PDW INDEX - A SIMPLE MODEL FOR THE PREDICTION OF LIVER FIBROSIS IN CHRONIC VIRAL HEPATITIS

Shahzad Ashraf*, Nadir Ali**

**Military Hospital, Rawalpindi, *Armed Forces Institute of Pathology, Rawalpindi

ABSTRACT

Objective: To assess the accuracy of platelets, platelet morphological parameters, mean platelet volume (MPV) and platelet distribution width, (PDW) to diagnose advanced fibrosis.

Study Design: Validation study

Place and Duration of Study: Combined Military Hospital, Malir, from Jun 2008 to Jun 2009.

Patients and Methods: Simplelaboratory tests, aspartate aminotransferase (AST) alanine aminotransferase (ALT)platelet count and platelet morphological parameters were measured in 91 chronic viral hepatitis patients. All patients had liver biopsy performed. A new index, PDW Index was derived to detect the opposing effects of liver fibrosis on platelet count, MPV, and PDW. The predictive value of the index for advanced fibrosis (F3-F4) was assessed through descriptive statistics and area under the ROC curves.

Results: Two cut-offs were chosen to qualify different stages of fibrosis. A value of > 8.00 predicted advanced fibrosis, F3-F4, with a specificity of 94% and positive predictive value of 78%. A value of < 6.00 ruled out advanced fibrosis with a negative predictive value of 93% and a sensitivity of 82%. The area under the ROC curve for advanced fibrosis was 0.840. PDW Index values outside of these cut-offs correctly classified 60% of patients.

Conclusion: A simple index comprising platelet as only parameters have high diagnostic value for the advanced stages of fibrosis.

Keywords: Advanced fibrosis, PDW Index, Platelets Mean Platelet Volume, Platelet Distribution Width.

INTRODUCTION

Chronic viral hepatitis is a major public health problem worldwide. It is estimated that in the coming years, there will be two to three fold rise in its prevalence and complications.Thrombocytopenia (platelet count < 150,000/μ*l*) is a commonly encountered condition in chronic liver disease[1]. According to a review, the prevalence of thrombocytopenia in patients with chronic hepatitis C ranged from 16% to 45% for this threshold value, and more than half of studies reported a prevalence of 24%[2]. Patients with thrombocytopenia who also have elevated transaminases, and coagulopathy are invariably considered to have cirrhosis. Thrombocytopenia has been reported in upto 76% of patients with cirrhosis[3]. Thrombocytopenia in patients with chronic liver disease (CLD) is not only an impediment to more invasive investigations but also affects management including liver transplantation.

The causes of thrombocytopenia in chronic liver disease (CLD) are varied. Traditionally, low platelet count has been attributed to portal hypertension and hypersplenism,other postulated mechanisms are:aberrant immune response resulting in immune mediated platelet destruction due to antiplatelet antibodies and/or immune complexes, decreased production by the bone marrow due to the disease process itself affecting megakaryocytes or direct detrimental effects of the offending virus. Moreover, interferon treatment also adversely affects platelets[1,4]. Conversely, in patients with immune thrombocytopenia purpura (ITP), the prevalence of hepatitis C infection was 30%[5].

Modern hematology analyzers, in addition to platelet count, also routinely measure platelet morphological parameters, such as mean platelet volume (MPV), and platelet distribution width (PDW). Usually inferences are not drawn from these parameters.

Correspondence: Lt Col Shahzad Ashraf, House No. 361, Street No. 33, F-11/2, Islamabad.
Email: shahzad_ashraf1@yahoo.com
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Increase of mean platelet volume has been observed in patients with chronic hepatitis C6 and also in chronic hepatitis B7 as compared to controls. Moreover, patients with advanced fibrosis have higher values as compared with patients with mild fibrosis[6]. Earlier, it had been shown that, platelet distribution width, PDW, was a better indicator of altered platelet homeostasis than MPV in cirrhosis, and it was markedly increased in cirrhosis as compared to controls[8]. The autoantibody associated immune dysfunction in chronic hepatitis C has been likened to that in chronic immune thrombocytopenia purpura[5,9]. The measurements of PDW and MPV are useful in the diagnosis of immune thrombocytopenia[10].

Various simple tests and indices have been proposed for the noninvasive prediction of hepatic fibrosis, which are based on routine laboratory parameters; the earliest one was: AST to ALT ratio[11], followed by, AST to platelet ratio index (APRI)[12], and Fib - 413 (age, AST, ALT, platelets), etc. Moreover, platelets have been an integral component of some of the more sophisticated tests, such as Forn's Index[14], and Fibrometer test[15].

