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Portal Venous Pulsatility Index: A Novel Biomarker for Diagnosis of High-Risk Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Objective: To assess the accuracy of portal vein pulsatility (VPI) for non-invasive diagnosis of high-risk non-alcoholic fatty liver disease (NAFLD).

Study Design: Cross-sectional study.

Place and Duration of Study: Pakistan Institute of Medical Science, Islamabad Pakistan, from Jan to May 2022.

Methodology: Duplex Doppler ultrasound was used to examine the main portal vein in patients with a biopsy-proven Non-alcoholic fatty liver disease (NAFLD) diagnosis. Patients were evaluated by Doppler ultrasonography after fasting for four hours in accordance with standard methodology. The maximum (Vmax) and minimum (Vmin) blood velocities in the portal veins were measured using the spectral waveform.

Results: Out of 240 NAFLD patients, 102(42.50%) were males, and 138(57.50 %) were females. According to the Non-alcoholic Steatohepatitis clinical research network (NASH CRN) scoring system, 95(39.58%) patients had F0 disease, 80(33.33%) had F1, 30(12.5%) patients F2, 24(10%) patients had F3 and 11(4.58%) had F4. 50(53.76%) patients in the low-risk group and 43(46.24%) patients in the high-risk group had diabetes. Of 102 males, 73(71.56%) had low risk, and 29(28.44%) had high risk. While out of 138 females, 79(57.24%) females had low risk, and 59(42.76%) females had a high risk of NAFLD. Venous pulsatility index, NAFLD fibrosis score, FIB-4, BARD score, and APRL had statistically significant differences (p<0.05).

Conclusion: Venous pulsatility index is a reliable marker for detecting high-risk NAFLD. It is a readily available non-invasive investigation and can be reliably used as a screening tool for detecting NAFLD in high-risk patients, avoiding invasive investigation.

Keywords: Duplex doppler ultrasound, Non-alcoholic fatty liver disease (NAFLD), Venous pulsatility index (VPI).

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INTRODUCTION

In the absence of excessive alcohol consumption, non-alcoholic fatty liver disease (NAFLD) manifests as fat buildup in the liver parenchyma (hepatic steatosis), making it the most common liver disease in the world.[1] NAFLD has been linked to other aspects of metabolic syndromes, such as obesity, dyslipidemia, and diabetes, and affects around a third of adults in the United States.[2,3] Patients with NAFLD with liver fibrosis are the most likely to have a poor prognosis. Five stages of fibrosis have been established by the Non-alcoholic Steatohepatitis Clinical Research Network (NASH CRN) for NAFLD: F0, no fibrosis; F1, portal fibrous with no septa; F2, portal fibrosis with few septa; and F3, the bridge between the central and the portal veins.[4,5]

Long-term liver-specific and all-cause mortality is significantly increased in patients with liver fibrosis at stage F2 or above. "high-risk NAFLD" has arisen to describe this group of patients.[6] Identifying patients with NAFLD at high risk for relapse is crucial for NAFLD management since it identifies those most likely to benefit from treatment and study.[7]

An ultrasonic scanner can measure the pulsatility of the portal vein in a quantitative, non-invasive, and quick manner.[8,9] Although a few studies have examined the distribution of VPI in patients with NAFLD, the accuracy of this technique for detecting high-risk NAFLD has yet to be established.[10] Because biopsy-proven NAFLD is associated with high risk, we studied the diagnostic usefulness of VPI in a sample of these patients. We assessed whether VPI adds diagnostic value to the current NAFLD fibrosing score (FS), BARD (body mass index, aspartate aminotransferase-to-alanine aminotransferase ratio, diabetes mellitus) score and APRI (AST-to-platelets) scores in term of diagnostic value.

METHODOLOGY

The cross-sectional study was conducted at the Pakistan Institute of Medical Science, Islamabad Pakistan, from January to May 2022, after ethical approval

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from the Ethical Review Board Committee of Shaheed Zulfiqar Ali Bhutto Medical University, (ltr no. F1-1/2015/ERB/SZBMU/914). The sample size was calculated using the WHO sample size calculator, taking pooled NAFLD prevalence of 19.3%.[10]

Inclusion Criteria: All the adult patients of either gender who had a biopsy-proven diagnosis of NAFLD were included in the study.

Exclusion Criteria: Known cases of alcoholic liver disease and Known cases of chronic liver disease due to other aetiology like hepatitis were excluded from the study.

Patients were recruited after the written informed consent. TOSHIBA® APLIO 500 ultrasound machine was used to perform ultrasound investigations within the prescribed period. All the patients had pulsed-wave Doppler ultrasonography of the portal vein assessed after fasting for four hours in accordance with the standard methodology. Supine and breath-hold at the end of regular exhalation were used for imaging purposes. The highest (Vmax) and minimum (Vmin) estimated portal venous velocities were measured using spectral waveform. VPI (Vmax–Vmin) / Vmax was calculated from these observations and utilized to determine VPI.

