Hepatic Artery Resistive Index (HARI) and Bard Fibrosis Score: Risk Assessment of Advanced Liver Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease (NAFLD)*

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ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is a metabolic disorder with a wide clinical continuum of liver diseases like focal hepatic steatosis, steatohepatitis, advanced fibrosis, and cirrhosis that usually progress in a rectilinear fashion. Through this course, NAFLD endure certain hemodynamic changes in the hepatic arterial blood flow. Thus, identification of patients with advanced liver fibrosis is indispensable.

Purpose: To determine the concordance of Hepatic Artery Resistive Index (HARI) and Bard Fibrosis Score in the assessment of advanced liver fibrosis among patients with NAFLD and across its different disease severity.

Material and Methods: Observational descriptive study design was used. 94 NAFLD patients without history of excessive alcohol consumption were invited and voluntarily participated in the research investigation. Ultrasound scanning of the liver to include color Doppler parameters (Peak systolic volume [PSV], end diastolic volume [EDV] and HAR/) and determination of BARD Fibrosis score (Body mass index [BM/], fasting blood sugar [FBS] and AST/ALT ratio) were done. Different grading across NAFLD was established.

Results: The HARI of NAFLD with BARD Fibrosis scores of 1, 2, 3, and 4 has an average index of 0.84, 0.75 0.54 and 0.52, respectively. There is an unwavering inverse correlation between HARI to BARD Fibrosis scoring system (r=-0.84). Across the different severity of NAFLD, grade III (severe) has the lowest mean HARI at 0.53 followed by grade II (moderate) at 0.76 and grade I (mild) at 0.81. Correspondingly, the BARD Fibrosis score showed inverse ranking pattern across the different severity of NAFLD. Grade I (mild) has the lowest BARD fibrosis score followed by grade II (moderate) and grade III (severe), which yielded having a mean score of 1.00, 3.29 and 3.56, respectively.

Conclusion: The HARI has demonstrated a significant negative correlation with advanced liver fibrosis when correlated with BARD fibrosis score. Thus, this study showed that the conventional Doppler US with hepatic artery indices and laboratory variables are helpful in detecting fibrous tissue accumulation in the course of NAFLD.

Keywords: Non-alcoholic fatty liver disease, hepatic artery resistive index, BARD Fibrosis score, liver fibrosis, ultrasonographic grading.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a metabolic disorder with a wide clinical continuum. It is frequently associated with obesity, diabetes mellitus, hyperlipidemia, hypertension and metabolic syndrome[1]. It is characterized by histopathological or imaging that suggests lipid deposition within the hepatocytes and no history of excessive alcohol consumption. NAFLD afflict approximately 1 billion of the general population worldwide and is a burgeoning global health concern[1]. The population prevalence of NAFLD in Asia is around 25%[3]. Data regarding prevalence of NAFLD in the Philippines have been lacking due to limited published peer-reviewed research. NAFLD is

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considered to be benign, but it can progress to nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis and hepatocellular carcinoma (HCC)[1]. Reported incidence of developing HCC in NAFLD patients with fibrosis/ cirrhosis is between 6.7-15% at 5 to 10 years and 2.7% at 10 years in NAFLD patients without fibrosis/ cirrhosis[31]. Hence, there is an emergent need to assess the presence hepatic fibrosis to prevent mortality. Liver biopsy has been regarded as the gold standard in identifying these liver-related morbidity and mortality, but it has a well-known limitation, including its invasiveness and a rare, but with potential life-threatening complications. Liver ultrasonography (US), an inexpensive and a non-invasive diagnostic modality with 94% sensitivity and 95% specificity becomes popular and is now widely used in detecting NAFLD and other focal liver disorders[21]. Despite advances in its diagnosis, the diagnostic accuracy of conventional US to reveal a sign of progressive fibrosis is low except in advanced stages of disease (e.g. cirrhosis). This has led to host of an innumerable non-invasive approach of assessing hepatic fibrosis in patients with NAFLD. Elastography is the new innovative imaging technique that uses shear wave that assess the degree of hepatic fibrosis. Although the use of elastography has improved the evaluation of liver stiffness in patients with NAFLD, it comes with a finitude use because it requires more specific training and is not readily available in various institutions[2]. Another approached used in the study by Claudio Tana, *et al*., is the measurement of hepatic artery resistive index (HARI), which is significantly altered in patients with NAFLD. It also demonstrated an inverse correlation with US severity of hepatosteatosis and a positive correlation in the degree of fibrosis. However, due to limited target population in the study, the authors recommended a larger sample size and the results were considered only as a preliminary and must be validated by a large study group[2]. The use of different liver fibrosis scoring system garnered relevance in NAFLD that requires serial assessment of fibrosis longitudinally over time. Among the various fibrosis scoring system, NAFLD and BARD fibrosis scores have relatively high sensitivity and specificity. Both scores predict well the presence of significant fibrosis and reducing the need for liver biopsies[7]. In this study, BARD fibrosis score was used because it is more economical and simpler to use. It only requires three serum biomarkers (AST, ALT and FBS) in comparison with the NAFLD fibrosis score which utilizes five serum biomarkers (AST, ALT, FBS, Platelet count and Albumin).

