

Assessment of liver fibrosis in Chronic hepatitis B: Performance of hematological parameters

Evaluation de la fibrose hépatique dans l'hépatite B chronique: Performance des paramètres hématologiques

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ABSTRACT

Introduction: Hepatitis B is a major global health problem. Assessment of liver fibrosis is important for treatment decision. Liver biopsy (LB) represents the "Gold Standard" in the assessment of fibrosis. Several parameters have been identified for predicting the development and progression of liver disease; among them, hematological parameters.

The aim of our study was to assess the performance of these hematological parameters in the assessment of fibrosis in chronic hepatitis B.

Methods: We conducted a retrospective study involving all patients with chronic hepatitis B managed in Gastroenterology department of Mohamed Taher Maamouri hospital during the period from January 2013 to December 2022, who underwent a liver biopsy and routine laboratory tests.

According to the METAVIR scoring system, patients were divided into two groups: patients without significant fibrosis (F0, F1) and patients with significant fibrosis (F2, F3, F4). The predictive accuracy for liver fibrosis was assessed by receiver operating characteristics (ROC) analysis.

Results: A total of 119 patients were included. Liver biopsy revealed significant fibrosis in 20.2% of the patients. The mean platelet count was significantly lower in patients with significant fibrosis, as compared to patients with non-significant fibrosis ($p < 0.001$). The AUROC of RDW was 0.857 with a cut-off value of 41.8 FL (sensitivity 88.9%; specificity 70.9%; Positive and negative predictive values 50% and 95.1% respectively).

Conclusion: Blood count parameters are non-invasive markers of liver fibrosis in patients with chronic hepatitis B. Thus, significant fibrosis can be ruled out in patients with RDW < 41.8 FL, which could help avoid liver biopsy in these patients.

Key words: Chronic hepatitis B, Evaluation, Liver fibrosis, Biopsy, Blood count

RÉSUMÉ

Introduction : L'hépatite B est un problème majeur de santé mondiale. L'évaluation de la fibrose hépatique est importante pour la décision thérapeutique. La biopsie hépatique représente la « référence » dans l'évaluation de la fibrose. Plusieurs paramètres ont été identifiés pour prédire le développement et la progression des maladies du foie ; parmi eux, les paramètres hématologiques.

L'objectif de notre étude était d'évaluer la performance de ces paramètres hématologiques dans l'évaluation de la fibrose dans l'hépatite B chronique.

Méthodes : Nous avons mené une étude rétrospective impliquant tous les patients atteints d'hépatite B chronique pris en charge au service de gastroentérologie de l'hôpital Taher Maamouri entre janvier 2013 et décembre 2022, qui ont subi une biopsie hépatique et des analyses de laboratoire de routine. Selon le système de notation METAVIR, les patients étaient divisés en deux groupes : les patients sans fibrose significative (F0, F1) et les patients atteints de fibrose avancée (F2, F3, F4). La précision prédictive de la mucoviscidose hépatique a été évaluée par analyse des caractéristiques de fonctionnement du récepteur (ROC).

Résultats : Un total de 119 patients ont été inclus. La biopsie hépatique a révélé une fibrose significative chez 20,2 % des patients. Le nombre moyen de plaquettes était significativement plus faible chez les patients atteints de mucoviscidose significative, comparé aux patients atteints de mucoviscidose non significative ($p < 0,001$). L'AUROC de RDW était de 0,857 avec une valeur de coupure de 41,8 FL (sensibilité 88,9 % ; spécificité 70,9 % ; Valeurs prédictives positives et négatives 50 % et 95,1 % respectivement).

Conclusion : Les paramètres de numération sanguine sont des marqueurs non invasifs de la fibrose hépatique chez les patients atteints d'hépatite B chronique. Ainsi, une fibrose significative peut être écartée chez les patients présentant une RDW $< 41,8$ FL, ce qui pourrait aider à éviter la biopsie hépatique chez ces patients.

Mots clés: Hépatite B chronique, Évaluation, Fibrose hépatique, Biopsie, Numération sanguine

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INTRODUCTION

Chronic viral hepatitis B is a major public health problem worldwide, with significant morbidity and mortality. In Tunisia, the national prevalence of HBs Ag was 1.7% in 2016, with varying endemicities depending on the region (1). The prognosis of this hepatopathy is conditioned by the degree of hepatic fibrosis, which plays a key role in the therapeutic decision and monitoring protocol. Liver biopsy (LB) is the "gold standard" for assessing hepatic fibrosis. Nevertheless, the indications for liver biopsy have declined significantly in recent years, due to its invasive nature, the risk of complications, the inter-observer variability and the sampling errors. To overcome these shortcomings, other non-invasive tests have been developed as Fibrosis 4 (Fib 4), AST To Platelet Ratio Index (APRI) (1) and the gamma-glutamyl transpeptidase to platelet ratio (GPR) (2).

