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THROMBOCYTOPENIA AS A SURROGATE FOR CIRRHOSIS AND A MARKER FOR THE IDENTIFICATION OF PATIENTS AT HIGH RISK FOR HEPATOCELLULAR CARCINOMA

Original Research

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Acknowledgement: The authors extend their gratitude to the hospital research committee for their support and guidance throughout the study.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality, primarily arising in patients with cirrhosis due to chronic hepatitis B (HBV) or hepatitis C (HCV) infections. The global epidemiology of HCC is influenced by viral hepatitis prevalence, metabolic disorders, and liver fibrosis progression. Thrombocytopenia has emerged as a potential surrogate marker for cirrhosis and an early indicator of HCC risk. Identifying a reliable platelet cutoff value may improve the early diagnosis and risk stratification of patients prone to liver malignancy.

Objective: To evaluate thrombocytopenia as a surrogate marker for cirrhosis and assess platelet count as a diagnostic indicator for advanced HCC in patients with chronic liver disease.

Methods: A cross-sectional hospital-based study was conducted over six months (January–June 2022) at a tertiary care hospital. A total of 40 cirrhosis patients (20 males, 20 females) aged 30–65 years were enrolled. Blood serum samples were collected in glass vials containing 20% EDTA to prevent coagulation. Sociodemographic data were obtained following written informed consent. Statistical analysis was performed using SPSS (version 22). Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), and Kaplan-Meier analysis were applied to determine platelet cutoff values for cirrhosis and HCC risk prediction.

Results: The platelet cutoff value was determined as 150 × 10^3/mm^3 for HBV (sensitivity 79.5%, specificity 82.4%, accuracy 85.1%, PPV 39.4%, NPV 98.5%) and 170 × 10^3/mm^3 for HCV (sensitivity 86.5%, specificity 60.8%, accuracy 67.6%, PPV 44.9%, NPV 92.8%). Thrombocytopenia (<145 × 10^3/mm^3) was observed in 15% of HBsAg-positive, anti-HCV-negative patients in year 1 and 5% in year 2. Among HCC patients, 60% were thrombocytopenia suspects, with 45% confirmed cases. A significant reduction in platelet count was noted in cirrhosis patients progressing to HCC.

Conclusion: Thrombocytopenia strongly correlates with cirrhosis and serves as an early, cost-effective marker for identifying patients at risk of developing HCC. Implementing platelet count assessment in routine clinical practice may improve early detection and timely management of liver disease progression.

Keywords: Cirrhosis, Hepatitis B, Hepatitis C, Hepatocellular carcinoma, Liver fibrosis, Platelet count, Thrombocytopenia.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major global health concern, ranking as the third leading cause of cancer-related mortality worldwide and affecting hundreds of thousands of individuals annually. In Pakistan alone, HCC is responsible for over 600,000 deaths each year, with a significant burden attributed to chronic liver diseases. It is the fifth most common malignancy in men and the eighth in women, highlighting the urgent need for improved diagnostic and therapeutic strategies (1-3). While advancements in the treatment of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections have contributed to a declining incidence of HCC associated with viral hepatitis, the rising prevalence of non-alcoholic fatty liver disease (NAFLD) as a precursor to HCC is an emerging public health challenge. With nearly one-third of the global population affected by NAFLD, the transition from metabolic dysfunction to cirrhosis and malignancy underscores the necessity for early detection and risk stratification (4-6).

