Journal of Advanced Research in Medicine
Volume 11, Issue 4 - 2024, Pg. No. 7-13
Peer Reviewed & Open Access Journal

Research Article

Evaluating Platelet-to-Lymphocyte Ratio as a Predictive Biomarker of Liver Fibrosis in Chronic Hepatitis B

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DOI: https://doi.org/10.24321/2349.7181.202410

I N F O

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How to cite this article:
Raj U, Singh J. Evaluating Platelet-to-Lymphocyte Ratio as a Predictive Biomarker of Liver Fibrosis in Chronic Hepatitis B. J Adv Res Med 2024; 11(4): 7-13.

Date of Submission: 2024-08-14
Date of Acceptance: 2024-09-20

A B S T R A C T

Introduction: This study evaluates the platelet-to-lymphocyte ratio (PLR) as a predictive, non-invasive biomarker for assessing liver fibrosis in patients with chronic hepatitis B (CHB). Liver fibrosis staging is crucial for disease management, and a reliable non-invasive marker could reduce the need for liver biopsy.Methods: A cross-sectional observational study was conducted at Dr. RML Hospital, New Delhi, including 120 CHB patients. Patients were categorized based on fibrosis severity (F0-F4) using transient elastography (FibroScan). PLR was calculated by dividing the platelet count by the lymphocyte count. Statistical analysis included ROC curve analysis to determine the predictive accuracy of PLR, with sensitivity, specificity, and predictive values assessed at an optimal cut-off.

Results: PLR was significantly lower in patients with advanced fibrosis (mean PLR: 106.07 ± 10.97) compared to those with mild or no fibrosis (mean PLR: 115.55 ± 11.17) ($p < 0.001$). ROC analysis indicated a PLR cut-off of 112.5, with a sensitivity of 81.67% and a specificity of 66.67% for predicting advanced fibrosis (F4). The area under the curve (AUC) was 0.73, indicating moderate diagnostic accuracy.

Conclusion: PLR shows a significant correlation with liver fibrosis severity and may serve as a cost-effective, non-invasive biomarker for fibrosis assessment in CHB patients. These findings suggest that PLR could aid in early disease monitoring and risk stratification, reducing reliance on invasive liver biopsy.

Keywords: Liver Fibrosis, PLR, CHB

Introduction

More than 350 million people have been identified as having chronic hepatitis B, which is likely to have infected more than 4 billion people. Prevalence regions are classified as high if they are greater than or equal to 8%, low to intermediate if they are between 2 and 7%, and low if they are less than 2%. By calculating the percentage of the population that tests positive for hepatitis B surface antigen (HBsAg), prevalence areas are determined. Hepadnaviruses, the human hepatitis B virus (HBV), are small, contained viruses with circular, partly double-stranded DNA that replicate by reverse transcription.[1]

Genotypes

Ten genotypes and several subgroups of HBV were identified using genomic categorization based on genome comparisons.

- In North America and the United States, genotype A is the most prevalent.
- East Asia and the Far East are the usual locations for genotypes B and C.
- Although genotype D was found all throughout the world, Southeast Asia and the Middle East had the highest prevalence.
- Genes predominate in West Saharan regions.
- Central America has been discovered to harbor genotype F.
- The most recent genotypes, I and J, were identified in Japan and Vietnam, respectively; genotype G was found in parts of Mexico; and genotype H.[2]

Clinical Associations

- HBeAg seroconversion: hepatitis B and C viruses
- Interferon therapy response: A > B=C > D
- Precore or core promoter mutation frequency: genotypes A and F
- Hepatic disease progression: more common in B and C
- Evolving chronic hepatic failure: a non-case study

Most genomic structural mutations are detected by comparing nucleotide sequences with wild-type HBV that do not alter the amino acid sequence in a particular ORF. The strongest clinical association appears to be:HBeAg seroconversion would occur in patients with HBV genotype B before in those with genotype C. Compared to genotypes C and D, genotypes A and B react more favorably to interferon (IFN) therapy. Based on the host's immunological response to the hepatitis B virus, the level of HBV-associated hepatic involvement. Long-term resistance to reinfection and complete clearance depend on humoral and cellular reactions. The cellular immune system is primarily responsible for disease pathogenesis. When host T cells attack viral antigens in lymphoid organs, an antigen-specific T-cell response is induced. The previous process produces T cells that are specific for viral antigens, which mature and multiply before migrating to the liver to fulfill their effector function.