Advanced liver fibrosis in patients with NAFLD are associated with severe hepatic dysfunction and risk for malignant progression. Hepatocellular carcinoma (HCC) which accounts for 70%-85% of the primary liver malignancies is considered the most prevalent histological subtype[2]. in addition, with the advent of potential occurrence of anti-fibrotic drug for the treatment of liver fibrosis, the accurate assessment of fibrous tissue accumulation in NAFLD patients becomes even more relevant, not only for identifying patients for treatment, but also in the evaluation of its efficacy.

In this study, we explore the use of different noninvasive means in assessing liver fibrosis in NAFLD, from serum biomarkers to predictive fibrosis score and imaging measures.

OBJECTIVES

Primary objective: To determine the concordance of Hepatic Artery Resistive index (HARi) and Bard Fibrosis Score in the assessment of advanced liver fibrosis among patients with Non-Alcoholic Fatty Liver Disease (NAFLD).

Secondary objective: To determine the concordance of Hepatic Artery Resistive index (HARi) and Bard Fibrosis Score across different severity of Non-Alcoholic Fatty Liver Disease (NAFLD).

PURPOSE

The goal of this study is to present additional non-invasive and innovative techniques in the assessment of advanced liver fibrosis in the course of NAFLD.

SIGNIFICANCE OF THE STUDY

For the clinicians:

This study will serve as a basis for the clinician to formulate a standardized assessment guideline or tool that will utilize the sonographic

value of hepatic artery resistive index (HARi) through Doppler ultrasound and BARD Fibrosis Score (ie. using clinical and serological methods/markers) in monitoring advanced liver fibrosis for patients with nonalcoholic fatty liver disease (NAFLD).

This study will expedite in the assessment of advanced liver fibrosis in the course of NAFLD which can condense the need for possible biopsy. Through the cutoff value of HARi, it will aid in the selection of NAFLD patients to undergo invasive biopsy for evaluation of the degree of inflammatory activity (grading) and extent of fibrosis (staging).

This study will succor in identifying NAFLD patients to receive management of advanced liver fibrosis (ie. antifibrotic) and in the evaluation of its effectiveness.

For NAFLD patients:

This study will serve as an alternative, non-invasive and cost-effective measure (other than BARD Fibrosis score) that assesses the risk for advanced liver fibrosis. The sonographic value of HARi may help prevent unnecessary follow-up imaging and hence, curtail the diagnostic expenditure on the part of the patient.

This study will minimize patient anxiety (ie. patients with hemophobia and/or with needle phobia) because it will provide an option to lessen serial blood test necessary in the determination of liver function test.

REVIEW OF RELATED LITERATURE AND STUDIES

Non-alcoholic fatty liver disease (NAFLD) is a global disease characterized by an imaging or histological evidence of lipid deposition in the hepatocytes afflicting patients with predisposing risk factors such as diabetes mellitus, hypertension, and hypercholesterolemia[2]. NAFLD is an incipient disease, which remain incognito for years. The majority of patients suffering from NAFLD are asymptomatic[6]. Patients should have no known specific etiology of liver disease such as excessive alcohol consumption, viral hepatitis or neoplasia in diagnosing NAFLD[2]. NAFLD is estimated to afflict 1 billion of world's general population[1]. The population prevalence of NAFLD in Asia is around 25%[3]. it has now become a global burden in NAFLD patients developing complications like nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, hepatocellular carcinoma and other liver related disease[1,4]. Among these complications, advanced hepatic fibrosis has a greatest risk of developing complications of chronic liver disease[1]. Thus, crucial issues in patients with NAFLD are identification of the different complications, most particularly the advanced liver fibrosis.

Conventional ultrasound (US), an inexpensive and with rapid execution for trained radiologist is effective in detecting hepatic steatosis[2]. it is also used to detect several extrahepatic disorders. However, it has its own limitation which yielded low diagnostic accuracy to reveal signs of early hepatic fibrosis except in advanced stages of chronic liver disease, such as cirrhosis. The introduction of elastography has improved the evaluation of liver stiffness which is also used in evaluation of NAFLD patients. This technique led the American Gastroenterological Association which instituted guideline on the role of Elastography in the evaluation of liver fibrosis[32]. There are two different kinds of techniques: ultrasound-based or magnetic resonance- based. Main limitations of elastography are those obese patients, with waist circumference ≥102 cm or thick parietal walls which yielded significant failure of measurement of liver stiffness[2]. Although elastography technique has been widely used worldwide, but it is not readily available because it needed an additional equipment that will be installed in the current ultrasound machine or MRi.