Thrombocytopenia, defined as a platelet count below 150 × 10^9/L, is a common hematological abnormality observed in patients with chronic liver disease and cirrhosis. Although the etiology of thrombocytopenia in these patients is multifactorial, including hypersplenism, bone marrow suppression, and decreased thrombopoietin production, its presence serves as an important surrogate marker for hepatic dysfunction and disease progression (7,8). Severe thrombocytopenia, particularly at levels below 35 × 10^9/L, poses an increased risk of spontaneous bleeding, purpura, and other hemorrhagic complications, which can be life-threatening. While many patients with HCC remain asymptomatic until advanced disease stages, the association between declining platelet counts and cirrhosis suggests that thrombocytopenia may serve as an early indicator for patients at high risk of developing HCC. Identifying such high-risk individuals could allow for timely surveillance and intervention, potentially improving prognosis and reducing mortality (9). Despite significant progress in liver disease research, there remains a critical need for accessible and cost-effective screening tools, particularly in resource-limited settings. Advanced-stage HCC is notoriously difficult to treat, with limited curative options and high costs associated with therapeutic interventions. Therefore, focusing on early markers of hepatic decompensation, such as thrombocytopenia, could enhance clinical decision-making and optimize treatment outcomes. This study aims to evaluate thrombocytopenia as a surrogate marker for cirrhosis and an early identifier of patients at high risk for HCC, ultimately contributing to improved early detection strategies and better patient management (10).

METHODS

This hospital-based cross-sectional observational study was conducted to determine the prevalence of thrombocytopenia in patients with cirrhosis and to evaluate platelet count as a potential molecular marker for identifying individuals at high risk of developing hepatocellular carcinoma (HCC) at the earliest stages of liver damage. The study was carried out at a tertiary care hospital in Rawalpindi from January 2022 to June 2022. A total of 40 patients diagnosed with cirrhosis, including 20 males and 20 females, were enrolled in the study. Participants were selected within the age range of 30 to 65 years. Ethical approval was obtained from the institutional review board (IRB) of the hospital, and written informed consent was secured from all participants prior to data collection. The study adhered strictly to the ethical guidelines and protocols issued by the hospital's research committee, ensuring compliance with biomedical research standards (11).

Blood samples were collected from all patients using sterile techniques and placed in glass vials containing 20% ethylenediaminetetraacetic acid (EDTA) to prevent coagulation. Socio-demographic data were gathered through structured interviews and documented in standardized data collection forms. To ensure the reliability of the study findings, only patients with confirmed cirrhosis, as diagnosed by ultrasound and positive Alpha-Fetoprotein (AFP) testing, were included. Participants at high risk of developing HCC were also enrolled based on predefined clinical criteria. Patients younger than 30 years, individuals diagnosed with malignancies other than HCC, and those with pre-existing heart disease, immunological disorders, or neurological conditions were excluded to eliminate potential confounding factors (12). Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 22. The prevalence of thrombocytopenia and its association with socio-demographic variables were evaluated. Continuous variables were expressed as mean ± standard deviation (SD) for descriptive analysis. The Kaplan-Meier method, along with the log-rank test, was employed to assess the association between platelet count and disease progression, identifying significant trends related to the shortest time to HCC development (13).

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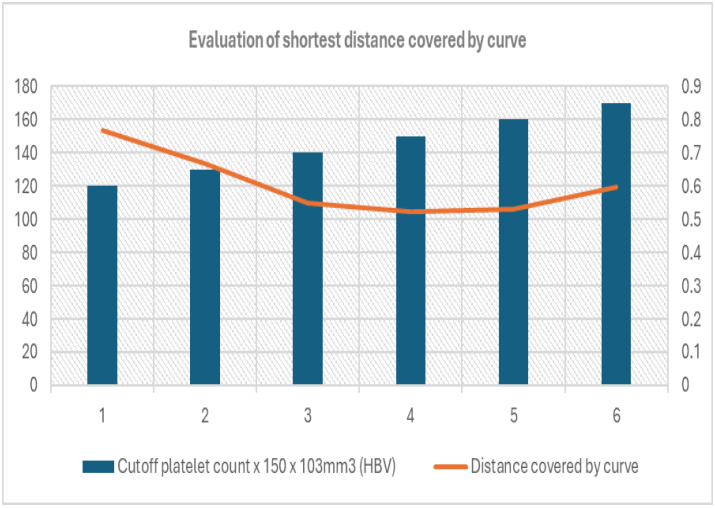
RESULTS