Hepatic-infiltrating hepatitis B-specific CD8+ cells and innate immune system cells would use cytokine-mediated noncytopathic pathways to remove HBV DNA molecules from the liver during an acute hepatitis B infection. The risk of cirrhosis and HCC is increased by combination infections with HIV, hepatitis C, or HDV. Serious side effects include hepatocellular cancer and hepatic decompensation can result from cirrhosis.

Factors associated with an increased risk of HCC include

- Male gender
- Aged 45 years or greater
- Having a first-degree relative with HCC
- Presence of cirrhosis
- HBeAg positivity
- Reversion from anti-HBe to HBeAg positivity
- Increased HBV DNA levels regardless of the HBeAg

High-risk groups for HBV infection include intravenous drug users, patients (and staff) receiving haemodialysis, children born to infected mothers, people who have sex with other men, healthcare workers, and home contacts of known patients with chronic HBV infection. Most of the global burden of HBV illness is caused by vertical transmission. Another possibility is a faecal-oral transmission, however, this is quite rare. The average incubation time for HBV infection is 30 to 180 days, and while recovery is frequent in immunocompetent people, a small number of cases might develop into a chronic condition, which is serologically characterised as the persistence of HBsAg for more than six months. Although a relatively benign course of chronic HBV infection has been recorded during childhood, 3–5% and 0.01–0.03% of chronic carriers develop cirrhosis or hepatocellular carcinoma (HCC) before maturity, respectively.[3]

Natural Course of Acute Hepatitis B

Ten to twenty percent of cases of acute infection are asymptomatic, whereas 80–90% of cases have clinical acute hepatitis. 90% of cases are self-recovering, whereas 5% to 10% of patients have chronic infections. Acute liver failure occurs in less than 1% of patients with acute infection. Acute liver failure resulted in mortality in 0.1–22.7 % Clinical symptoms and jaundice generally disappear after 1 to 3 months. In general, increased serum ALT levels and serum HBsAg titers drop and vanish concurrently, and HBsAg is eliminated in around 80% of patients by 12 weeks following disease onset. Persistence of HBsAg after 6 months implies the development of a chronic infection state, with only a small likelihood of recovery during the next 6 to 12 months Figure 1.

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202410

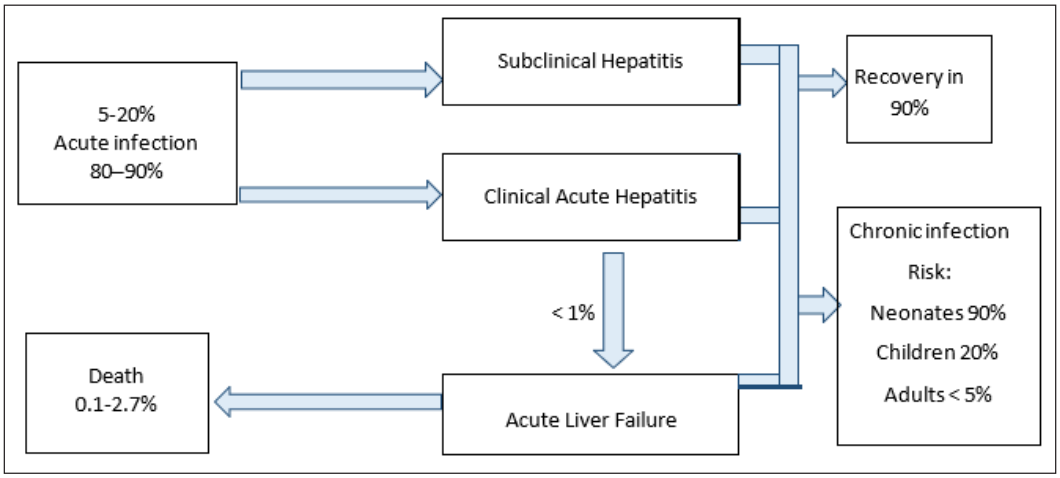

Figure 1.Natural Course of Acute Hepatitis B

HBV infection is divided into four stages

1. Immune tolerance
2. Immune clearance
3. Inactive carrier state
4. Reactivation

In a previous edition of Sleisenger & Fordtran's Gastrointestinal and Liver Disease textbook, there were 4 stages as described above for chronic hepatitis B, but recently, as per the new edition, there are 5 stages of chronic hepatitis B, which are as follows:[4]

1. Chronic infection with HBeAg+
2. Chronic hepatitis with HBeAg+
3. HBeAg-negative chronic infection
4. HBeAg-negative chronic hepatitis
5. HBsAg negative

Total bilirubin, serum albumin, PT-INR, and platelet count are used to determine the severity of the liver disease. In HBV infection, liver biopsy is optional; however, these tests are required to determine the histologic grade of inflammation and the stage of fibrosis.

