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ASSOCIATION OF IMMATURE PLATELET FRACTION WITH SIGNIFICANT LIVER FIBROSIS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease globally, and liver fibrosis is the most important predictor of poor clinical outcomes. Immature platelet fraction (IPF) is a new parameter of platelet turnover and inflammation, but its relationship with liver fibrosis in MASLD is not well studied.

Objective: To determine the association between immature platelet fraction and significant liver fibrosis in patients with MASLD.

Methods: This is an analytical cross-sectional study, which included 155 adults with MASLD who were recruited from Medical Teaching Institute, Mardan Medical Complex, Mardan, from 1st October, 2025 to 31st March, 2026, using consecutive sampling. Data on demographics, clinical, and lab findings, including IPF, were obtained. Transient elastography was used to assess liver fibrosis, and significant fibrosis was defined as stage ≥F2. SPSS 26 was used for analysis, and $p \leq 0.05$ was considered significant.

Results: Liver fibrosis was detected in 51(32.9%) patients. The IPF scores were significantly higher in patients with significant fibrosis compared to patients with no fibrosis ($p<0.001$). ROC analysis showed IPF had good diagnostic accuracy (AUC=0.841), with an optimum cut-off of 5.8% and a sensitivity of 82.4% and a specificity of 76.9%. When entered as independent variables into multivariable logistic regression, elevated IPF was independently associated with significant fibrosis ($p<0.001$) along with older age, diabetes mellitus, elevated AST, and decreased platelet count.

Conclusion: Immature platelet fraction is an independent and readily available biomarker associated with significant liver fibrosis in MASLD and may improve non-invasive fibrosis risk stratification in routine clinical practice.

KEYWORDS: Non-invasive biomarkers, transient elastography, platelet indices, liver fibrosis, metabolic dysfunction-associated steatotic liver disease; MASLD.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly referred to as non-alcoholic fatty liver disease (NAFLD), is the most common chronic liver disease in the modern world and has become a critical public health problem with the global obesity, type 2 diabetes mellitus, and metabolic syndrome epidemic.[1] The recent shift from the term NAFLD to MASLD is an attempt to shift the focus from the role of NAFLD as a metabolic disease to the role of metabolic dysfunction in its pathogenesis and a more clinically oriented approach to diagnosis and management.[2] MASLD is a range of liver diseases that can include simple steatosis and metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma.[3] Liver fibrosis is the best predictor of liver-related morbidity, liver-related mortality, and overall mortality, even though hepatic steatosis is considered to be a benign event.[4]

Globally, MASLD affects approximately 30–38% of the adult population, with prevalence steadily increasing over the past two decades.[5] The prevalence is highest among people experiencing overweight and obesity, at 60–80% and 70–90%, respectively, and among people with type 2 diabetes mellitus.[6] Nearly one-quarter of people with MASLD progress to MASH, and about 15-25% develop clinically significant liver fibrosis over the course of the disease.[7] Advanced fibrosis significantly raises the likelihood of hepatic decompensation, portal hypertension, HCC development, cardiovascular complications, and mortality.[8] The prevalence of sedentary lifestyle, obesity, insulin

resistance, and diabetes in South Asian countries, including Pakistan, is on the rise, and consequently the identification of patients at risk for fibrosis is becoming a pressing clinical need.[9]

The progression of liver fibrosis occurs through continuous damage to the hepatocytes, chronic inflammation, and activation of hepatic stellate cells, leading to the accumulation of excessive amounts of extracellular matrix proteins.[10] Many studies have shown that fibrosis stage, not necessarily hepatic steatosis or inflammation, is the primary factor affecting long-term clinical outcomes in MASLD.[3, 11] Therefore, early detection of significant fibrosis (F2+) has become an essential part of the care plan and plays a pivotal role in patient surveillance, management, and referral for specialist care.[12]

Liver biopsy is the standard method for staging hepatic fibrosis, but is not routinely used due to its invasiveness, sampling variability, procedural complications, patient aversion, and cost.[13] Transient elastography, magnetic resonance elastography, and serum fibrosis scores like the fibrosis-4 (FIB-4) index and NAFLD fibrosis score have been widely adopted.[14]