The study assessed the relationship between thrombocytopenia and hepatic damage, evaluating platelet cutoff values for HBV and HCV in cirrhotic patients. The platelet cutoff value for HBV was determined to be 150 × 10^3/mm^3, with a sensitivity of 79.5%, specificity of 82.4%, accuracy of 85.1%, positive predictive value (PPV) of 39.4%, and negative predictive value (NPV) of 98.5%. The shortest distance covered by the curve for this cutoff was 0.523. For HCV, the platelet cutoff was 170 × 10^3/mm^3, with a sensitivity of 86.5%, specificity of 60.8%, accuracy of 67.6%, PPV of 44.9%, and NPV of 92.8%. The shortest distance covered by the curve for this cutoff was 0.218. The distribution of other platelet cutoff values and their corresponding sensitivity, specificity, and predictive values demonstrated a progressive variation in cirrhosis detection efficiency. Analysis of viral etiology in thrombocytopenic cirrhosis patients with a platelet count below 145 × 10^3/mm^3 revealed that 15% of cases were HBsAg positive and anti-HCV negative in the first year. Cases of HBsAb negative and anti-HCV positive were recorded in 30% of patients in the first year and 10% in the second year. HBsAb positive and anti-HCV negative cases were reported in 10% of patients in the first year and 15% in the second year. Additionally, HBsAg positive and anti-HCV negative cases accounted for 15% in the first year and 5% in the second year.



Among cirrhosis patients, the proportion of those presenting with viral etiology was evaluated over two years. In the 30-45 years age group, 30% of cases exhibited HBV or HCV etiology. In the 45-65 years age group, 30% in the first year and 30% in the second year were identified as cirrhotic with viral etiology ($p < 0.01$). HBsAg positive and anti-HCV negative cases remained constant at 30% in both years. However, HBsAb negative and anti-HCV positive cases declined from 35.5% in the first year to 22.5% in the second year ($p < 0.01$). HBsAb positive and anti-HCV positive cases reduced from 20% in the first year to 10% in the second year ($p < 0.01$). HBsAg negative and anti-HCV negative cases were 2.5% in both years. Regarding disease progression, 50% of the cirrhosis patients were identified as being at risk of developing HCC over the study duration. Alpha-fetoprotein (AFP) levels of <25 ng/ml were recorded in 20% of cirrhosis patients in the first year, increasing to 45% in the second year ($p < 0.01$). Conversely, AFP levels >25 ng/ml were reported in 10% of cases in the first year and 25% in the second year ($p < 0.01$). ALT levels <75 IU/L were recorded in 25% of cases in the first year and 20% in the second year ($p < 0.01$), while ALT levels >75 IU/L increased from 20% in the first year to 35% in the second year ($p < 0.01$). AST/ALT ratios <2 were found in 35.5% of cirrhosis patients in the first year, decreasing to 12.5% in the second year ($p < 0.01$), whereas AST/ALT ratios >2 increased from 12.5% in the first year to 42.5% in the second year ($p < 0.01$). Thrombocytopenia was identified in 60% of HCC patients as suspected cases, whereas 40% were not thrombocytopenic. Upon confirmation, 45% of HCC patients tested positive for thrombocytopenia, whereas 5% were negative. Among confirmed thrombocytopenic HCC cases, 50% of patients were diagnosed, while no cases were identified among control patients. Tumor size analysis showed that 45% of patients had tumors <2 cm, while tumors ranging from 3-4 cm, 5-9 cm, and >10 cm were found in 20%, 20%, and 10% of cases, respectively. AFP levels exceeding 20 ng/ml were recorded in 50% of HCC patients ($p < 0.01$).

