirrhosis is still being important public health concern, due to the rising of global incidence and mortality. The severe liver damage was caused by hepatocellular insult, such as hepatitis virus infection, alcohol abuse, autoimmune disease, genetic disease, and other cause. The progression to acute-on-chronic liver failure (ACLF) was associated with systemic inflammation response syndrome, compensatory anti-inflammatory response syndrome, and immune paralysis/organ failure.[1,2] The recently score to classify disease severity and predict survival are chronic liver failure-sequential organ failure assessment (CLIF-SOFA) and model of end stage liver disease (MELD). However, the CLIF-SOFA and MELD have complex calculation and online-tools for their assessment. There need rapid and simpler predictor to immediate and accurate triage of the patient.[1]

The inflammatory response is crucial to the pathogenesis and prognosis of ACLF. Usually, clinical evaluation of the inflammatory state relies on various indicator of routine peripheral blood test, such as leucocyte count, platelet count and distribution, neutrophil-lymphocyte ratio.[2] Thrombocytopenia in cirrhosis patient is often directly proportional to the severity of liver failure. The etiology of thrombocytopenia is multifactorial in cirrhosis, such as the decreased production of thrombopoietin, hypersplenism, and portal hypertension.[3,4] Platelet to white blood cell ratio (PWR) may be a marker of systemic inflammatory response, that can be used as a prognostic predictor of acute ischemic stroke and cancer.[5,6]

The aim of this study is to review systematically the role of PWR to predict the mortality in ACLF cirrhosis patient. PWR may have valuable role to guide clinician easily to predict the liver failure.

METHOD

The purpose of this systematic review is to determine the role of PWR to predict ACLF in cirrhosis patient. One author (BG) searched online relevant article and one investigator (RA) reviewed all titles. The structural questions were constructed based on patient, intervention, comparison, outcome (PICO) criteria.

Table 1. Structural questions based on PICO

PICO criteria	Variable
Patient	Patient age > 18 years with liver cirrhosis of any aetiologies and had acute decompensated liver failure (ACLF)
Intervention	PWR (Platelet to White Blood Cell Ratio) count
Comparison	Other predictive marker (MELD, CLIF SOFA)
Outcome	Mortality in 28-90 days

The exclusion criteria were non-observational study, study did not focus in decompensated cirrhotic patients, study did not compare PWR to other predictive marker, the main outcome of the study was other than short term mortality (28 days-90 days), and no full text available.

Article published between 2016 and 2022 were identified by searching Pub-Med, Cochrane library, and EMBASE database. Keywords were platelet to white blood cell ratio (PWR), acute-on-chronic liver failure (ACLF), and chronic liver disease (CLD). Cirrhosis was diagnosed by liver biopsy or supported by imaging technology (hepatic ultrasound and/or CT, MRI). Acute on chronic liver failure met the Pacific Association for the study of the liver criteria. ACLF was initially selected as the main subject, and then PWR ratio was added as prognostic predictor. The Cochran seven step model was used to perform the review as follow (Table 2). Criteria used to assess the methodological quality based on the Newcastle-Ottawa scale (Table 3).

Table 2. Cochrane seven step model

Step Model	Explanation
Step 1	Specifying the year
Step 2	Determining inclusion criteria - Article must be published in English - The design of study selected were only cohort prospective or retrospective study - The study must have the availability of full text.
Step 3	Study selection. Liver cirrhosis patient was selected as the main subject. Then, the PWR indicator as primary or secondary diagnostic value was added. The steps for selecting article were summarized in figure 1.
Step 4	Assessment of study quality. In this step, only full text of the papers were studied. Criteria that used to assess the methodological quality was based on the Newcastle-Ottawa scale (range 1-9)
Step 5	Data extraction. The extracted data was consisted of author, year publication, country publication, design, participant, follow up duration, main outcome, and limitation of the study. After studying the full text of the papers, 6 papers that had important PWR research in patients with ACLF were selected.
Step 6	Data analysis. Data from the review of the studies were presented in table 5.
Step 7	Presentation of results

Table 3. Newcastle-Ottawa scale

	Indicator	Score
Selection	Representative of exposed cohort	1
	Selection of non-exposed cohort	1
	Ascertainment of exposure	1
	Demonstration that outcome was not at the start	1
Comparability	Control for main factor	1
	Control for additional factor	1
Outcome	Assessment	1
	Follow-up was long enough	1
	Adequacy to follow up	1
	Total	9

RESULTS

Chronic Liver Disease

Chronic liver disease (CLD) is the 14th most common cause of death and caused 1.3 million deaths per year worldwide. The prevalence of this disease is underestimated because was not diagnosed in initial stage, and it usually goes to the decompensated stage at a rate pf 5-7% per year. Etiology of CLD mentioned in Table 4.

