GAVIN PUBLISHERS

Archives of Pediatrics

Altun D, et al. J Archives of Pediatrics 2: JPED-109.

Research Article

DOI:10.29011/2575-825X.100009

Platelet to Lymphocyte Ratio in Hepatitis B

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Citation: Altun D et al. (2017) Platelet to Lymphocyte Ratio in Hepatitis B. Arch Pediatr 2: 109. DOI: 10.29011/2575-825X.100009

Received Date: 18 January, 2016; **Accepted Date:** 23 February, 2017; **Published Date:** 03 March, 2017

Abstract

Background & Aims: We aimed to investigate diagnostic performance ofplatelet to lymphocyte ratio (PLR),aspartate amino transferase to platelet ratio index (APRI) and neutrophil to lymphocyte ratio (NLR) as comparative in chronic hepatitis B (CHB) patientsacquired at childhood.

Methods: We retrospectively analyzed 164 male patients diagnosed with CHB acquired at childhood as study group. The control group consisted of 164 heathy subjects.Liver biopsy was performed and fibrosis scoresand histological activity index (HAI) were assessed according to the Ishak scoring system. The patients were divided into twogroups on the basis of the fibrosis scores as follows: F0-1 No/early stage fibrosis, F2-6 significant fibrosis. APRI, NLR and PLR of patients were calculated from blood samples taken at the same time as the biopsy.

Results: Histopathologic analysis showed that 71(43.3%) patientshad F0–1 and 93(56.7%) patients had ≥F2. APRI scores and NLR of the study group were significantly higher than those of the control group ($p<0.001$, $p=0.02$, respectively), whereasPLR was significantly lower ($p=0.01$). In addition, correlation analyses revealed that PLR has a negative and significant relationship with both fibrosis and HAI. ((r:-0,220, p:0,005), (r:-0,146, p:0,02), respectively).

Conclusions: The present study has shown, for thefirst time, PLR isstrongly associated with histological severity and canbe used to identify patients with advanced disease in CHB. Our findings suggested PLR,in combination with other noninvasive parameters such as APRI score and NLR,may assist in identifying individuals at high risk of having advanced and progressive disease.

Keywords: APRI- fibrosis-hepatitis B-neutrophil to lymphocyte ratio-platelet to lymphocyte ratio

Abbreviations

ALT:	Alanine transaminase
AST:	aspartate transaminase
APRI:	Aspartate amino transferase to platelet ratio index
CHB:	chronic hepatitis B
HBV:	hepatitis B virus
HCC:	hepatocellular carcinoma
NLR:	neutrophil to lymphocyte ratio
PLR:	platelet to lymphocyte ratio

Introduction

Worldwide, it is estimatedthatmorethan 4 billionpeoplehavebeeninfectedwithhepatitis B virus (HBV), and 350 millionindividualshavebeendiagnosedwithchronichepatitis B (CHB)[1]. Although a rather benign course of chronic HBV infection during childhood has been described, 3-5% and 0.01-0.03% of chronic carriers develop cirrhosis or hepatocellular carcinoma (HCC) before adulthood. Considering the whole lifetime, the risk of HCC rises to 9-24% and the incidence of cirrhosis to 2-3% per year [2]. Disease morbidity and mortality in CHB depends on the continuation of viral replication and progression of the disease to cirrhosis and HCC. The goal of treatment is to improve quality of

life and survival by preventing progression of the disease to advanced stages like cirrhosis and HCC. Therefore, establishing the status of hepatic fibrosis is important to decide the treatment and management[3]. Liverbiopsy has long been an essential tool for assessing the degree of liver fibrosis [4]. Currently, theplace of liver biopsyas the standard of reference for assessing liver fibrosis has been challenged by the increasing awareness of a number of drawbacks related to its use (invasiveness, sampling error, inter-/intraobserver variability). In parallel with this, noninvasive assessment of liver fibrosis has experienced explosive growth in recent years and a wide spectrum of noninvasive methods ranging from serum assays to imaging techniques have been developed [5].