Currently, hematological parameters of the complete blood count (CBC) have been identified as non-invasive serum markers of hepatic fibrosis in several studies. The most widely studied parameters are: neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV), red cell distribution width (RDW) and platelet distribution width (PDW). However, very few Tunisian studies have validated the reliability of these hematological parameters in the assessment of hepatic fibrosis.

The aim of our study was to evaluate the performance of the hematological parameters of the complete blood count in the diagnosis of fibrosis during chronic viral hepatitis B in a Tunisian population.

METHODS

We carried an observational, monocentric and retrospective study from 2013 to 2022.

Study population

Inclusion criteria:

We have included all the patients with chronic hepatitis B who underwent LB between 2013 and 2022.

Non-inclusion criteria:

Patients with incomplete data, inappropriate biopsy samples, co-infection with hepatitis C or D virus and human immunodeficiency virus (HIV), autoimmune liver disease, hepatocellular carcinoma, concomitant tuberculosis, transaminase levels greater than 10 times the upper limit of normal, heavy alcohol consumption (> 20 g/day), acute heart failure and pregnancy.

Outcome criteria:

A correlation between the hematological data of the CBC and the histological data in the evaluation of the degree of fibrosis was sought.

Data collection:

Data were collected retrospectively from the records of

patients with chronic hepatitis B.

For each patient, we collected the demographic characteristics, the comorbidities, the body mass index (BMI), the biological data (CBC: hemoglobin (Hb), white blood cell count (WBC), lymphocyte count, neutrophil count, platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), red blood cell distribution width (RDW), the renal blood test (plasma urea and creatinine), the liver function tests (aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (TB) and conjugated bilirubin (CB) levels, prothrombin time (PT), albumin level (ALB) and histological data (hepatic fibrosis and activity were recorded according to the Metavir score (2,3)). Histological signs suggestive of viral B infection and therapeutic management of patients were also sought. According to Metavir score, we divided the patients in two groups:

Group 1: patients without significant fibrosis (F0-F1)

Group 2: patients with significant fibrosis ($\geq$ F2)

Statistical study

Statistical analysis was performed with SPSS 27. Means were compared using the student's t- test. The ROC curves (receiver operating characteristics) were used to assess the accuracy of hematological markers of the CBC in predicting significant fibrosis.

After verifying that the area under the ROC curve (AUROC) was significant ($p < 0.05$), we determined the cut-off values that corresponded to the maximum of the Youden index (Sensitivity (Se) + Specificity (Sp) -1). The significance level (p) was set at 0.05.

Positive predictive values (PPV) and negative predictive values (NPP) of hematological settings were calculated using Bayes' theorem:

$$PPV = \frac{p \cdot Se}{p \cdot Se + (1-p) \cdot (1-Sp)}$$

$$NPV = \frac{(1-p) \cdot Sp}{(1-p) \cdot Sp + p \cdot (1-Se)}$$

P is defined by the prevalence of significant fibrosis.

Ethical considerations

Given the retrospective nature of our study, no consent could be obtained from the included patients regarding the use of personal data mentioned on the medical records. Strict anonymity of personal data was respected throughout. There were no conflicts of interest in this work.

RESULTS

General characteristics of the study population

One hundred and nineteen (119) patients were included in our study. The mean age of the patients was 41.7 years [14- 67] years. The sex ratio male to female (M/F) was 1.05.

More than the half of our patients (56.5%) had a body mass index ≥ 25 Kg/m². Diabetes, dyslipidemia and

hypertension were noted in 6%, 6% and 4.2% of cases respectively.

HBe Ag was positive in 3% of patients. The viral load (HBV PCR) was requested in all patients included in our study, with a mean value of 16800 IU/ml [20-26106].

Biological data

Hematological parameters of the complete blood count:

Thirteen patients had anemia. Leukopenia was noted in 5% of cases. Neutropenia and lymphopenia were noted in 2.5% and 5.8% of cases respectively. Thrombocytopenia was noted in 13.4% of cases. The clinic-biological characteristics of the studied population are shown in table 1.