Platelet count is a very useful marker to measure in patients with advanced CLD due to its ease of performance, simplicity and cost effectiveness. The combined use of MPV, PDW and platelet count could be helpful in understanding the platelet disorderas a manifestation of the underlying disease. We conducted this study to evaluate platelet count, and platelet indices, MPV and PDW for assessment of fibrosis in patients with chronic liver disease.

PATIENTS AND METHODS

This validation study was carried out at Combined Military Hospital Malir Cant from Jun 2008 to Jun 2009. One hundred patients with chronic viral hepatitis B and C were enrolled in the study. Exclusion criteria were: chronic liver disease other than HBV and HCV, metabolic, genetic and extra-hepatic causes of liver fibrosis, advanced cirrhosis (Child-Turcotte-Pugh) class B and C, other etiologies that can potentially affect platelets, MPV and PDW, such as: hypoplastic marrow, malignancies including hematologic malignancies, splenectomy, massive splenomegaly (causes other than CLD), immune causes of thrombocytopenia, atherosclerotic heart disease, chronic obstructive pulmonary disease, renal failure, HIV, anti-platelet drugs, and incomplete data.All patients gave informed consent for participation.

Complete blood picture, platelet count, MPV, and PDW were measured on automated hematology analyzer, Sysmex KX-21, within 2 hours of receiving sample. Serum bilirubin, aspartate aminotransferase (AST) alanine aminotransferase (ALT) alkaline transferase (ALP), urea, and creatinine were determined on microlab 200 using commercial reagents. High control, normal control and low control sera were run before and during the analysis of each batch. Prothrombin time (PT), international normalized ratio (INR), and PTT were performed using commercial tissue thromboplastin reagent. Control cells were run at the start of each day.HCV RNA PCR was performed with Amplicor Roche reagent kit. HBV viral genome was determined by using PCR-restriction fragment length polymorphism of the surface genome of HBV. The DNA was extracted from sera by using a Qiagen (Hilden, Germany) viral DNA kit or equivalent. Ultrasound examination of abdomen was performed using the Toshiba ECO-CEE machine, evaluating spleen, liver, portal vein diameter, to mark the biopsy site, and to rule out any anatomical abnormality of liver in the vector of the biopsy site.

A liver biopsy was done using 18 gauge Surecut liver biopsy needle using the subcutaneous intercostal approach. The biopsy was scored according to the Knodell HAI. The biopsy material was considered adequate if it contained > 6 portal tracts or if significant pathology was discerned otherwise, as determined by two histopathologists, who were unaware of the patients' clinical details.

The patient characteristics were given as mean ± SD or median and as the interquartile range as appropriate. The data followed the log normal distribution. Kappa, κ coefficient was used to measure interobserver agreement between histopathologists. Platelet count, platelet parameters, and other tests/indices were assessed in univariate analysis (student t-test) for their association with advanced fibrosis (F3-F4).Different ratios and indices of platelet parameters and platelet count were constructed. The best model, an arithmetic index, PDW Index, to diagnoseadvanced hepatic fibrosis was derived as:

PDW Index: $\frac{(PDW/\sqrt{MPV})^2}{\text{Platelet count}} \times 100$

The efficacy of PDW Index, and all other composite indices were assessed by ROC curve analysis. The diagnostic accuracy was also highlighted by sensitivity, specificity, positive, negative predictive values and likelihood ratios. The *p* value of < 0.05 was considered statistically significant. The statistical software used was SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

One hundred patients aged between 20 to 56 years were enrolled in the study, out of which 91 were included in the data analysis. Nine patients were dropped due to insufficient details. The patients' mean age was 33.5 + 6.3 years (median 32). There were 44 (48%) females. In virological profile, 77 (85%) had molecular evidence of HCV RNA viremia, 14 (15%) for HBV DNA viremia. The mean length of biopsy was 1.12+ 0.54 cm (median 1.00). Advanced fibrosis (24%) were consideredin stages 3 (bridging fibrosis) and stage 4 (cirrhosis histopathologically), table 1. For fibrosis, the kappa κ co-efficient between histopathologists was good 0.75. The association between platelet parameters, AST and ALT with different stages of fibrosis in univariate analysis is shown in table-2.