Aspartate amino transferase to platelet ratio index (APRI) has been used to determine chronic hepatitis C (CHC) patients with advanced fibrosis [6]and it also predicts significant fibrosis in CHB [7].Recently, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have attracted attention as inflammatory biomarkers. They can be calculated easily from complete blood counts and are easily accessible markers which indicate the state of inflammation in the body. NLR is considered to evaluate disease prognosis in HCC [8,9]. It can be used also as a novel non-invasive marker to predict advanced disease in non alcoholic steatohepatitis[10]. However, there are few studies conducted to assess APRI or NLR for predicting the fibrosis stage of patients with HBV-related fibrosis and inflammation. The aim of the present study was to investigate the diagnostic performance of these markers as comparative for the prediction of significant fibrosis and inflammation in CHB patients who had HBV since their childhood. In the meantime, this study aimed to evaluate the efficacy of PLR to predict significant fibrosis in CHB for the first time in the literature.

Materıals And Methods

Study population

This study was conducted between January 2012 and October 2014 at Etimesgut Military Hospital in Turkey. We retrospectively analyzed 164 male patients diagnosed with CHB acquired at childhood who had undergone percutaneous liver biopsy. Inclusion criteria were accepted as follows: positive surface antigen of HBV and elevated aspartate transaminase (AST), alanine transaminase (ALT) levels for at least 6 months, HBV DNA ≥10000 copy/mL, patients with pretreatment liver biopsies and have received diagnosis by 18 years age.Exclusion criteria for participation were determined as positive serology for hepatitis C virus, human immunodeficiency virüs and hepatitis D, presence of any other causes of liver disease, any evidence of hepatic decompensation or prior antiviral treatment and alcohol use.

The control group consisted of 164 individuals with normal liver tests without systemic disease. Their gender and ages were similar with study group. All cases were evaluated for clinical and medical background. Our study was conducted in accordance with the principles of the Helsinki Declaration. This retrospectively designed study was approved by the Ethical Committee of our hospital. All study subjects gave informed concent for the liver biopsy.

Data collection and calculation of indirect fibrosis markers

The medical record data of study group and control group were collected via retrospective chart review. Age, diagnosis age of CHB, duration of CHB in years, AST, ALT, HbeAg status, HBV DNA levels, histopathological results were recorded for groups. Laboratory data was obtained from blood samples taken at the same time as liver biopsy and used for calculations. APRI score was calculated with the formula (AST/upper limit of normal)/platelet (10^9/L) × 100 [6]. An AST value of 37 was used as the upper limit of normal for our laboratory. NLR and PLR were calculated by dividing the absolute neutrophil and platelet count by the absolute lymphocyte count.

Histopathologicalassesment

Liver biopsy was performed using a 16-gauge Mengini needle under local anesthesia condition. Liver tissues were fixed for 24 hours in 10% neutral buffered formalin, routinely processed and the embedded in parafin wax. Four-micron-thick sections were cut and stained with hematoxylin & eosin, Periodic acid-Schiff. All slides were examined with a light microscope. A single experienced pathologist performed histopathological examination in a blinded fashion. Patients' fibrosis scores and histological activity index (HAI) were calculated according to the Ishak scoring system[11]. Fibrosis score was recognized as follows: F0-1 No/early stage fibrosis, F2-6 significant fibrosis. Significant liver fibrosis was defined as an Ishakscore of ≥ 2.

Statistical analysis

Statistical analysis was performed using IBMSPSS 22.0 (SPSS Inc., Chicago, IL, United States). The study was comprised of study and control groups. In each group, descriptive statistics were applied. Pearson qui-square test (x2) was used to compare frequencies or means. The appropriate test for normal distribution of variables was performed byKolmogorov-Smirnov test. Nonparametric methods were used for non-normally distributed values (Mann-Whitney U). Because of non-normally distributed, continuous variables were expressed as median (minimum-maximum). Categorical variables were presented as frequency and percentage. Spearman's correlation analysis was used for ordinal and scale variables. A p-value of < 0.05 was considered statistically significant.