Elevated ALT and AST were noted in 23.2% and 17.2% of cases, respectively. Cholestasis was noted in 9.7% of cases.

Histological data of patients

Hepatopathy activity:

Absent or minimal activity (A0-A1) was noted in the majority of cases (89%) while we reported 11% cases of A2.

Liver fibrosis:

Ninety-five patients (79.8%) had no significant fibrosis (F0-F1) and 24 patients (20.2%) had significant fibrosis F≥2.

Other histological features:

The ground-glass hepatocytes, indicating accumulation of HBs Ag in the hepatocyte endoplasmic reticulum, was

noted in 36.8% of cases, liver steatosis was present in 33.9% of cases and sanded nuclei in 2.8% of cases.

Therapeutic management of patients

Antiviral B treatment was prescribed for 20 patients. All of these patients were treated with the nucleoside analogue entecavir.

Correlation between hematological parameters and liver fibrosis

The study of correlation between hematological parameters and liver fibrosis is summarized in table 1.

Study of the sensitivity and the specificity of hematological parameters in predicting liver fibrosis: The table

Table 1. Correlation between hematological parameters and liver fibrosis

The variables/ Means	All the patients (n=119)	Patients without significant fibrosis (n=95)	Patients with significant fibrosis (n=24)	P
Platelets (/μL)	195313.95± 72368.65	221989.47± 51773.5	159217.39± 63109.54	<0.001
MPV (fL)	9.98±8.05	10.65±11.33	9.55±1.35	0.68
PDW (%)	15.47±1.07	15.46±1.05	15.51±1.51	0.9
RDW (fL)	44.21±10.39	41.56±6.84	52.47± 14.48	<0.001
PLR	109.32±63.35	109.39±52.84	104.79± 104.98	0.7
NLR	1.22±1.64	1.7±1.16	2.43±2.9	0.05

MPV: mean platelet volume, PDW: platelet distribution width, RDW: red distribution width, PLR: platelet to 1.05 lymphocyte ratio, NLR: neutrophil to lymphocyte ratio

Table 2. Sensitivity and Specificity of hematological parameters in predicting liver fibrosis

Parameters	AUROC [95% CI]	P	Cut-off / Correlation	Sensitivity	Specificity	PPV	NPV
Platelet count	0.77 [0.65–0.89] for ruling out significant fibrosis -0.228: associated to significant fibrosis	<0.001	>180000/μL	80%	66%	37.3%	92.9%
RDW	0.857 [0.765–0.950]	<0.001	≥41.8 fL	88.9%	70.9%	50%	95.1%

AUROC: Area under the ROC curve, RDW: red distribution width, PPV: Positive Predictive Value, NPV: Negative Predictive Value

Discussion

In our study, platelet count, RDW and NLR were associated to significant fibrosis.

In our study, platelet levels were statistically correlated with liver fibrosis. Platelet levels were inversely correlated with fibrosis' stage (AUROC= -0.228, P<0.001). A platelet count of more than 180000 /μL rules out the diagnosis of significant fibrosis, with a sensitivity of 80% and a specificity of 66%, an AUROC of 0.77; CI [0.65-0.89].

Our results were consistent with those reported in the literature. In a Chinese study published in 2020, which included 941 patients with chronic HBV infection, platelet count was inverse ly correlated with fibrosis' stage (r = -0.295, p = 0.032) and was independently associated with F4 fibrosis (OR=0.978; 95% CI, 0.960-0.997; p = 0.026) (4). In the same study, the area under the ROC curve for platelet count to distinguish between cirrhosis

and chronic hepatitis B was 0.927 (sensitivity=78.76%; specificity=92.22%) (4). Platelet levels in patients with F4 fibrosis were lower than in patients with fibrosis ≤ F3 (p = 0.013). Thus, the authors of this study concluded that platelet count represents a non-invasive marker for assessing the degree of liver fibrosis in patients with chronic HBV infection (4). It has also been demonstrated that the performance of the platelet count in the assessment of liver fibrosis is comparable to that of the APRI and FIB-4 scores (5). This is linked to activated platelets, which release inflammatory mediators that promote HBV viral clearance (6). They also release anti-fibrotic molecules, which improve liver function by reducing hepatic fibrosis (6). Studies have suggested that platelets may reduce the expression of TGF-β, the main fibrogenic cytokine involved in liver fibrogenesis (5). Platelets also reduced the production of collagen by inactivating hepatic star cells (5).