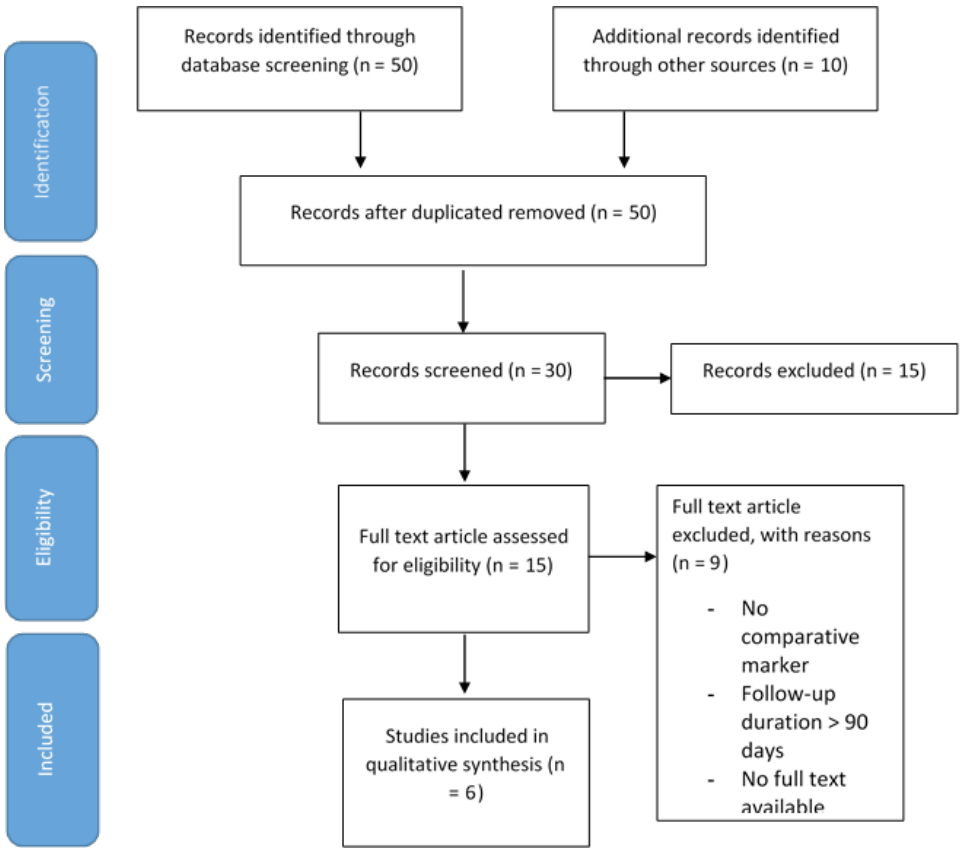

Figure 1. Flow chart of study

Table 4. The etiology of chronic liver disease (CLD)

The etiology of CLD	
Alcohol	The liver is the primary target organ of ethanol damage. Excessive alcohol consumption causes three types of chronic liver disease, such as steatosis (fatty liver), steatohepatitis, fibrosis, and cirrhosis.[7-9]
Hepatitis C	Hepatitis C virus (HCV) is an infectious disease that primarily affects the liver, causing acute or chronic hepatitis. Chronic hepatitis C is a slowly progressive disease which causes persistent inflammation, 20% will progress to cirrhosis in 20-30 years. There is an annual risk of 1-6% of progressing to hepatocellular carcinoma, and 3-6% present hepatic decompensation.[7,8]
Hepatitis B	Hepatitis B virus (HBV) is an infectious disease that can lead to life-threatening condition, such as fulminant hepatitis, cirrhosis and hepatocellular carcinoma (HCC). Of the patients with chronic hepatitis B, 15-30% progress to liver cirrhosis and 6% develop HCC in 5 years.[7,8]
Non-Alcoholic fatty liver disease (NAFLD)	NAFLD is defined by accumulation of fat in liver that exceed 5% of its weight. NAFLD is chronic pathology that included simple steatosis to non-alcoholic steatohepatitis, which has the risk of progressing to liver cirrhosis in 3-8% of cases over course 5 years.[7,9]
Autoimmune disease	Autoimmune disease represents less than 5% etiology of CLD, include autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis.[7]

Results of Literature Search

The review flow was presented in Figure 1. The article searched identified 50 citations. Of those 50 citations, 30 titles appeared relevant and were retrieved. Of those 30 titles, 15 articles appeared relevant and were retrieved. Six observational articles were selected for review. The exclusion reasons were study that did not focus in decompensated or acute on chronic liver failure in cirrhotic patients, did not compare PWR to other predictive marker (such as MELD, CLIF-SOFA), no full text available, and the main outcome of the study was not short term mortality of ACLF patients.