Results

In this study, 164 patients with mean age of 21 years (range, 20–34 years) and 164 healthy subjects with mean age of 21 years (range, 20–32 years) were included in the study and control group, respectively.The gender of both groups was male because our hospital was a military hospital. The control and patient groups were age-matched.The demographic and laboratory data of the groups were summarized in Table 1. CHB diagnosis ages of patients was minimum 6 months and maximum 18 years.

Histopathologic examination showed that71 (43.3%) patients had fibrosisscore F0–1, whereas 93 (56.7%) patients were found to have fibrosis score ≥ F2 fibrosis.

APRI scores and NLR of the study group were significantly higher than those of the control group (p< 0.001, p= 0.02, respectively). PLR was significantly lower than those of the control group(p=0.01). In addition, as expected, platelet count, AST and ALT values were significantly different from those of the control group (p< 0.001). While platelet and lymphocyte count was lower, AST, ALT levels and neutrophil count were higher in the patient group (Table 1).

	Patients (n = 164)	Controls (n = 164)	p value
Sex (M/F)	164/0	164/0	-
Age (years)	21(20-34)	21 (20-32)	< 0.80
AST (IU/L)	43 (23-351)	22 (13-199)	< 0.001
ALT (IU/L)	77 (44-826)	22 (7-82)	< 0.001
Neutrophil count (10^3µL)	3.8 (0.7-8.3)	3.5 (1.6-7.2)	0.03
Lymphocyte count (10^3µL)	2.03 (0.7-4.1)	2.07 (1.09-3.97)	0.48
Platelet count (10^3µL)	230 (95-394)	253 (144-372)	< 0.001
APRI score	0,5 (0,2-4,1)	0,2 (0,1-2,1)	< 0.001
NLR	1.8 (0.3-6.2)	1.6 (0.7-4.2)	0.02
PLR	109 (57-253)	118 (56-279)	0.01

Values are expressed as n (%), median (minimum-maximum). AST: Aspartate amino transferase; ALT: Alanine amino transferase; NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; APRI: Aspartate amino transferase/platelet ratio index. Mann-Whitney U

Table 1. Comparison of demographic and laboratory parameters in the groups

In CHB patients, when significant fibrosis was compared with early-stage fibrosis, the groups showed no difference in APRI scores while there was a significant difference in terms of NLR and PLR (p=0.02, p=0.007), respectively) (Table 2).

	No/mild fibrosis (n = 71)	Significant fibrosis (n = 93)	pvalue
Sex (M/F)	71/0	93/0	-
[1]Age (years)	21(20-30)	21 (20-34)	0,77
[1]AST (IU/L)	40 (25-166)	45 (23-351)	0,10
[1]ALT (IU/L)	76 (44-553)	89 (45-826)	0,06
[1]Neutrophil count (10^3µL)	4 (1,89-7,3)	3,76 (0,76-8,32)	0,23
[1]Lymphocyte count (10^3µL)	1,87 (0,74-3,56)	2,1 (1,21-4,14)	0,02
[1]Platelet count (10^3µL)	233 (137-394)	229 (95-357)	0,66
[1]APRI score	0,5 (0,2-4,1)	0,5 (0,2-2,5)	0.29
[1]NLR	2,01 (0,95-6,28)	1,83 (0.37-4,12)	0.02
[1]PLR	120 (65,7-253,4)	107 (58-182)	0.007
[2]HbeAg (negative/positive)	40/31	48/45	0,54
[1]HBV DNA (10^3copy/mL)	3300 (0-9900000)	55000 (0-9900000)	0,11

Values are expressed as n (%), median (minimum-maximum). AST: Aspartate amino transferase; ALT: Alanine amino transferase; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; APRI: Aspartate amino transferase/ platelet ratio index. [1]Mann-Whitney U, [2]Pearson qui-square test (x2).