Two cutoff values of PDW Index were chosen in the presence and absence of advanced fibrosis. At a cutoff value of 8.00 or more, for advanced fibrosis, the PDW index had a specificity of 94% and a PPV of 78%. Further increasing the cutoff value of the PDW Indexto 10.00 (for the assessment of F3-F4 fibrosis), increased the PPV to 84%, but only half, 11 (50%) out of 22 patients could be diagnosed. With this cutoff value, although the PPV of the index increased, but half of the patients with advanced fibrosis remained unclassified. For the cutoff value of 8.00 or more, the area under the ROC for advanced fibrosis (F3-F4) was 0.840 (95% CI; 0.721-0.958) (Figure-1), and the area under the ROC for stage 3 (F3) fibrosis was 0.801 (95% CI; 0.671-0.930).

At the opposite end, a PDW Index value of 6.00 or less ruled out advanced fibrosis with a sensitivity of 82% and a high negative predictive value of 93%. The descriptive statistics including likelihood ratios are depicted in table 3.The PDW Index values of less than 6.00 (for absence of advanced fibrosis) and more than 8.00 (for presence of advanced fibrosis), correctly identified 60% of patients; when compared with liver biopsy as the standard of reference.

An AST to Platelet ratio index, APRI, ratio of > 1.5, for the diagnosis of advanced fibrosis had sensitivity 40%, specificity 93%, PPV 70% and NPV 83%. For APRI value of < 0.5, for advanced fibrosis, sensitivity was 86%, specificity 60%, PPV 42% and NPV was 92%.

For the above mentioned cutoff values for APRI, for advanced fibrosis, the area under the ROC was 0.878 (95% CI; 0.797 – 0.980), Fig 1; andthe area under the ROC for F3 fibrosis was 0.854 (95% CI; 0.752 – 0.956). The areas under the ROC's for APRI were comparable to the original study by Wai, *et al*. It can be seen that for advanced fibrosis (F3 – F4), the area under the ROC of PDW Index is comparable to that of APRI, and has only slight difference at the second decimal point.

DISCUSSION

For the noninvasive assessment of liver fibrosis, in addition tothe commonly performed laboratory parameters, there are many sophisticated indices available. Either these panels involve specialized markers of fibrogenesis or fibrolysis, such as: amino terminal propeptide of type III collagen (PIIINP), and tissue inhibitor of metalloproteinase 1 (TIMP-1)[16] or indices with complicated formulas, such as Fibrometer[15]. Notwithstanding the type of marker, in the routine daily management of chronic viral hepatitis patients; the measurement

Table-1: Demographic and histopathological characteristics of patients.

Age (yrs)	33.5 + 6.3; median 32
Female	44 (48%)
BMI	23.6 + 3.72; median 24
Hepatomegaly	22 (24%)
Splenomegaly	6 (6.5%)
HCV RNA	77 (85%)
HBV DNA	14 (15%)
Stage 0 (F0) No Fibrosis	28 (30.8%)
Stage 1 (F1) Portal Fibrosis	41 (45%)
Stage 3 (F3) Bridging Fibrosis	20 (22%)
Stage 4 (F4) Cirrhosis	2 (2.2%)
Advanced Fibrosis (F3-F4)	22 (24%)

of these complex indices is either practically difficult or suffer from lack of availability in most clinical laboratories, besides being costly. These factors are further compounded in the developing countries with their increasing burden of chronic viral hepatitis patients.

The current study was contemplated to evaluate and compare the diagnostic accuracy of platelet parameters and platelet count, for the

The sensitivity, specificity, and the predictive values are also similar to other simple indices of liver fibrosis. The negative predictive assessment of advanced fibrosis and compare with APRI.

Our study has shown that a platelet only derived index compares with the renowned noninvasive index, APRI, for the prediction of significant fibrosis. It's most important aspect is its simplicity (can be performed at the bedside with the help of calculator by looking at Blood CP; and doesn't use any biochemical markers). Additionally, it will be very helpful in our country with limited resources.

value was high in our study, at a threshold value of 6.00, it was 93% with a sensitivity of 82%. Thus, the index is very useful in excluding the advanced stages of fibrosis, with the level of confidence comparable to the more sophisticated models, such as Forns Index, with a NPV value of 96%[14].