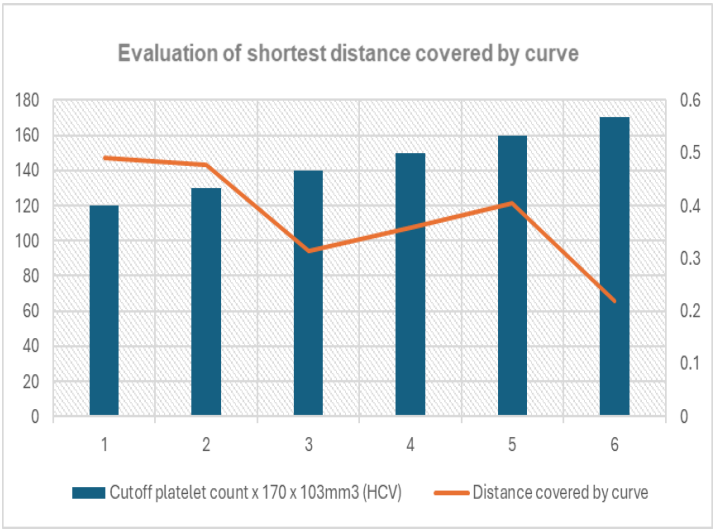


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Table 1: Values of sensitivity, specificity, accuracy, and positive and negative predictive value for different cut off platelets counts for the determination of cirrhosis condition in HBV and HCV patients

Cutoff platelet count x 150 x 103mm3 (HBV)	**Sensitivity %**	**Specificity %**	**Accuracy %**	**PPV %**	**NPV %**	**Distance covered by the curve**
120	71.4	93.3	91.0	55.6	96.6	0.766
130	76.2	91.7	90.0	51.6	96.2	0.665
140	76.2	85.7	85.6	42.1	95.4	0.550
150	79.5	82.4	85.1	39.4	98.5	0.523
160	90.5	78.9	80.1	25.4	98.4	0.530
170	90.5	78.9	80.1	32.3	98.2	0.598
Cutoff platelet count x 170 x 103mm3 (HCV)	**Sensitivity %**	**Specificity %**	**Accuracy %**	**PPV %**	**NPV %**	**Distance covered by the curve**
120	52.8	84.2	75.9	55.7	82.8	0.491
130	53.0	80.5	75.7	55.6	83.2	0.477
140	56.1	76.5	74.2	51.8	83.1	0.314
150	68.2	72.2	74.2	48.7	84.4	0.358
160	74.2	69.4	70.5	47.1	86.4	0.404
170	86.5	60.8	67.6	44.9	92.8	0.218

Table 2: Diagnosis of sonographic cirrhosis in thrombocytopenic patients and cutoff platelet count, x 103/mm3

Variables	**No. of Patients**	**First-year**	**Second year**	**p-value**
Presentation of viral etiology with Thrombocytopenia <145 x 103mm3	HBsAg (+), anti-HCV (-)	6 (15%)	-	<0.001
	HBsAB (-), anti-HCV (+)	12 (30%)	4 (10%)	
	HBsAB (+), anti-HCV (-)	4 (10%)	6 (15%)	
	HBsAG (+), anti-HCV (-)	6 (15%)	2 (5%)	

BHsAg stands for Hepatitis B surface antigen; HCV hepatitis C virus

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Table 3: Proportion of Cirrhosis patients and their viral etiology

Variables		First-year	Second year	p-value
Gender (males/females)		(10/10)	(10/10)	-
Age (years)	30-45	6 (15%)	6 (15%)	-
	45-65	12 (30%)	16 (30%)	<0.01
Presentation of viral etiology	HBsAg (+), anti-HCV (-)	2 (30%)	2 (30%)	-
	HBsAB (-), anti-HCV (+)	13 (32.5%)	9 (22.5%)	<0.01
	HBsAB (+), anti-HCV (+)	8 (20%)	4 (10%)	<0.01
	HBsAG (-), anti-HCV (-)	1 (2.5%)	1 (2.5%)	-
Stage	Cirrhosis	10 (25%)	10 (25%)	-
	Cirrhosis and risk of HCC development	10 (25%)	10 (25%)	-
AFP	<25 ng/ml	8 (20%)	18 (45%)	<0.01
	>25ng/ml	4 (10%)	10 (25%)	<0.01
ALT	<75 IU/L	10 (25%)	8 (20%)	<0.01
	>75 IU/L	8 (20%)	14 (35%)	<0.01
AST/ ALT ratio	<2	13 (35.5%)	5 (12.5%)	<0.01
	>2	5 (12.5%)	17 (42.5%)	<0.01