Information on liver fibrosis staging was gleaned from pathology reports maintained in the patient's medical records. Several board-certified general pathologists unaware of the VPI values examined these slides. The length of each specimen in millimetres and the number of portal tracts seen were documented for all pathological examinations. Histological evaluation required at least three portal triads to be visible and a 1-cm biopsy sample to be taken. If the biopsy NASH CRN fibrosis stage was F2 or greater, the subjects' conditions were classed as high-risk NAFLD; otherwise, they were classified as low-risk NAFLD.

Besides demographics (age, gender), medical history (diabetes) and anthropometric and body composition indexes (weight, height, BMI), other clinical data were gathered from the patient's medical records (platelet count and serum levels of albumin, alanine aminotransferase [ALT], and AST). In order to calculate NAFLD FS, FIB-4, BARD, and APRI, we used each patient's demographic, anthropometric, and laboratory data. To arrive at the NAFLD FS, we used the following formulas: 1.13+AST-to-ALT ratio (-0.013), platelet count (10^9/L), albumin (g/dL), age (years), BMI (kg/m^2), and impaired fasting glucose (-1, present; 0 absent). Platelet count and [ALT]1/2 were used to calculate the age-adjusted incidence of bleeding-induced thrombocytopenia (FIB-4). Asthma-to-alcohol ratio 0.8; BMI 28; diabetes, 1 point; BARD score was determined. APRI was calculated by multiplying (AST /ultimate normal limit)/10^9/L platelet count.[11]

Data was analyzed using Statistical Package for the social sciences (SPSS) version 23.00 and MS Excel 2016 software. For normally distributed variables, Mean±SD was determined. For non-normal values, median and IQR were determined. Categorical variables were analyzed in terms of frequency and percentage. The Wilcoxon signed-rank test and the Chi-square test were both employed. When the *p*-value was ≤0.05, it was considered significant.

RESULTS

Of 240 NAFLD patients, 102(42.50%) were males, and 138(57.50%) were females; the Mean age of patients was 49.23±9.83 years, ranging from 23-77 years. According to the NASH CRN scoring system, 95 (39.58%) patients had F0 disease, 80(33.33%) had F1, 30 (12.5%) patients F2, 24(10%) patients had F3 and 11(4.58%) had F4 disease shown in Figure.

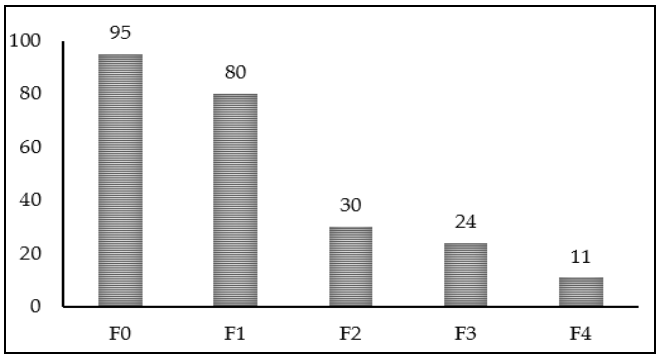

Figure: Fibrosis Stages (n=240)

143(59.58%) patients had a low risk of NAFLD, and 97(40.42%) had a high risk of NAFLD. Mean age, weight, height, BMI, platelet count, albumin, AST and ALT of low-risk patients were 48.61±10.84 years, 86.72± 15.70 kg, 1.66±0.35 m, 32.67±3.53, 249.64±77.28x 10^9/L, 4.60±0.34 g/dL, 46.92±44.42 U/L, 66.38±49.20 U/L respectively. (Table-I) 50(53.76%) patients in the low-risk group and 43(46.24%) patients in the high-risk group had diabetes. Out of 102 Males, 73(71.56%) had low risk, 29(28.44%) had high risk, while out of 138 females, 79(57.24%) females had low risk, and 59(42.76%) females had a high risk of NAFLD shown in Table-I. The median risk score for Non-alcoholic Fatty Liver Disease is shown in Table-II. Venous pulsatility index,

NAFLD fibrosis score, FIB-4, BARD score, and APRL had statistically significant differences (p <0.05).