In our study, the positive predictive value for the advanced stages was 78%, with high specificity, 94%. High specificity is desirable as it rules in the disorder. The PPV is comparable to simple indices. For the diagnosis of cirrhosis, in the study by Giannini et al[11], for cirrhosis, the AST/ALT ratio or platelet count < 130 x 109/L, the PPV was 79.8%, in the study by Wai et al, the PPV of APRI for significant fibrosis (Ishak > 3), was 88%[12]. The Fib–4 panel for severe fibrosis (Metavir, F3-F4) had a PPV of 82.1%[13]. Forns index comprising (age, cholesterol, GGT and platelets) for significant fibrosis (Scheuer stages [2,3,4]) had a PPV of 66%[14]. In the study by Giannini et al[11] the proportion of cirrhotics was 36%; by Wai *et al*[12] patients with significant fibrosis were 47%; by Vallet–Pichard et al[13] severe fibrosis was 17.2%; by Forns *et al*[14] significant fibrosis was 25%.

The predictive values are dependent on the prevalence of the underlying condition.The proportion of patients with advanced fibrosis was 24% in our study, which is generally, regarded as the prevalence of advanced fibrosis in the community at large[14]. This is in contrast to studies cited earlier in which sicker patient population was recruited; in a way there was a selection bias towards advanced disease, such as

in the study by Wai et al, and Giannini et al. While the results of the study are truly reflective of the sick population of a particular disease, in clinical practice they are applied to all patients of that disease.

In our study, the advantage is that: the statistics generated are applicable to every day clinical practice. To further reduce selection bias, consecutive patients were recruited in our study, who were treatment naïve, especially have not received interferon in the past, which might have an impact on platelet count and also liver fibrosis.

Table-2: Lab parameters and stages of fibrosis in patients.

Variable	Stage F0-F1	Stage F3-F4	
ALT (U/L)	88.2 + 27.22	93.6 + 30.60	0.58
AST (U/L)	40.4 + 12.68	51.6 + 20.89	0.49
Platelet count (x109/L)	266 + 45.47	193 +46.87	<0.0001
MPV (f/L)	10.6 + 1.35	11.2 + 1.08	0.076
PDW (f/L)	12.3 + 1.62	13.6 + 1.96	0.004
PDW Index	5.7 + 1.53	9.5 + 3.67	<0.0001

Table-3: Descriptive statistics for F3-F4 fibrosis in patients.

PDW Index	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio*	Negative likelihood ratio*	Accuracy
Value 6.00	0.82	0.84	0.62	0.93	1.63	0.06	83%
Value 8.00	0.64	0.94	0.78	0.89	3.40	0.12	86%

N.B.* The Likelihood ratios are weighted for the prevalence of (24%).

The earliest of the markers was the AST/ALT ratio. In studies, value of > 1 was significant for cirrhosis, with a sensitivity of 31.5% to 81.3% and specificity of 55.3% to 97%. Apart from variable performance, it doesn't identify significant fibrosis, only reflects cirrhosis. APRI is also an easily available ratio, for significant fibrosis, the sensitivity ranges from 41% to 91% and specificity of 47% to 95%[17]. According to a meta-analysis, for severe fibrosis in chronic HCV, the sensitivity of APRI was 61%, and specificity was 64%[18].

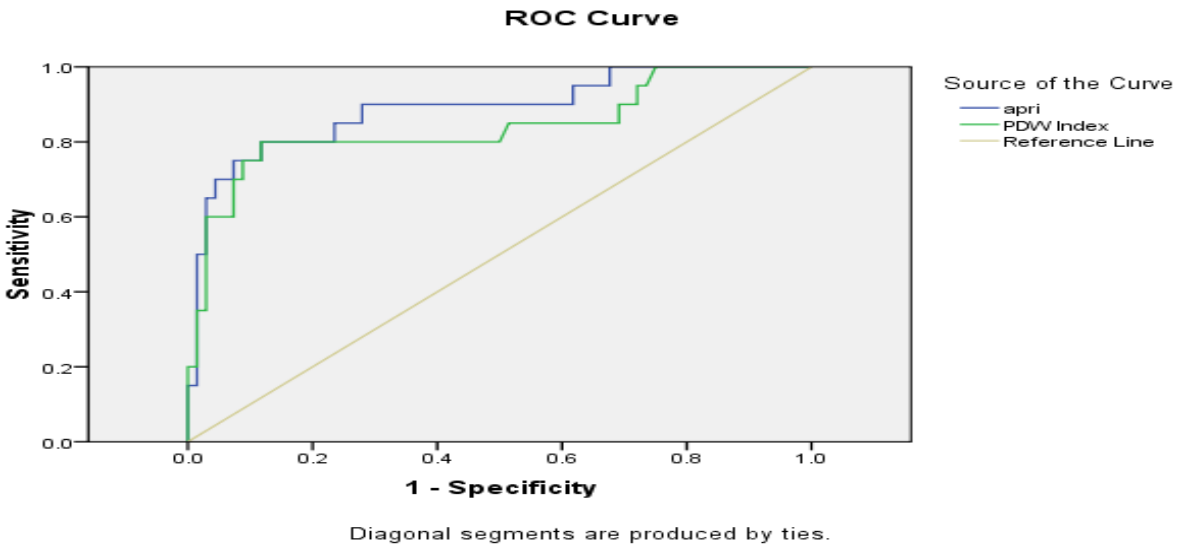
The association between platelet count and liver fibrosis is well known. According to one review, in patients with chronic liver disease (CLD) from HCV, and also in patients with CLD in general, both prevalence and severity of thrombocytopenia increase in parallel with the extent of disease, usually becoming more evident when patients develop advanced fibrosis and cirrhosis[1,4].