In addition to their role as haemostatic factors, platelets have gained a new reputation as a player in hepatic inflammation and fibrogenesis.[15] Platelet turnover is affected by three mechanisms: platelet consumption, changes in the production of thrombopoietin (TPO), and increased destruction of platelets in the periphery during chronic liver injury.[16] The immature platelet fraction (IPF), which is an automatic measure of modern haematology analysers, is the percentage of newly released reticulated platelets in the circulation and is a sensitive indicator of bone marrow platelet production.[17] An increased platelet turnover and increased thrombopoietic activity are indicated by elevated IPF, which can happen in chronic inflammatory conditions and liver disease.[18] IPF gives dynamic platelet count information and could provide more accurate information about current pathological processes related to hepatic fibrosis than the conventional platelet count.[18]

New research has proposed that IPF is related to the severity of chronic liver diseases, portal hypertension, cirrhosis, and liver fibrosis.[18] In several studies, liver fibrosis values for patients with advanced hepatic fibrosis have been significantly higher than those with mild fibrosis, suggesting that IPF may be an appropriate non-invasive liver fibrosis biomarker.[19, 20] The proposed mechanisms are hypersplenism leading to increased destruction of platelets, and/or increased activity of inflammatory cytokines, and/or compensatory stimulation of thrombopoiesis.[21] There is, however, limited and inconsistent evidence of the association of IPF with relevant liver fibrosis in the MASLD population, with a relatively small number of studies specifically in South Asian populations.

Evaluation of immature platelet fraction is a promising area of study given the ever-increasing burden of MASLD and the need for simple, cost-effective markers that would be able to identify those with clinically significant fibrosis. Since IPF is routinely generated with the repeat of every automated complete blood count test and at no extra cost or specialised equipment, its use as a component of routine clinical assessment may provide a tool to enhance early risk stratification, especially in resource-limited healthcare environments. However, local evidence regarding its association with significant liver fibrosis in Pakistani patients with MASLD is scarce. Hence, this study aimed to investigate the association of IPF with SLF in patients with metabolic dysfunction-associated steatotic liver disease and thus assess the use of IPF as a readily accessible, non-invasive fibrosis marker for the assessment of fibrosis risk and clinical management.

METHODS

This was a hospital-based analytical cross-sectional conducted at Medical Teaching Institute, Mardan Medical Complex, Mardan during the study period of six months from 1st October, 2025 to 31st March, 2026. The sample size was determined by OpenEpi version 3.01, which uses a prevalence of significant liver fibrosis (stage ≥F2) of 27% of patients with MASLD. The 95% confidence level, margin of error of 7%, and an expected frequency of 27% were chosen.[22] The minimum sample size calculated was 155 participants.

A non-probability consecutive sampling technique was used. Patients who met the inclusion criteria were consecutively enrolled until the required sample size was met. Patients were included who met the international diagnostic criteria for MASLD, were 18 years or older, and had both a diagnosis of MASLD based on liver steatosis shown by ultrasonography or transient elastography and were of either gender. Therefore, patients who were not evaluated for liver stiffness (LS) using transient elastography and did not have a complete blood count with immature platelet fraction (IPF) at the time of enrollment were excluded.

Patients with heavy alcohol intake, chronic viral hepatitis (B or C), autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, hepatocellular carcinoma, decompensated cirrhosis, acute liver failure, pregnancy, active systemic infection, hematological disorders affecting platelet production or destruction, recent blood transfusion within the last three months, current chemotherapy, immunosuppressive therapy or drugs known to significantly influence platelet indices were excluded. Patients who had missing laboratory data or who had unreliable data from transient elastography were also excluded.

Eligible patients were consecutively enrolled during the study period following IRB approval and written informed consent from all patients. A structured proforma was used to record demographic information including age, gender, BMI, diabetes mellitus, hypertension, dyslipidaemia, smoking status and other clinical information. Venous blood

was taken aseptically for complete blood count including immature platelet fraction, liver function tests, fasting blood glucose, glycated haemoglobin, lipid profile and other routine biochemical investigations. Complete blood count and immature platelet fraction were analyzed using an automated haematology analyzer according to the manufacturer's recommendations with routine internal quality control procedures.

Liver fibrosis scores were obtained using the transient elastography (FibroScan®) method and conducted by a highly trained operator who was unaware of laboratory results. The liver stiffness measurements were considered to be reliable if at least ten valid acquisitions were performed with an interquartile range to median ratio of less than 30%. Liver stiffness measurement (LSM) was used to define significant liver fibrosis as a score of ≥F2, based on validated cut-off values for MASLD. Patients were then divided into two groups: those with significant fibrosis and those without.