Table 2. Between group comparisons in CHB patients according to fibrosis stage.

In addition, correlation analyses revealed that PLR has a negative and significant relationship with both fibrosis and HAI ((r: -0,220, p:0,005), (r: -0,146, p:0,02), respectively).

In the mean time, correlation analyses revealed that NLR has a negative and significant relationship with fibrosis (r = -0.225, p:0,004). There isn't correlation with HAI (r = -0.071, p = 0.363).

Correlation analyses revealed that HBV DNA has a positive and significant relationship with both fibrosis and HAI ((r: 0,159, p:0,04), (r: 0,315, p:<0,001),respectively).

Discussion

Diagnosis and follow-up of chronic liver diseases has long relied on liver biopsy, and only recently has its value as a method to assess the severity of liver diseases (or to follow-up disease progression) been questioned. Although biopsy is used to stage most cases of liver disease, it is well known that this procedure has several limitations [12,13].Liver biopsy is an invasive procedure with associated morbidity: pain occurs in 20% of patients and

major complications (such as bleeding or hemobilia) in 0.5% [13]. Therefore, liver biopsy has poor tolerance, particularly if it needs to be repeated over time in an individual patient. For this reason, noninvasive diagnosis of liver fibrosis is one of the fields that has evolved most rapidly in recent years. Moreover, patients are now aware of the availability of noninvasive methods to assess the degree of liver damage and are thus reluctant to undergo an invasive procedure [4]. In addition, non-invasive tests can be repeated over time, and in cases of indeterminate results, two or more methods can be combined [4].

In the case of patients with CHB, the number of studies assessing noninvasive markers is smaller. As one of them, APRI score was developed by Wai et al. in 2003 [6]. APRI score, which is often used daily practice such as AST and platelet count and can be calculated from the two test affected in the liver fibrosis is easy and non-invasive method [6]. It is indicate that the development of liver fibrosis may impair thrombopoietin production and, therefore, contribute to the reduction of the platelet count [14]. Splenomegalycontributesto a decrease of the circulating platelet pool. Advanced liver fibrosis, causing an altered production of thrombopoietin, portal hypertension and, consequently, splenomegaly, plays the main role in the pathogenesis of thrombocytopenia in chronic viral hepatitis. Other factors may play a minor role in platelet reduction, such as anti-platelet antibodies and bone marrow inhibition by the viral infection, and/or metabolic or toxic events [15]. Progression of liver fibrosis may reduce the clearance of AST, leading to increased serum AST levels [16]. Inaddition, advanced liver disease may be associated with mitochondrial injury, resulting in more marked release of AST,which is present in mitochondria and cytoplasm, relative to ALT [17]. The some authors suggested that, in their studies, APRI score, which issued to predict significant fibrosis and cirrhosis in CHC,was not suitable for patients with CHB. They explain this by the presence of a fluctuating course with acute attacks in CHB patients while the progression of fibrosis in CHC is more quiet [6,18,19]. In contrast, multiple studies had shown that it is of great value and has high accuracy in predicting advanced fibrosis in different forms of liver disease [20-22]. Shin et al. studied a large number of CHB patients and suggested a strong positive linear correlation between fibrosis and APRI [7]. Sebastiani et al. assessed the utility of several noninvasive markers in a cohort of 110 patients with chronic hepatitis B who had undergone liver biopsy [23]. They showed fibrotest and APRI achieved the highest diagnostic accuracy in identifying patients with significant fibrosis [23].

Celikbilek M et al. found that APRI score was higher in significant fibrosis but it was not statistically significant. However, in CHB patients with cirrhosis APRI score was significantly higher. They alsomentioned that their study results also showed a statisticalassociation between age and cirrhosis. Cirrhotic patients were found to be more elderly compared to the non-cirrhotic patients. They said this can be explained by the increased cirrhosis rates witholder age [24].