There are different approaches that were evaluated to identify patients at high risk of significant fibrosis and one of which, is through measuring the hepatic resistive index (HARi). Measuring HARi is not routinely assessed and evaluated in the routine ultrasound request because many of the clinician has lack of information regarding the importance of the HARi value in clinical practice. in the study of Claudio Tana, *et al*., mentioned that HARi is altered in patients with NAFLD and a reduction in HARi value is inversely

proportional to the severity of diffuse fatty liver disease[4]. The usual range in normal, as well as post-transplant, is between 0.55 and 0.80[22]. it is measured by resistive index (Ri) = (peak systolic velocity [PSV] minus end diastolic velocity [EDV]) divided by PSV. in particular, the detection of low HARi value in NAFLD patients, can predict presence of advanced liver fibrosis[4]. Claudio Tana, *et al*., demonstrated a significant correlation with degree of fibrosis, suggesting that the fibrous tissue accumulation may result in increased in arterial rigidity and, therefore, causing an increase to resistance flow, and that the different tissue composition of liver (adipose and fibrous) can influence HARi[2]. Liver biopsy remains the gold standard technique to detect early liver fibrosis, but it's an invasive procedure and with various complications. Because of its limitation, it leads to the development of different clinical algorithm that is used to assess the risk of NASH evolution and development of early liver fibrosis. Some guidelines suggest the use of non-invasive markers to assess liver fibrosis such as NAFLD fibrosis score, BARD score, fibrosis-4 (FiB-4) calculator, Original European Liver Fibrosis Panel (OELF) score, Enhanced Liver Fibrosis (ELF) score, Palekar's score, BAAT score, Gholam's score and Nippon score?. These markers are based on readily available laboratory tests. Among these scoring systems, NAFLD and BARD fibrosis scores were established specifically for assessing and predicting advanced liver fibrosis which have relatively high sensitivity and specificity. Both scores predict well the presence of advanced fibrosis and reducing the need for liver biopsies?. The main strength of the BARD score over the NAFLD fibrosis score is its simplicity because it utilizes three serum biomarkers: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and fasting blood sugar (FBS). The NAFLD fibrosis score utilizes five serum biomarkers: AST, ALT, FBS, Platelet count and Albumin. Hence, in this study, BARD fibrosis score was used to predict liver fibrosis in NAFLD patients and only requires simple clinical data. in this study, it showed positive correlation of BARD fibrosis scoring system when compared to HARi in assessment of advanced liver fibrosis in the course of NAFLD.

In the study of Claudio Tana, *et al*., where the investigators uses NAFLD fibrosis score and when compared to HARI revealed a negative correlation between HARI and NAFLD fibrosis score. Low HARI resulted from high tissue stiffness secondary to fibrous tissue accumulation that can be attributed to increased arterial rigidity and therefore resulted to increase of resistance arterial flow. However, the investigators recommended that it must be validated by large study population before recommending and incorporating into clinical practice. Thus, the present study utilized large population group of NAFLD and exceeded the sample size used by Tana, et al. which aimed to evaluate the concordance between HARI with a simple clinical fibrosis scoring system, the BARD fibrosis score.

Currently, there is no drug treatment available for treating NAFLD. A combination of healthy diet and increased physical activity remains the mainstay of NAFLD management. In order to prevent the hepatic, extra-hepatic, including metabolic complications of NAFLD, it is important to manage the condition early. To date, no drugs has been approved as an antifibrotic drugs however, there are clinical antifibrotic trials currently registered at ClinicalTrials.gov designed for antifibrotic pharmacologic therapies. Since liver fibrosis is the most significant factor for determining the prognosis of NAFLD, therefore it is important to identify early changes of liver parenchyma through routine, inexpensive, readily available ultrasonographic evaluation and more specifically, through determination of HARI value to patients with NALFD. The study provided additional information in the assessment of advanced liver fibrosis in conjunction with the simple, obtainable and validated clinical fibrosis score.

The prevalence of NAFLD has grown correspondingly with the rise of obesity, sedentary lifestyle, unhealthy dietary pattern, and metabolic syndrome [10]. Therefore, a plan should be carried out immediately when NAFLD is diagnosed through dietary modifications and increase exercise activity. Challenges still remain, as noted, including NAFLD that will require pharmacologic intervention to prevent or reverse advanced fibrosis, and the lack of a standardized, and accepted noninvasive endpoints for assessment of fibrosis.