IBM SPSS Statistics version 27.0 was used to enter and analyze data. A Shapiro-Wilk test was used to test continuous variables for normality. Data that were normally distributed were reported as mean ± SD and compared by the independent samples Student's t-test; data that were non-normally distributed were reported as median values (IQR) and compared by the Mann-Whitney U test. The diagnostic value of immature platelet fraction (IPF) was assessed using a receiver operating characteristic curve (ROC), and the area under the curve (AUC) was calculated along with the optimal cut-off value, sensitivity, specificity, positive predictive value, and negative predictive value. Univariate analysis yielded variables with a p-value <0.20, and clinically relevant variables, including age, gender, BMI, diabetes mellitus, platelet count, ALT and AST, were then added to a multivariable binary logistic regression model to determine independent risk factors for significant liver fibrosis. The odds ratios (ORs) presented were adjusted, and the 95% confidence intervals (CIs) were indicated. A two-tailed p-value <0.05 was considered statistically significant throughout the analysis.

RESULTS

A total of 155 patients with MASLD were included in the analysis. The mean age was 49.8±11.2 years, with a slight male predominance (56.8%). The majority of the participants were obese and suffered from type 2 diabetes mellitus, and dyslipidaemia and hypertension were prevalent comorbidities. Transient elastography (TE) showed significant liver fibrosis (F ≥ F2) in 32.9%, and median IPF was 4.9% (IQR: 3.6–6.8) (Table 1).

Table 1. Baseline demographic and clinical characteristics of the study population (n = 155)

Variable	n (%)/mean ± SD
Age (years),	49.8 ± 11.2
Male	88 (56.8)
Female	67 (43.2)
BMI (kg/m²)	31.4 ± 4.6
BMI ≥30 kg/m²	102 (65.8)
Type 2 diabetes mellitus	91 (58.7)
Hypertension	76 (49.0)
Dyslipidaemia	84 (54.2)
Current smoker	31 (20.0)
ALT (U/L)	61.8 ± 25.4
AST (U/L)	48.7 ± 18.9
Platelet count (×10⁹/L)	208.4 ± 58.6
Immature Platelet Fraction (%), median (IQR)	4.9 (3.6–6.8)
Liver stiffness (kPa), median (IQR)	7.9 (6.0–10.6)
Significant fibrosis (≥F2)	51 (32.9)
No significant fibrosis (<F2)	104 (67.1)

The patients with significant liver fibrosis were significantly older, with higher BMI, higher prevalence of diabetes mellitus, hypertension, and dyslipidaemia compared to the patients without significant fibrosis. Additionally, they exhibited much elevated serum aminotransferase activity, decreased platelet counts, and markedly elevated immature platelet fraction values. There were no significant differences between the two groups with respect to gender or smoking status (Tle 2).

Table 2. Comparison of demographic and clinical variables according to liver fibrosis status

Variable	Significant Fibrosis (n=51) n (%)/mean ± SD	No Significant Fibrosis (n=104) n (%)/mean ± SD	p-value
Age (years)	54.2 ± 10.1	47.6 ± 11.2	<0.001
Male gender	33 (64.7)	55 (52.9)	0.164

BMI (kg/m²)	33.0 ± 4.4	30.6 ± 4.5	0.002
Diabetes mellitus	39 (76.5)	52 (50.0)	0.002
Hypertension	33 (64.7)	43 (41.3)	0.008
Dyslipidaemia	34 (66.7)	50 (48.1)	0.031
Current smoker	13 (25.5)	18 (17.3)	0.231
ALT (U/L)	69.5 ± 28.6	58.0 ± 22.8	0.011
AST (U/L)	58.2 ± 20.7	44.0 ± 15.8	<0.001
Platelet count (×10⁹/L)	181.6 ± 48.4	221.6 ± 58.3	<0.001
IPF (%), median (IQR)	7.2 (6.1–8.6)	4.0 (3.2–5.1)	<0.001

Immature platelet fraction had good diagnostic accuracy in predicting significant liver fibrosis, and the area under the ROC curve was 0.841. The best cut-off for IPF was 5.8%, with a high sensitivity and specificity, suggesting good discriminatory power for detecting clinically significant fibrosis (Table 3).