Platelet transfusion can therefore improve liver function in patients with cirrhosis (5).

It has been concluded that platelet count is a non-invasive marker of liver fibrosis, hence the value of including this parameter in the calculation of several non-invasive tests of fibrosis, such as the ASAT/platelet ratio (APRI), the Fib4 score and the Forns index (7).

The red blood cell distribution width is a biological marker of anaemia; however, the presence of a chronic inflammatory state may modify the values of this parameter. A chronic inflammation, such as chronic viral hepatitis B, leads to an increased production of pro-inflammatory cytokines which inhibit the erythropoietin-induced maturation of erythrocytes, hence an increase in the number of immature erythrocytes released into the circulation, leading to higher RDW values (8).

In our study, there was a statistically significant correlation between the degree of liver fibrosis and the RDW (41.5 fL in F0-F1 patients versus 52.4 fL in patients with significant fibrosis; $p < 0.001$). The AUROC of RDW in predicting significant fibrosis was equal to 0.857 [95% CI: 0.765-0.950] ($p < 0.001$). Our results corroborate the data in the literature.

A meta-analysis published in 2023 including 3272 HBV-infected patients showed that RDW values were higher in patients with viral B cirrhosis compared with those with moderate fibrosis ($F < 3$) (9). In the same meta-analysis, a multivariate analysis of predictors of fibrosis showed that RDW was significantly associated with disease severity, with an odds ratio of 1.80 ($p = 0.004$) (9). In addition, the RDW was independently associated with liver fibrosis with an AUROC of 0.672 (specificity = 42.5% and sensitivity = 91.5%) (9). It has also been shown that each 1% increase in RDW values increased the risk of liver fibrosis by 12% (10).

In our study, we identified a cut off point predictive of significant fibrosis, which was equal to 41.8 fL with a sensitivity of 88.9% and a specificity of 70.9%. Thus, a statistically significant correlation with significant fibrosis was noted in patients with a $RDW \geq 41.8$ fL ($p < 0.001$). The PPV and NPV were 50% and 95.1% respectively. It was concluded that this haematological setting was predictive of advanced liver fibrosis and the severity of necrotic-inflammatory activity in patients infected with hepatitis B virus. Thus, significant fibrosis can be ruled out in patients with a $RDW < 41.8$ fL with an excellent NPV of 95.1%, avoiding LB in these patients.

Mean platelet volume (MPV) is a routine parameter used to assess platelet function and activation. It reflects the average size of platelets. Changes in this parameter may be associated with the severity of certain pathologies. An increase in MPV may be associated with cardiovascular disease, stroke, pulmonary embolism or chronic renal failure, while a decrease in MPV values may be associated with anaemia, ulcerative colitis or systemic lupus erythematosus (11). Several studies have also shown that an increase in MPV correlates with the severity of certain chronic liver diseases.

Indeed, it has been shown that inactive HBs Ag carriers have higher MPV values than the control group (12). It has been proven that interleukin-6 (IL-6) contributes

to the necrotic-inflammatory activity in chronic viral hepatitis B. Thus, an increase in IL-6 is associated with an increase in necrotic-inflammatory activity. Thus, an increase in IL-6 may increase platelet size by interfering with megakaryopoiesis (13).

In our study, MPV did not correlate with liver fibrosis ($p = 0.68$) and the area under the MPV ROC curve was not statistically significant in predicting significant fibrosis ($p = 0.2$).

In the literature, several studies have shown that MPV is an independent variable determining the severity of liver inflammation, but not liver fibrosis (12). The authors concluded that MPV may increase in patients with chronic hepatitis B, however, this increase was not associated with liver fibrosis as assessed by histology (12).

Thus, this parameter should not be considered as an independent factor of liver fibrosis due to its non-specificity since it may interfere with other factors such as smoking, obesity, hyperlipidaemia and metabolic syndrome.

The PDW measures variations in platelet size. In our study, the mean PDW was not correlated with liver fibrosis ($p = 0.9$).

In the literature, the results of the studies evaluating the performance of PDW in the assessment of fibrosis were discordant. In a Chinese study including 677 patients with chronic hepatitis B (7) this parameter was negatively related to the stage of fibrosis with an AUROC of 0.591, whereas in other studies, a positive correlation was reported between this parameter and the degree of fibrosis (11,14). Hence the need for further studies.