Although there are studies which suggest that lowplatelet counts are related to advanced hepatic fibrosis,other studies have shown opposite findings [18,25,26]. As consistent with above knowledge, in current research the platelet counts were significantly lower in the patients with CHB and significant fibrosis group than those of the control group and early-stage fibrosis, respectively. The AST values were higher in the patients with CHB and significant fibrosis group than those of the control group and early-stage fibrosis, respectively. As in that of Celikbilek M et al., although APRI score was significantly higher in patients group than control group, we did not find statistically significant relation with APRI score and significant fibrosis. However, one of our study limitations is we have not elderly patients so we have a few cirrhosis patient. For this reason, we didn't create a different group whose compose of cirrhotic patients. We thought that the lack of statistically significant relation with APRI score and significant fibrosis can attribute to the small number of our cirrhotic. Additionally, our results can be asssessed as preliminary data for CHB started in childhood and used in comparison of studies for elderly population.

Unlike previous reports, to further evaluate the association betweeninflammatory markers and liver fibrosis, we did additional analyses in which both NLR and PLR levels were taken into account. In the meantime, our study was composed of the greater number of CHB patients and along with healthy subject. As the other non-invasive markers, NLR and PLR can be easily calculated and are cost-effective tests shows the body's immune response [10]. Recently, NLR has been recommended as a new marker for systemic inflammation [27]. Celikbilek M et al. founded that in their study, NLR showed no difference in the CHB and control group, but negative and significant relationship between HAI with NLR. And they mentioned this negative relationship demonstrates the important role of lymphocytes in liver damage in CHB. According to their findings, fibrosis stage and cirrhosis were not associated with NLR. All the spectra of biopsies of patients with CHB give rise to the study of the relationship between histological findings with APRI score and NLR [24]. In present study, NLR of the study group were significantly higher than those of the control group. NLR of the significant fibrosis were lower than those of the early-stage fibrosis. Although, there isn't correlation with HAI, there is negative and significant correlation between fibrosis with NLR.

Lymphomononuclear cells play a fundamental role in inflammatory pathways during the development of cirrhosis [28]. In our study, we noted that the lymphocyte count was markedly

higher in patients with significant fibrosis compared with patients with no/minimal fibrosis. It can reflect the mononuclear inflammation occurring at the tissue level[28]. Thus, it was found NLR of the significant fibrosis were lower.

Although most published studies assessing NLR have been made in patients with chronic hepatitis, to our knowledge, our study is the first to evaluate the PLR in CHB disease. In the literature, PLR has been studied in various inflammatory states and neoplastic diseases such as chronic calcific pancreatitis, gastric cancer, non-small cell lung cancer and hepatocellular carcinoma[29-32]. Furthermore, it has been demonstrated that this ratio can be used as a prognostic factor for post-transplant HCC recurrence [33,34]. Moreover, in the light of current reports, NLR is a good predictor for the risk of dropout, while PLR is a good predictor for the risk of post-liver transplant recurrence [34]. Our current findings showed that PLR values were considerably lower both CHB patients according to control group and in cases with significant liver fibrosis.

One of our study limitations, all of our patients were male. However, Kekilli M et al. revealed that no significant difference between the two groups regarding sex in their study which is composed of 92 male and 37 female [35].

Conclusions

In conclusion, the present study has shown, for thefirst time, that in patients with childhood CHB, PLR is associated with histological severity and canbe used to identify patients with advanced disease. Ifour data are confirmed in future studies, we believethat a standardized cut-off value for PLRwould simplify the identification of advanced fibrosis inpatients with CHB. Thus, we suggest that PLR,a low-cost and useful test, provides a beneficial andspeedy evaluation of fibrosis in patients with CHB. Inlight of our findings, it is suggested that PLR,in combination with other noninvasive parameters such as APRI score and NLR,may assist in identifying individuals at high risk ofhaving advanced and progressive disease. Continued research in this area will give us the opportunity to offer our patients more precise and noninvasive diagnostic tools.

Funding

This article was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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