Study Characteristics

Details of characteristic of the study included were presented in Table 5. All study had retrospective cohort design with single laboratories value measurement. Included study enrolled 1,348 patient ACLF in total. Most population of each study had subject from single center, except study from Qiang et al. Most studies were established in China region, except study from Khan et al. The predominant etiology of cirrhosis in ACLF patient in all studies included were hepatitis B infection. Chronic active hepatitis B (CHB) was defined as hepatitis B virus (HBV) surface antigen (HBsAg)-positivity and HBV DNA $\geq$ 2.0 log IU/mL at least 6 months duration. Cirrhosis was diagnosed by liver biopsy or supported by imaging technology (hepatic ultrasound and/or CT, MRI). Acute on chronic liver failure met the Pacific Association for the study of the liver criteria.

Four study used survivor and non-survivor ACLF patients as comparison. Study from Xu et al used chronic HBV as comparator with ACLF, and study from Jie et al used healthy control as ACLF comparator. All studies used short term mortality as main outcome in ACLF (30 days and 90 days). All studies used regression logistic model to predict PWR as risk factor for the mortality. From all studies included, three studies had high level and three moderates of methodological quality, based on Newcastle-Ottawa scale for cohort study.

Role of PWR in Predict Mortality in ACLF Hepatitis B-Cirrhotic Patients

Five studies (Xu et al, Jie et al, Liu et al, Zhang et al, Khan et al) showed that lower PWR ratio was associated significantly with mortality in ACLF patients.[10-13] Whereas study from Qiang et al showed higher platelet to lymphocyte ratio (PLR) was related significantly with mortality in ACLF patients. The mechanism underlying the correlation between PWR and severity of hepatitis B was unclear. Decreased peripheral platelet count was associated with liver fibrosis in patients with chronic hepatitis B.[14]

Retrospective cohort study form Xu et al included 211 ACLF patient. The study showed that the mean PWR value was lower significantly in ACLF group. The optimal cut-off value was 29.64 (sensitivity 67.8%, specificity 61.8%). PWR value was identified as independent risk factor for survival in ACLF patient. This study also identified the plausible factor that decreased the PWR, there were ascites and infection ($p = 0.003$).[2]

Retrospective cohort study from Jia et al included 433 ACLF-related HBV patient and showed significantly lower PWR than healthy control. This study also showed that there was moderate positive correlation between PWR and RBC ($r = 0.2348$, $p < 0.0001$) and HBV DNA ($r = 0.1887$, $p < 0.001$) in ACLF patient.