Table 3. Receiver operating characteristic (ROC) analysis of immature platelet fraction for predicting significant liver fibrosis

Parameter	Value
Area under ROC curve (AUC)	0.841
95% Confidence Interval	0.773–0.909
p-value	<0.001
Optimal IPF cut-off (%)	≥5.8
Sensitivity (%)	82.4
Specificity (%)	76.9
Positive Predictive Value (%)	63.6
Negative Predictive Value (%)	89.9
Overall diagnostic accuracy (%)	78.7

On univariate logistic regression analysis, age, the level of AST, diabetes mellitus, hypertension, dyslipidaemia, lower level of platelets, and elevated level of IPF were significantly associated with significant liver fibrosis, while gender and ALT did not show statistically significant associations (Table 4).

Table 4. Univariate analysis of factors associated with significant liver fibrosis

Variable	Crude OR	95% CI	p-value
Age ≥50 years	2.41	1.21–4.81	0.012
Male gender	1.63	0.81–3.29	0.171
BMI ≥30 kg/m²	2.28	1.10–4.71	0.026
Diabetes mellitus	3.25	1.55–6.81	0.002
Hypertension	2.61	1.31–5.22	0.006
Dyslipidaemia	2.16	1.08–4.31	0.029
Current smoker	1.64	0.71–3.77	0.244
ALT >60 U/L	1.88	0.95–3.73	0.071
AST >45 U/L	3.47	1.71–7.02	<0.001
Platelet count <200×10⁹/L	3.86	1.91–7.81	<0.001
IPF ≥5.8%	8.74	4.06–18.82	<0.001

Immature platelet fraction was the strongest independent predictor of significant liver fibrosis after adjustment for potential confounding variables in the multivariable logistic regression model ($p < 0.001$). Elderly age, diabetes mellitus, and significant fibrosis were independently correlated with AST and lower platelet count, and after adjustment, obesity, hypertension, and dyslipidaemia were no longer significant. The performance of the regression model was good in terms of calibration, and the overall predictive ability was satisfactory (Table 5).

Table 5. Multivariable binary logistic regression analysis for predictors of significant liver fibrosis

Variable	Adjusted OR	95% CI	p-value
Age ≥50 years	2.11	1.01–4.43	0.046
BMI ≥30 kg/m²	1.82	0.89–3.74	0.101
Diabetes mellitus	2.56	1.17–5.59	0.019
Hypertension	1.58	0.71–3.50	0.262
Dyslipidaemia	1.39	0.65–2.98	0.389
AST >45 U/L	2.71	1.25–5.88	0.011
Platelet count <200×10⁹/L	2.94	1.32–6.52	0.008

Immature Platelet Fraction ≥5.8%	6.83	2.98–15.66	<0.001
Hosmer-Lemeshow goodness-of-fit (χ^2): 6.14 *p-value: 0.631* *Nagelkerke R^2: 0.452* *Overall classification accuracy: 82.6%*			

DISCUSSION

The present study demonstrated that IPF was significantly higher among patients with MASLD who had significant liver fibrosis compared with those without fibrosis. Furthermore, a high IPF score was an independent factor of significant fibrosis after adjusting for other demographic, metabolic, and biochemical parameters. These results indicate that platelet turnover is associated with the degree of hepatic fibrogenesis in the course of the disease, and suggests that IPF may be a potential non-invasive and cost-effective liver fibrosis biomarker for stratifying fibrosis risk in MASLD patients.

The high prevalence of significant liver fibrosis in the present cohort of MASLD patients was similar to that reported in other fibrosis burdening studies in MASLD. In a study conducted by Eddowes et al., it was noted that almost 25-33% of those individuals who underwent a biopsy showed NAFLD, with clinically significant fibrosis representing the main factor that accounted for the outcomes of the liver over the course of the years.[22] Likewise, Younossi et al. (2023) reported that 25–35% of patients with MASLD/NAFLD had stage F2 or more fibrosis, underscoring the significant proportion of advanced disease and the need for timely diagnosis.[23]

The most important finding of the present study was the independent association between elevated IPF and significant liver fibrosis. Median IPF values were significantly higher in patients with fibrosis, and an IPF threshold of 5.8% was well discriminating, with an AUC of 0.841. There are limited studies directly examining the association between IPF and MASLD, but the present study results are biologically plausible and consistent with previous studies in chronic liver disease. A study by Ismaiel et al., 2025 showed that the more advanced the cirrhosis, together with platelet count, had better discriminative value between cirrhotic and non-cirrhotic liver disease.[24] Similarly, Soliman et al. 2021 reported that high IPF was associated with increased Child-Pugh class and portal hypertension in their findings, implying that increased peripheral platelet destruction leads to increased compensatory thrombopoiesis.