Natural Course of Chronic Hepatitis B

Patients with chronic hepatitis B may have a varying course of the disease; out of all patients, 5–10% may directly be converted to hepatocellular carcinoma, but the majority develop cirrhosis; out of all patients having cirrhosis, 15% of patients may progress to decompensation in the next 5 years, while 15% of patients may progress to HCC, and 15% of patients may succumb to death in the next 5 years.

Chronic infection is defined as the presence of HBsAg for at least six months (with or without concurrent HBeAg). Fibrosis, cirrhosis, and hepatocellular cancer can all be caused by chronic infection (HCC). The sixth most common cancer worldwide is liver cancer.[5]

Pedal oedema, icterus, spider angiomas, and ascites are prevalent in patients with decompensated cirrhosis. Hypersplenism, a decrease in serum albumin (without nephropathy), or a prolongation of the prothrombin time (PT) should always be taken into consideration while evaluating the progression of cirrhosis Figure 2.

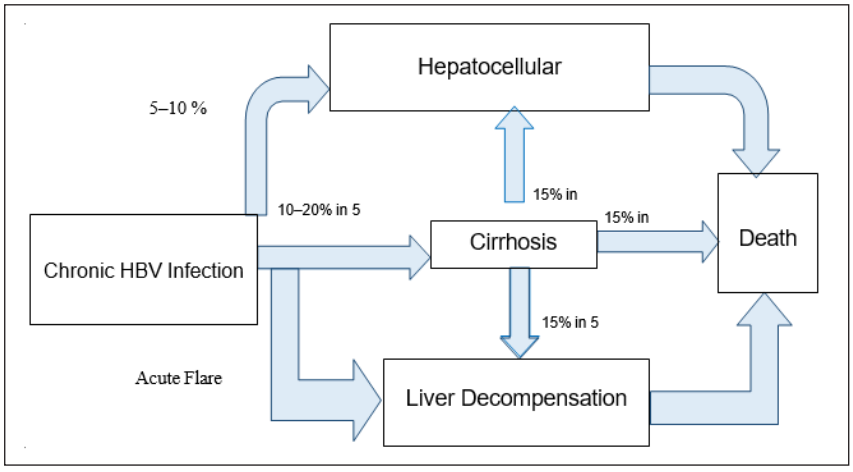

Figure 2.Natural Course of Chronic Hepatitis B

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202410

Serum aspartate aminotransferase levels in patients with advanced cirrhosis are greater than alanine aminotransferase levels.

A prognostic clinical sub-classification with four distinct stages with significantly different mortality probabilities has been proposed.[6,7]

- Stage 1 (compensated with no esophageal varices) has an estimated mortality of 1% per year.
- Stage 2 (compensated with varices) annual mortality rate of 3.4%
- Stage 3 (decompensated with ascites) annual mortality rate of 20%
- Stage 4 (decompensated with gastrointestinal bleeding) annual mortality rate: 57%

Pathogenesis of Haematological Complications

The most common haematologic complication is thrombocytopenia: There are two major causes of thrombocytopenia.

1. Decreased hepatic thrombopoietin synthesis
2. Fibrosis in the liver: increased portal hypertension that can lead to platelet sequestration in the spleen[8]

Other methods are needed because traditional imaging can produce false-negative results in cases of early cirrhosis. Indicators of non-invasive fibrosis are becoming more common; they are particularly helpful at the extremes of the liver's fibrosis spectrum, such as cirrhosis and no fibrosis. A liver biopsy is a crucial benchmark for determining the degree of liver fibrosis, yet this invasive procedure may contain categorisation errors.[9] Non-invasive and economical options are being researched since people are reluctant to get a biopsy. As a result, numerous non-invasive liver biopsy substitutes are being created. Four components (FIB-4), the aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) ratio (AAR), the AAR/ platelet ratio index (AARPRI), and imaging techniques including elastography are the foundation of the fibrosis index. A novel technique for assessing liver fibrosis is transient elastography (TE; FibroScan, Echosens, France), which uses low-frequency elastic waves and ultrasound to measure liver stiffness. When it comes to identifying fibrosis, FibroScan offers excellent sensitivity, specificity, and accuracy (the sensitivity and specificity are both 90%).[10]

NLR and PLR are also used to evaluate the stage of liver fibrosis. In patients with an HBeAg-negative persistent HBV infection, non-invasive techniques are becoming more and more crucial for closely monitoring the risk of cirrhosis and hepatocellular cancer. The main inflammatory cells are neutrophils and lymphocytes, and during inflammation, their numbers momentarily change.[11] A complete blood count can be used to obtain PLR, a cheap inflammatory marker.