Table 5. Description of included study

Author (year published and country)	Study design and study participant	Follow up duration	Data collection method	Summary of findings	Hazard ratio (PR) or odds ratio (OR) (95% confidence interval/ CI) and p value	PWR cut off
Xu et al (2021), China[2]	Cohort retrospective, 100 chronic hepatitis B/CHB patients, 104 liver cirrhosis, and 211 ACLF	30 days	Single laboratory value measurement	The mean PWR value was lower significantly in ACLF group (13,33), than CHB (25.68), and LC group (27.82) The mortality rate was higher in the low PWR group than high PWR	P < 0.0001 HR = 0.900 (95% CI: 0.853-0.949)	29.64 (sensitivity 67.8% and specificity 61.8%)
Jie et al (2018), China[10]	Cohort Retrospective, 433 patients with ACLF related HBV and 97 healthy control	90 days	Single laboratory value measurement	The mean PWR value in the ACLF patients was 14.03 ± 7.17, and was statically significantly lower than those in healthy control (39,16 ± 9,80) The mortality rate was significantly higher in patients with low PWR value than high PWR value	P < 0.0001 HR = 0.660 (95% CI: 0.438-0.996)	Not mentioned
Liu et al (2020), China[11]	Cohort, retrospective, 89 patients ACLF (HBV as predominant etiology) (47 non-survivors and 42 survivors)	28 days	Single laboratory value measurement	The non-survivor group with ACLF had lower PWR value compared to survivor group (4,19 ± 1,96) vs (10.86 ± 5,73), due to the increase number of white blood cells and decrease platelet In univariate analysis, PWR was associated significantly with 28 days of mortality in ACLF	P < 0.0001 OR = 0.955 (95% CI: 0.918-0.994)	7.83 (sensitivity 76.60% and specificity 69.05%)
Zhang et al (2020), China[12]	Cohort retrospective, 131 subjects with HBV-decompensated cirrhosis (116 survivors and 15 non survivors)	30 days	Single laboratory value measurement	The non-survivor group had lower PWR value significantly than survivor group (10.9 ± 7.0 vs 16.9 ± 12.2). PWR score was significantly independent risk factor with mortality in decompensated liver cirrhosis patients	P = 0.005 OR = 0.910 (95% CI: 0.833-0.994)	14.2 (sensitivity 73.3% and specificity 63.8%)
Khan et al (2021), Pakistan[13]	Cohort retrospective, 63 patients with ACLF with HBV predominant (26 non-survivors and 37 survivors)	90 days	Single laboratory value measurement	PWR score was lower significantly in mortality group than non-mortality group (16,4 ± 9.9 vs 11.2 ± 8.8) PWR was calculated and value ≤ 8 was found significantly associated with higher risk of mortality in patients with ACLF	P = 0.0005 OR/HR not mentioned	The cut off ≤ 8 has 81% sensitivity and 50% specificity
Qiang et al, (2020), China[14]	Cohort retrospective, 421 ACLF-HBV patients from 3 centers (222 survivors and 199 non-survivors)	90 days	Single laboratory value measurement	PLR score was significantly higher in non-survivors than survivors (102,15 vs 85,2) PLR was significantly associated with 90 days mortality in patients with HBV-ACLF in univariate analysis, but not significant in multivariate analysis	P = 0.0001 HR = 1.003 (95% CI: 1.001-1.005)	Not mentioned

PWR: platelet to white blood cell ratio, ACLF: acute-on-chronic liver failure, HBV: hepatitis B virus, PLR: platelet to lymphocyte ratio

Table 6. Quality assessment of study included

Study	Quality assessment			Total score	Level of methodological quality
	Selection	Comparability	Outcome		
Xu et al (2021)	3	2	2	7	High
Jia et al (2018)	3	1	3	7	High
Liu et al (2020)	3	1	2	6	Moderate
Zhang et al (2020)	3	1	2	6	Moderate
Khan et al (2021)	3	1	2	6	Moderate
Chiang et al (2020)	3	2	3	8	High

This study also showed negative correlation between PWR and MELD score (r = -0.1410, p = 0.0032), implying the important role of PWR in prediction for the severity of cirrhosis patient. The limitation of this study was the use of healthy control as the comparison subject, so it could overestimate the results.[10]

Retrospective cohort study from Liu et al included 47 non-survivor and 42 survivor ACLF patients. The non-survivor group had lower PWR value significantly than survivor group. Furthermore, PWR was the significant risk factor to predict 28 days mortality in ACLF patients. This study also showed that albumin-bilirubin index (ALBI) and model of end stage liver disease (MELD) score had negative correlation with PWR (r = -0.330, p = 0.002). The cut-off of PWR value was 7.83 (sensitivity 76.60% and specificity 69.05%).[11]

Retrospective cohort study from Zhang et al included 15 non-survivor and 113 survivor was about the relation of decompensated cirrhosis and HBV. The study showed that the non-survivor group had lower PWR ratio significantly and being the independent risk factor to predict 28 days mortality, and had same efficacy with MELD score. The cut off PWR value was 14.2 (sensitivity 73.3% and specificity 63.8%). This study showed that low PWR value was associated significantly with higher white blood count, INR, blood urea nitrogen, mortality rate, and MELD score.[12] The same result was shown by retrospective study by Khan et al with 63 patients (26 non survivor and 37 survivor). Diagnostic accuracy of PWR in predicting mortality was 70.27%.[13]

DISCUSSION

This study had reviewed systematically the role of PWR to predict mortality in ACLF cirrhotic patients. ACLF patients had severe disease, rapid progression, high incidence of complication, and high short-term mortality rate. Half of studies included in recent review had high level of evidence. PWR calculation form complete blood count is very inexpensive and easy to obtain. The current study shows that the non-survivor ACLF patients had significantly lower PWR values than survivor patients. Importantly, PWR values showed independent risk factor of short term mortality in ACLF patients. The range of hazard ratio of PWR to predict mortality in ACLF was 0.665-0.995, with p value < 0.0001. Whereas the cutoff range of PWR value to predict non survivor in ACLF patient was 7.83-14.2 (sensitivity 73.30-81.00% and specificity 50.00-69.05%).