The findings of the present study also align with the emerging data on the use of platelet markers to assess fibrosis. A recent study has shown that platelet-related indices significantly enhanced the prediction of significant fibrosis in biopsy-proven MASLD, especially when combined with the existing non-invasive scoring systems like FIB-4. In the same way, investigators showed that the response of platelets to injury and disease severity was quite different, further substantiating the idea that platelet activation and turnover play a role in hepatic fibrogenesis beyond simply being a response to portal hypertension.[25, 26]

Diagnostic accuracy of IPF in this study is comparable with some commonly used non-invasive biomarkers. Traditional platelet count is a relatively late event in the disease course and could be normal in patients with early fibrosis.[27] In contrast, IPF is reflective of dynamic platelet production and peripheral platelet consumption, and thus detects pathological changes before absolute thrombocytopenia can be seen.[28]

High AST level was also independently associated with significant fibrosis, as observed earlier, where high levels of AST were correlated with the deposition of extracellular matrix and progression of fibrosis. EST levels are elevated among those with advanced fibrosis and have been included in validated fibrosis prediction models like FIB-4 and APRI in numerous published studies, including Ciardullo et al., 2024 and Rinella et al., 2026, and international MASLD consensus groups. The results also confirm the strength of our regression model.[29, 30]

Multiple biological mechanisms contribute to the increased susceptibility to IPF with liver fibrosis. Splenic sequestration and peripheral destruction of platelets from peripheral blood increase with progressive fibrosis and portal hypertension, causing release of immature reticulated platelets from the bone marrow. Chronic liver inflammation also causes liver-mediated thrombopoiesis and increased platelet activation. The activation of platelets has also been shown to exert an inflammatory effect on Kupffer cells and hepatic stellate cells, leading to extracellular matrix deposition, thus directly participating in hepatic fibrogenesis, and not simply as passive markers.

In summary, the present findings add to the current literature, specifically by examining the relationship of IPF to liver fibrosis in patients with MASLD and establishing its independent association with clinically significant liver fibrosis. The use of IPF as part of a modern complete blood count, which is automatically generated without extra cost or specialized equipment, could support the identification of patients in a timely manner who require further fibrosis assessment or specialist referral. Further larger prospective multicenter studies with liver biopsy confirmation are needed to validate optimal cut-off values to diagnose IPF and to see if an additional use of established fibrosis scores with IPF improves diagnosis.

Limitations

There were various limitations of this study. It's a cross-sectional design and did not allow for causal association between IPF and liver fibrosis progression. Secondly, this study was carried out in one tertiary care center with a non-

probability consecutive sampling method; the findings might not be generalizable to the entire MASLD population. Third, liver fibrosis was evaluated by the non-invasive technique of transient elastography, which is a well-validated method for fibrosis staging, rather than liver biopsy, the histological gold standard. Fourth, the value of the dynamic changes of IPF over time and the prognostic value could not be assessed due to the lack of longitudinal follow-up. Third, it is not possible to rule out completely residual confounding due to factors not measured in the multivariable models that affect platelet kinetics.

CONCLUSION

Immature platelet fraction was significantly correlated with clinically significant liver fibrosis and was an independent predictor of liver fibrosis, even after controlling for established metabolic and biochemical risk factors, in patients with metabolic dysfunction-associated steatotic liver disease. In this study, good diagnostic performance of IPF confirms that it could be a simple, inexpensive, and readily available, non-invasive biomarker to identify patients at high risk of significant fibrosis. The use of IPF in routine clinical practice could aid in early risk stratification, timely referral, and timely management, especially in resource-limited areas, which is a routine process in automatic CBC analysis without any extra cost. Multicentre, prospective and histological-validated studies of larger patient populations are needed to verify these results and to set up standardised diagnostic cut-off values.

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