Pathogenetic mechanisms for thrombocytopenia in chronic liver disease with underlying fibrosis include: hypersplenism secondary to portal hypertension, with sequestration and destruction of platelets in the enlarged spleen[9,19]. However, treating portal hypertension, did not ameliorate thrombocytopenia, and decreased platelets have been noted in patients without hypersplenism. Additionally, studies have shown in patients with chronic viral hepatitis without splenomegaly,

platelet count is inversely related to the stage of fibrosis, i.e, higher count in earlier stages and lower count in advanced stages of fibrosis. Interestingly, this was not associated with necroinflammatory activity[20]. Thus, the degree of thrombocytopenia correlates with liver fibrosis.

increase in PDW was statistically more significant than increase in MPV, table-2. Moreover, both showed inverse correlation with platelet counts, and increased in patients with advanced fibrosis, table-2. When platelets decrease in number, bone marrow megakaryocytes are stimulated by thrombopoietin and produce larger platelets.

Figure-1: APRI and PDW Index ROC vs Stage F3-F4 Fibrosis APRI area under the ROC .878(95% CI; .797-.980) PDW Index area under the ROC .840 (95% CI; .721-.958.



Other mechanisms are: possibly bone marrow suppression (resulting in suppression of megakaryocytes), the use of drugs, and stimulation of the immune system resulting in the formation of anti-platelet antibodies and/or immune-complexes that bind to platelets and facilitate their premature clearance[21]. Thus in summary, the major mechanism for thrombocytopenia is the peripheral destruction and sequestration. Impaired thrombopoises to compensate for the peripheral destruction is most likely a contributory mechanism[22]. In this regard, the platelet kinetics in cirrhosis are similar to idiopathic immune thrombocytopenia purpura[9]. This means that analogous mechanisms may also contribute to the increase in PDW seen in patients with advanced liver disease that contribute to increase in PDW in ITP.

In destructive thrombocytopenia, PDW is increased more than MPV[23, 24]. In our study, the

Thus platelets with a larger volume are expected to be seen in destructive thrombocytopenia when megakaryocytic stimulation is present. Conversely, platelets with low MPV are expected to be seen in thrombocytopenic states seen in marrow hypoplasia or aplasia[23,24].

A very important exception occurs in splenic sequestration, in which a low MPV is seen, because spleen sequesters large platelets. Though MPV increases, it is postulated that the increase is less so because of splenic sequestration. In chronic liver disease the relative increase in PDW more than MPV, and inverse relationship with platelet counthas been put to use in PDW Index.

In addition to peripheral destruction of platelets, there are other postulated mechanisms for the increase of MPV, such as: consequence of chronic microthrombosis in the small vasculature of the portal bed in advanced fibrosis[25]. The increase in MPV has also seen thought to be due

to increased levels of IL-6 production due to inflammation from the fibrotic scar having impact on megakaryopoises, and subsequent release of young platelets in the circulation with elevated MPV[26].

The impact of chronic liver disease on platelet count and morphological parameters should be studied in a larger cohort. Studies should be done to unravel the relative importance of different mechanisms of thrombocytopenia in chronic liver disease with a view for therapeutic intervention.

CONCLUSION

Chronic viral hepatitis is an important cause of morbidity and mortality. The information about liver fibrosis is particularly important in management decisions. The simplicity of PDW Index, together with high diagnostic accuracy that matches in performance to other well known noninvasive indices of liver fibrosis is a great advantage in clinical practice. It will be a very useful screening test that can direct towards further evaluation.

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