BHsAg stands for Hepatitis B surface antigen; HCV hepatitis C virus, Alanine transaminase (ALT), Aspartate transaminase (AST), Alpha fetoprotein (AFP)

Table 4: Screening results for HCC in thrombocytopenic patients

Variables		No. of cases	Control patients	p- values
No. of HCC with thrombocytopenia	Suspected	24 (60%)	16 (40%)	<0.001
	Confirmed	18 (45%)	2 (5%)	
No. of HCC with thrombocytopenia	Confirmed	20 (50%)	0 (0%)	
Tumor size	<2 cm	18 (45%)	-	0.09
	>3-4cm	8 (20%)	-	
	>5-9 cm	8 (20%)	-	
	>10 cm	4 (10%)	-	
AFP	>20 ng/ml	20 (50%)	-	<0.01

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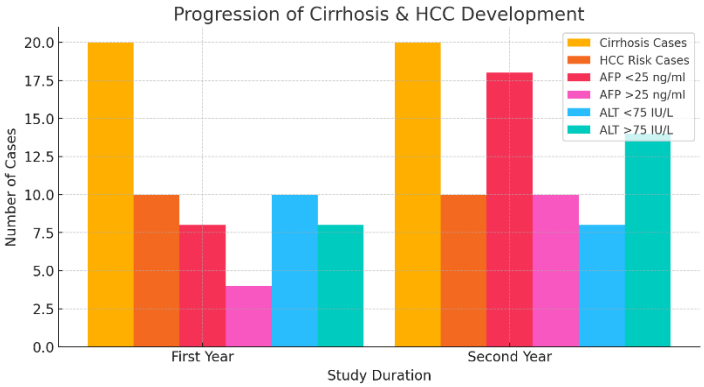

Figure 2 Progression of Cirrhosis & HCC Development

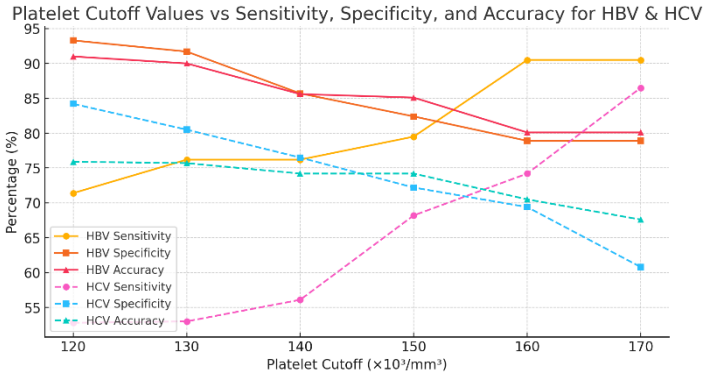

Figure 1 Platelet Cutoff Value Vs Sensitivity, Specificity and Accuracy of HBC & HCV