Stages of Fibrosis

Using the METAVIR scoring system on liver biopsy specimens, the stages can be divided into 0 to 4 as follows:

1. F0—no fibrosis
2. F1—portal fibrosis
3. F2—periportal fibrosis
4. F3—bridging fibrosis
5. F4—cirrhosis

As stages of fibrosis, cirrhosis and HCC are both linked to high rates of morbidity and death.[12] Ascites, varices, and decompensation all increase the risk of death. Reducing the duration of the sickness is one of the main goals of hepatitis B treatment. Male gender, advanced age, alcohol use, high alanine aminotransferase (ALT) levels, high HBV DNA levels, and maybe related hepatitis C or D virus and HIV are some of the factors that contribute to the progression of liver fibrosis.

This research aims to find a biomarker that can forecast the degree of liver fibrosis as determined by transient elastography. This study aims to determine whether PLR can be utilised as a non-invasive indicator of fibrosis in individuals with cirrhosis brought on by chronic hepatitis B and whether it can predict appreciable fibrosis in CHB patients. 37.63–149.13 and 43.36–172.68 are the typical PLR reference ranges for men and women, respectively.[13]

Methods

Study Design

Ethic Statement

The study protocol and informed consent documents were reviewed and approved by the Ethics Committee of Dr. Ram Manohar Lohia Hospital and Abvims New Delhi. All these chronic hepatitis patients provided written informed consent before participating in this study.

Study Place

Department of Medicine, ABVIMS, Dr. RML Hospital, New Delhi

Study Design

Cross sectional observational study

Study Period

1 Jan 2021–31 May 2022

Sample Size

At a 95% confidence interval and 90% power, the sample size was calculated for the platelet to lymphocyte ratio in chronic hepatitis B. (Altun D et al.) using the formula:

N>=2 (standard deviation) 2*(Zα + Zβ) 2 (mean difference) 2

Where Zα is the value of Z at a two-sided alpha error of 5%

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202410

and Zβ is the value of Z at a power of 90% and the mean difference is the difference in mean values of two groups.

Formula for mean and sd by using median and range: - Mean ($\bar{x}$) = (a + (2*m) + b) / 4

SD=square root of[((1/12)* ((a-(2*m)+b)2/4)+(b-a)2))] Where m = median; a and b are interquartile ranges.

Formula for pooled standard deviation = square root of $[(S1)^2 + (S2)^2) / 2]$ Where S1 is the standard deviation of group 1.

And S2 is the standard deviation of group 2.

Sample size = 120

Inclusion and Exclusion Criteria

Inclusion criteria included CHB patients with positive hepatitis B surface antigen (HBsAg) for over six months and elevated liver enzymes. Exclusion criteria were co-infections (HCV, HIV, or HDV), alcohol abuse, non-alcoholic fatty liver disease (NAFLD), recent antiviral therapy, decompensated liver disease, and hepatocellular carcinoma.

Data Collection and Analysis

Demographic information, complete blood count (CBC), liver function tests (LFTs), and PLR were gathered as baseline data. Transient elastography was used to evaluate the stage of fibrosis (fibroscan). By dividing the platelet count by the lymphocyte count, PLR was computed. PLR's predictive value was ascertained using statistical analysis, which included ROC curve analysis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed for PLR at a predetermined cut-off.

Results

PLR is 104–126 in non-F4 fibrosis and 95–117 in F4 fibrosis. Mean PLR was significantly higher in hepatitis B subjects with significant fibrosis (106.07 ± 10.97) as compared to subjects with no/ mild fibrosis (115.55 ± 11.17) (p value < 0.001) Table 1.

Table 1.Comparison of Platelet to Lymphocyte Ratio between Fibrosis and Without Fibrosis Study Subjects

Values	No/ Mild Fibrosis (N = 60)	Significant Fibrosis (N = 60)	p Value
PLR	115.55 ± 11.17	106.07 ± 10.97	< 0.001
Median (IQR)	118 (106.25–122.75)	106 (103.00–110.75)	

PLR: Platelet to Lymphocyte Ratio

IQR: Interquartile Range

The ROC curve depicts the relationship between sensitivity (or TPR) and specificity (1 - FPR). Classifiers that produce curves closer to the top-left corner perform better. A random classifier is supposed to deliver points along the diagonal as a baseline (FPR = TPR). The closer the curve gets to the ROC space's 45-degree diagonal, the less accurate the test. The area under the curve using PLR to predict fibrosis in chronic hepatitis B subjects was 0.73 (95% CI: 0.64–0.82) Figure 3.