Mechanism of PWR in Predicting Mortality in ACLF

The decrease peripheral platelet count is associated with liver fibrosis, hypersplenism, increased destruction of platelet, decreased platelet production, decreased thrombopoietin production, antiplatelet antibodies, disseminated intravascular coagulation, translocated toxin, and other gut-derived substance.[2,10,11] Additionally, there is additional mechanism for increased platelet destruction in chronic liver disease, which is the effect of elevated portal pressure. Thrombocytopenia can further aggravate liver damage and promote the progression of liver cirrhosis by decreasing the level of platelet-derived growth factor and hepatocyte growth factor. The lower platelet count, the more severe liver cirrhosis and platelet impairment.[15-17]

Bacterial infection is the most common cause of high white blood cell count and systemic inflammation in ACLF, related to products of bacterial translocation from the gut to systemic circulation. Immune function is severely damaged in ACLF patients. The circulating neutrophils exhibit impaired phagocytic function and bactericidal capacity, which are predictors of mortality in cirrhosis. The presence of various pro-inflammatory and anti-inflammatory factors can be detected in ACLF patients, such as TNF-aR2, TNF-a, sTNF-aR1, IL-2R, IL-2, IL-6, IL-8, IL-10. High level of serum IL-6 also increases the mortality in HBV-associated ACLF. Episodic aggravations of bacterial translocation or pro-inflammatory precipitants are related to the development of more organ failure.[18,19] As a result of decrease white blood cell and decrease of platelet, PWR will eventually decrease in patient with ACLF.[2]

Comparison of PWR to Others Predictive Marker (CLIF SOFA, MELD)

Model of end-stage liver disease (MELD) score was used firstly to assess the prognosis of patients after transjugular portosystemic shunt in 2021. It is later suitable for evaluating severity of various chronic liver disease. However, the MELD score does not consider inflammation, which significantly influences the prognosis.[20] Study from Jie et al showed that PWR had higher prediction power (area under curve (AUC) = 0.725 ± 0.029, $p < 0.001$) than MELD score (AUC = 0.649 ± 0.033, $p < 0.001$).[10] Same result showed in study from Zhang et al, the predictive powers of MELD score and PWR for mortality were not significantly different (AUC for MELD 0.830, AUC for PWR 0.721, $p = 0.142$).[12] Study from Kim et al also concluded that PWR level was more useful prognostic biomarker compared to MELD score.[21,22]

Chronic liver failure-sequential organ failure assessment (CLIF-SOFA) established by CANONIC study, is useful for diagnosing ACLF according to the number and type of organ failure. CLIF-SOFA is performed better than other predictive marker in predicting short term mortality for acutely decompensated cirrhosis.[21] However, although the CLIF-SOFA score has an excellent predictive value, the calculation process is burdensome and onerous. Study from Lu et al showed that AUC for CLIF-SOFA (0.804) was significantly higher than MELD (0.670), but there was no difference between CLIF-SOFA and PWR (AUC 0.759). PWR was also negatively associated with CLIF-SOFA.[11]

The study above indicated that PWR has a predictive efficacy, similar to CLIF-SOFA and MELD score in terms of predicting short-term mortality in ACLF patients. Since routine blood examination is a simple detection method, the PWR can provide clinicians with quick reference, because only incorporated two common hematological indexes. Low PWR may reflect the severity of liver injury and inflammation and may influence the prognosis of such patients.[12,13] Beside the PWR ratio, the increase of platelet to lymphocyte ratio (PLR) also reflects a deterioration and oxidative stress of cirrhotic patient due to the decrease of lymphocyte count.[14]

Overall, the limitation of study included in this review are short duration of follow up, limited number of patients in each study and subjects only from single center, the PWR correlation with other blood parameter was not assessed, the study design was retrospective, the laboratory data was not observed dynamically, which may cause bias.

CONCLUSION

The current study shows that the non-survivor ACLF patient had significantly lower PWR values than survivor. The range of hazard ratio of PWR to predict mortality in ACLF was 0.665-0.995, with p value < 0.0001. Whereas the cutoff range of PWR value to predict non survivor in ACLF patient was 7.83-14.2 (sensitivity 73.30-81.00% and specificity 50.00-69.05%). PWR had a useful predictive efficacy, similar to CLIF-SOFA and MELD score in terms of predicting short-term mortality in ACLF patients. PWR showed promising independent risk factor of short term mortality in ACLF cirrhotic patient.

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