The neutrophil to lymphocyte ratio is an easy-to-calculate ratio that represents a marker of systemic inflammation in several pathologies, such as cardiovascular disease or malignant tumours (15). A high ratio could predict a poor prognosis in many pancreatic, gastric or non-small cell lung cancers (15). Recently, a few studies have evaluated the performance of this ratio in predicting fibrosis in patients with chronic B infection. In our study, patients with significant fibrosis ($F \geq 2$) had a higher NLR (2.4 versus 1.7) than in patients with F0-F1 fibrosis ($p = 0.05$). However, the area under the ROC curve for this ratio was equal to 0.54 ($p = 0.09$).

Liu et al stated that a $NLR < 2.36$ was associated with a low risk of mortality, whereas a ratio > 6.12 was associated with a high risk of mortality in patients with hepatitis B (16). A high NLR has also been shown to be an independent risk factor for the development of hepatocellular carcinoma in patients with treated chronic hepatitis B (17).

Several studies have concluded that NLR represents a predictor of liver fibrosis in patients with chronic hepatitis B (15). However, compared with APRI, GGT/platelet ratio (GPR) and FIB-4, the performance of NLR in predicting inflammation and liver fibrosis was poorer (15).

The PLR was related to the prognosis of vestibular neuritis, cardiovascular disease and thromboembolic disease (15). In addition, this ratio was associated with the progression of hepatocellular carcinoma (15).

In our study, the PLR was higher in F0-F1 patients (109.3 versus 104.8) but this correlation was not statistically

significant ($p=0.7$).

Indeed, a significant negative correlation between the values of this ratio and the degree of hepatic fibrosis has been described in several studies (15,18).

Tables 2 and 3 summarise the various studies evaluating the performance of haematological parameters in the assessment of liver fibrosis.

Table 2. Correlation between haematological parameters and liver fibrosis in the literature

Authors	Year of publication	Number of patients	Haematological parameters predictors of fibrosis
Yang YT and al (China) [4]	2020	941	PLT ($p=0.026$)
Pan and al (China) [8]	2014	677	PLT ($p<0.001$) PDW ($p<0.001$)
Aslam H and al [10]	2023	3272	RDW ($p=0.004$)
Rongrong and al (China) [15]	2021	457	Neutrophils ($p=0.001$) PLT ($p=0.001$) PLR ($p<0.001$) NLR(0.001)
Fuat and al (Turkey) [19]	2011	59	PLT ($p=0.017$) MPV ($p=0.009$)
Our study (Tunisia)	2025	119	PLT ($p<0.001$) RDW ($p<0.001$) NLR ($p=0.05$)

PLT:platelets, PDW: platelet distribution width, PLR:platelet to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, MPV: mean platelet volume

Table 3. AUROCs of haematological parameters in the prediction of hepatic fibrosis in the literature

Authors	Year of publication	Number of patients	Haematological parameters predictors of fibrosis
Baode and al (China) [20]	2013	458	RDW /PLT (AUROC=0,825)
Karagoz and al (Turkey) [11]	2014	229	PLT (AUROC=0.657) RDW (AUROC=0.672) MPV (AUROC=0.677) PLT/RDW (AUROC=0.758)
Lee and al (Korea) [21]	2015	482	RDW/ PLT (AUROC=0.811)
Yang YT and al (China) [4]	2020	941	PLT (AUROC=0.927)
Aslam H and al [10]	2023	3272	RDW (AUROC= 0.672)
Ding and al (China) [15]	2021	457	PLR (AUROC=-0.414) NLR (AUROC =-0,172) Monocytes/ lymphocytes (AUROC= -0.062)
Our study (Tunisia)	2025	119	PLT (AUROC= -0,258) RDW (AUROC=0,857)

RDW:red distribution width, PLT:platelets, MPV:mean platelet volume, AUROC:area under the ROC curve

The strengths of our study were the large number of patients with chronic hepatitis B who carried a LB and the study of several hematological parameters which are accessible in routine practice. Nevertheless, our work has certain limitations, notably its monocentric and

retrospective nature and the exclusion of decompensated cirrhotic patients classified as Child B8, B9 and C because of the impossibility of performing LB, which makes our results inapplicable in these patients.

CONCLUSION

Haematological markers of CBC are non-invasive markers of liver fibrosis in patients infected with the hepatitis B virus, notably the platelet count and the RDW. Thus, significant fibrosis can be ruled out in patients with a RDW < 41.8 fL with an excellent NPV of 95.1%, which allows avoiding LB in these patients.

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