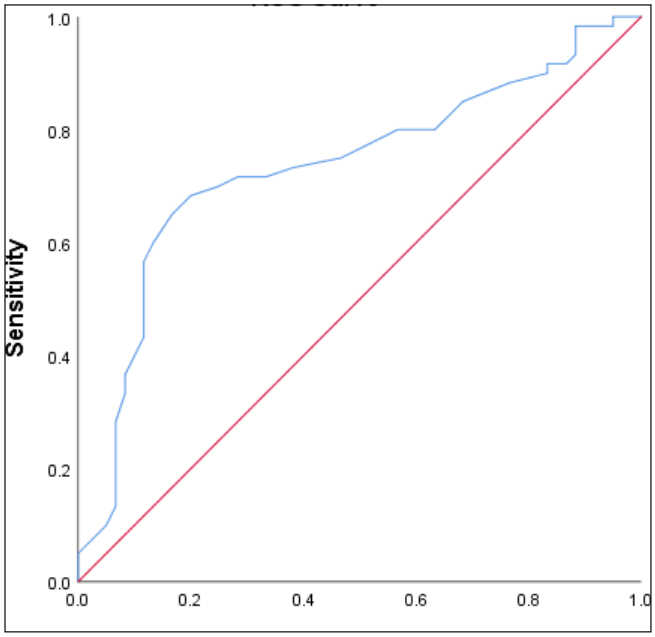

Figure 3.ROC Curve Analysis using Platelet Lymphocyte Ratio to Differentiate between Fibrosis and Without Fibrosis Study Subjects

The cut-off value was calculated using the Youden index from the ROC curve. At a cut-off of 112.5, the sensitivity, specificity, positive predictive value and negative predictive values of PLR to predict fibrosis were 81.67%, 66.67%, 71.01% and 78.43%, respectively Table 2.

Table 2.Sensitivity, Specificity, PPV, NPV, LR of PLR for Predicting Fibrosis in Chronic Hepatitis B Subjects

Values	PLR
AUC	0.73
Standard error	0.64–0.82
p value	< 0.001
Cut-off value	112.5
Sensitivity	81.67%
Specificity	66.67%

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202410

PPV	71.01%
NPV	78.43%
Accuracy	74.17%
LR+ve (95% CI)	2.45 (1.68–3.57)
LR-ve (95% CI)	0.28 (0.16–0.48)

AUC:Area under curve, Std: NPV: Negative predictive value, PPV: Positive predictive value

The study included 120 CHB patients, with an even distribution across fibrosis stages (50% with non-F4 fibrosis and 50% with F4 fibrosis). PLR was significantly lower in patients with advanced fibrosis (mean PLR: 106.07 ± 10.97) compared to those with mild or no fibrosis (mean PLR: 115.55 ± 11.17), suggesting an inverse relationship between PLR and fibrosis severity.

ROC analysis indicated a PLR cutoff of 112.5, yielding a sensitivity of 81.67% and a specificity of 66.67% in predicting advanced fibrosis (F4). The area under the curve (AUC) was 0.73, indicating moderate diagnostic accuracy. These findings support the potential utility of PLR in non-invasively predicting liver fibrosis progression in CHB patients.

Discussion

The inverse relationship between PLR and liver fibrosis severity in CHB patients aligns with the inflammatory pathophysiology of fibrosis. As fibrosis progresses, platelet counts tend to decrease due to hypersplenism and reduced thrombopoietin synthesis, leading to a lower PLR. Meanwhile, lymphocyte levels reflect the immune system's inflammatory response, which is exacerbated in advanced fibrosis.

This study's findings suggest that PLR, a simple and cost-effective measure, may serve as an effective marker for staging liver fibrosis. While PLR cannot replace liver biopsy, it offers a valuable adjunct tool for identifying patients at higher risk of progressing to advanced fibrosis, aiding clinicians in timely intervention. Future longitudinal studies with larger cohorts are needed to validate these findings and further establish PLR's role in fibrosis monitoring.

Conclusion

This study underscores the potential of the platelet-to-lymphocyte ratio as a non-invasive, accessible biomarker for assessing liver fibrosis in chronic hepatitis B patients. The significant correlation between reduced PLR and advanced fibrosis suggests that PLR may assist in stratifying patient risk, thus improving CHB management and reducing reliance on invasive procedures.

Conflict of Interest: None

Sourse of Funding: None

Authors' Contribution: URS wrote the manuscript and provided data, conducted the patient interview, and J conducted all statistical analyses. All authors reviewed the final manuscript.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: None

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ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202410