DISCUSSION

Hepatocellular carcinoma predominantly develops in patients with a history of cirrhosis, particularly in those with chronic HBV or HCV infection. Cirrhosis remains the most significant risk factor for HCC, and its early detection is critical for timely intervention. Although liver biopsy has historically been considered the gold standard for assessing the degree of hepatic fibrosis, non-invasive diagnostic markers such as platelet count have gained attention for their predictive value in cirrhosis and HCC risk stratification. The present study demonstrated a significant association between thrombocytopenia and cirrhosis, with platelet cutoff values determined at 150 × 10^3/mm^3 for HBV and 170 × 10^3/mm^3 for HCV. These thresholds exhibited notable sensitivity and specificity, reinforcing the role of thrombocytopenia as a potential surrogate marker for cirrhosis and early-stage liver dysfunction (14,15). The findings align with previous studies indicating that platelet count serves as a reliable indicator of hepatic fibrosis and portal hypertension. Non-invasive scoring models for liver fibrosis frequently incorporate thrombocytopenia due to its association with disease severity. A large nested case-control study involving thousands of cirrhotic and non-cirrhotic patients revealed that platelet counts begin to decline well before cirrhosis is clinically established, suggesting their utility in early detection. Additionally, research assessing platelet indices, including mean platelet volume, platelet distribution width, and platelet-large cell ratio, further supports their correlation with liver fibrosis in HCV-infected patients. The current study contributes to this growing body of evidence by establishing cutoff values that may assist in the clinical assessment of cirrhosis progression and HCC risk (16-18).

The prevalence of thrombocytopenia in cirrhotic patients within the study cohort underscores its potential as a diagnostic marker. Among patients with cirrhosis, those with chronic viral hepatitis demonstrated a progressive reduction in platelet count, with a higher proportion of thrombocytopenic individuals exhibiting advanced liver dysfunction. The study also revealed that thrombocytopenia was observed in 60% of HCC patients, with 45% testing positive upon confirmation, further emphasizing its role in disease progression. The presence of thrombocytopenia as an early indicator of cirrhosis is consistent with research highlighting premature platelet clearance, bone marrow suppression, and altered thrombopoiesis in chronic liver disease. The systemic review of laboratory and clinical parameters influencing platelet-based diagnostic indices reinforces these findings, demonstrating that thrombocytopenia is frequently observed in patients with chronic HBV and HCV infections, as well as those with established cirrhosis (19-22). Despite the strengths of the study, certain limitations must be acknowledged. The sample size was relatively small, limiting the generalizability of the findings. A larger, multi-center study would enhance the robustness of platelet-based cutoff values and allow for a more comprehensive assessment of their predictive power in diverse populations. Furthermore, the study did not account for confounding factors such as splenomegaly, coagulopathies, or other hematological disorders that could influence platelet counts independently of liver disease. Future research should incorporate a broader range of biomarkers, including platelet indices and fibrosis markers, to establish a more refined predictive model for cirrhosis and HCC risk assessment (23-25). The findings suggest that thrombocytopenia serves as a potential non-invasive marker for hepatic fibrosis and HCC risk stratification. Integrating platelet count evaluation into routine clinical practice may enhance early diagnosis and facilitate timely intervention, particularly in high-risk populations. Further longitudinal studies with larger cohorts and comparative analyses with other non-invasive fibrosis markers could solidify the role of thrombocytopenia in liver disease screening and prognostication (26,27).

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CONCLUSION

Early diagnosis and timely intervention for cirrhosis and hepatocellular carcinoma are critical for improving patient outcomes. This study highlights thrombocytopenia as a significant hematological manifestation in hepatic patients, reinforcing its role as a surrogate molecular marker for cirrhosis. The findings suggest that thrombocytopenia can serve as an accessible and cost-effective indicator for identifying individuals at high risk of developing hepatocellular carcinoma. Integrating platelet count evaluation into clinical practice may enhance early detection strategies, allowing for improved disease monitoring and timely therapeutic interventions. These insights contribute to advancing non-invasive diagnostic approaches, ultimately aiding in better management and prognosis of liver disease.

AUTHOR CONTRIBUTIONS

Author	Contribution
Bilal Ahmed Kayani*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Muhammad Junaid Farooq	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Faryal Riaz Khan	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Arslan Ahmed	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Nadia Riaz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Urooj Shuja	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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