Table-I: Demographic and Reproductive Variables (n=240)

Study Parameters	Nonalcoholic Fatty Liver Disease		
	Total	Low Risk (n=143)	High Risk (n=97)
Age (years)	56.40±11.73	48.61±10.84	49.43±12.10
Gender			
Male	102(42.50)	73(71.56)	29(28.44)
Female	138(57.50)	79(57.24)	59(42.76)
Diabetes			
Yes	93(38.75)	50(53.76)	43(46.24)
Weight (kg)	91.94±16.8	86.72±15.70	93.69±10.25
Height (m)	1.62±0.50	1.66±0.35	1.74±0.49
Body Mass Index	32.96±4.93	32.67±3.53	34.12±5.18
Platelet Count ($x10^9$/L)	238.77±68.91	249.64±77.28	208.91±79.33
Albumin (g/dL)	4.20±0.54	4.60±0.34	4.50±0.43
AST (U/L)	51.75±44.21	46.92±44.42	59.31±33.54
ALT (U/L)	65.36±46.81	66.38±49.20	70.12±46.22

Table-II: Clinical Risk Scores and Venous Pulsatility Index Value associated by Low and High risk of NAFLD pathologic (n=240)

Scoring System	Nonalcoholic Fatty Liver Disease			*p*-value
	Total	Low Risk	High Risk	
VPI	0.29 (0.22–0.36)	0.31 (0.25–0.38)	0.18 (0.13–0.24)	<0.001
NAFLD Fibrosis	-1.89 (-1.7–0.8)	-2.33 (-2.05–1.10)	-0.70 (-1.77–0.15)	<0.001
Fibrosis-4 Index	1.32 (0.80–1.83)	1.11 (0.77–1.69)	2.10 (1.47-2.93)	<0.001
BARD score	2 (1–2.99)	2 (1–3)	3 (1–3)	0.053
APRI	0.50 (0.31–0.71)	0.41 (0.27–0.59)	0.69 (0.40–1.04)	0.001

DISCUSSION

According to our findings, patients with a more advanced stage of liver fibrosis had lower VPI. VPI prediction also performs at a level comparable with shear-wave elastography (SWE) and serum biomarkers, as reported in multiple studies. The diagnostic accuracy of all existing clinical prediction models was statistically improved when VPI was included. Findings from this study show that in patients with NAFLD, VPI proves to be a previously unrecognized sonographic sign of moderate or more severe liver fibrosis.

Based on our presumption that liver fibrosis severity would not significantly change over this period, we decided that fibrosis progresses by one stage per 14.3 years in NAFLD patients and by one stage per 7.1 years in NASH patients, according to a systematic review.[11]

As previously described as possible indicators of liver disease by sonographic changes in the portal vein, such as flow reversal or a decrease in antegrade flow volume, portal vein pulse pulsatility has only been investigated recently.[12] When the liver capsule encircles the hepatic parenchyma, there is competition for blood flow between the portal vein and hepatic artery during peak systole, which increases the portal vein pulse rate. However, in 1995, Wachsberg *et al.*[13] found that this mechanism is not solely responsible because portal vein pulsatility can increase even when the arterial flow is blocked. In a 2002 study, Barakat *et al.* found that patients with chronic liver disease had a significantly lower VPI than healthy subjects. Patients with Child-Pugh class C disease had a lower value than those with Child-Pugh class A. According to Barakat *et al.* pathological fibrotic liver changes may reduce the transmission of changes in atrial pressure by decreasing hepatic vein blood flow.[14] Results of this study were comparable to the results inferred from our study. When Erdogmus *et al.*[15] studied NAFLD patients in 2008, they found that VPI was significantly lower than healthy subjects.

Due to fatty infiltration, the liver's vasculature became less flexible, resulting in this change. One hundred-five patients with NAFLD and 35 healthy subjects were studied by Balci *et al.*[16] who also found similar outcomes. Solhjoo *et al.*[17] confirmed their findings three years later, comparing the VPI of 31 NAFLD patients and 31 healthy individuals. There is no difference between the VPI scores of patients with NAFLD and those of healthy control subjects, according to Balasubramanian *et al.*[18] contradicting our study.

LIMITATIONS OF STUDY

One image reviewer quantified VPI, and our findings might need to be more generalizable to other reviewers. Where to measure maximum and minimum velocity on the spectrum waveform was only sometimes evident. The reviewer used the study's highest and lowest locations to determine maximum and minimum velocity. Image acquisition can be repeated in real-time to overcome this constraint in clinical practice. VPI was acquired using only one ultrasound machine model, limiting extrapolation to other ultrasound machines. Several sonographers obtained the pictures in ordinary clinical practice. This may have increased variability, reducing the study's capacity to find relationships between VPI and liver fibrosis. Multiple techs captured the photos showing that our results may be independent of the operator. Histopathologic grading of hepatic fibrosis has apparent limits. We utilized histopathologic grading because it is the most widely acknowledged.

CONCLUSION

Venous pulsatility index is a reliable marker for detecting high-risk NAFLD. It is a readily available non-invasive investigation and can be reliably used as a screening tool for detecting NAFLD in high-risk patients, avoiding invasive investigation.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MNNK & AA: Conception, study design, drafting the manuscript, approval of the final version to be published.

IZ & FUIH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AK & TK: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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