DEFINITION OF TERMS

- Alanine aminotransferase (ALT) test – detects the enzyme alanine aminotransferase in the blood. This enzyme found mainly in the liver. Elevation of which signifies possible liver disease.
- Aspartate aminotransferase (AST) test - detects the enzyme aspartate aminotransferase in the blood. This enzyme found mainly in the liver. Elevation of which signifies possible liver disease.
- AST/ALT ratio – ratio between concentration of the alanine and aspartate aminotransferase enzymes. Normal ratio is approximately 0.80. An elevated ratio is an indication of liver disease.
- Fasting blood glucose (FBS) – a test used to measure level of glucose in the blood.
- Body mass index (BMI) – a value derived from body mass (kilograms) divided by height (meters^2).
- BARD fibrosis score – BARD score will be calculated by assigning points to the following variables: BMI $\geq$28 kg/m2 = 1 point, BMI <28 kg/m2 = 0 point; AST/ALT ratio $\geq$0.8 = 2 points, AST/ALT ratio <0.8 = 0 point; pre-existing type II diabetes mellitus or fasting blood glucose (FBS) of $\geq$126 mg/dl = 1 point. The total possible score ranges from 0 to 4 points. According to the study of Ageely et.al, a score of 2-4 points indicate significant liver fibrosis[5].
- Liver echogenicity – reflects the return echo signal from the liver parenchyma. Liver echogenicity is high when the sound echo reflects increased sound waves, termed as hyperechogenic which is usually represented with lighter colors on medical ultrasonography. An increased lipid deposition in the hepatocytes will reflect hyperechogenic parenchyma.
- Hepatic Artery Resistive index (HARI) – is a sonographic index that assess the systolic and end-diastolic wave of the hepatic artery. Normal range value is between 0.55 to 0.80. Low resistive index is more specific for live disease[22]. It is determined with the following formula:

$$\frac{\text{Peak systolic velocity (PSV)} - \text{End diastolic velocity (EDV)}}{\text{Peak systolic velocity (PSV)}}$$

- Excessive alcohol consumption – an alcohol consumption of more than 20 grams per day for women and more than 30 grams per day for men.

METHODOLOGY

Research Design

An observational descriptive study design was done at Ultrasound Section of QCGH Department of Radiology.

All patients referred to the Ultrasound Section of QCGH Department of Radiology for liver, upper abdomen or whole abdominal ultrasound was evaluated. The ultrasound request was assessed based on the history and physical examination written in the request, along with the initial impression made by the attending physician. All clinical data listed in the request has been validated by the principal investigator.

Data collection Method

Research informed consent to participate voluntarily in the research investigation was discussed to the participant, as per ethics guideline of the Philippines. These include the purpose of the study, duration of research, procedure, potential risks, benefits, compensation of participation and its confidentiality. All participants invited made their informed decision, enrolled and participated in the research investigation. The participants also received their certificate of consent.

Ethics approval with *reference number 2019-0085* for this research investigation was obtained from Far Eastern University – Nicanor Reyes Medical Foundation Institutional Ethics Review Committee (FEU-NRMF IERC), a level III accredited research ethics committee. A letter of intent to conduct research investigation was also secured and was given to the chief of clinics, department chair and training officer of the Department of Radiology.

The duration of the research investigation spanned in less than 36 hours (or 1 ½ day). These involves a 10-15 minutes interview and answering the formulated questionnaire, 8 hours fasting, 5-minute blood extraction, 10-25 minutes ultrasound

examination and 24 hours releasing of the result (*during this time, interpretation and typing of the results are done*).

Additional clinical information (*ex. History of alcohol consumption, past medical history, current medications and exercise pattern*) was extracted and interviewed based on the formulated questionnaire which lasted for about 10-15 minutes. Names of the participant were not placed on the questionnaire and were replaced with a unique identification code for privacy and confidentiality.

The participant was instructed to have 8 hours fasting prior to laboratory and ultrasound procedure. On the day of the scheduled examination, the participant was probed to proceed first to the Clinical Chemistry Section of Department of Pathology for blood extraction (*for determination of ALT, AST and FBS levels*) that took about 5 minutes. Results of ALT, AST and FBS were utilised for BARD fibrosis score.

The sonogram of the liver, upper or whole abdomen was performed by the principal investigator using Philips HD11 XE Ultrasound Machine with a low frequency transducer (3.5MHz). The ultrasound examination took about 10-25 minutes depending on the type of requested procedure (*Liver, upper abdomen or whole abdominal ultrasound*).

Sampling Design Process

Population

Patients with Non-alcoholic fatty liver disease (NAFLD) of both sexes aged 18 years and above were considered eligible for this study.

Sampling Frame

The total number of patients with non-alcoholic fatty liver disease (NAFLD) in the Quezon City General Hospital (QCGH) is 198 and the total number of patients with normal sonogram of the liver is 86 based on the reviewed registry list maintained in the Ultrasound Section of Department of Radiology from February to March 2019.

Sample Size

Using Epi-Info application, the principal investigator arrived at a computed sample size of 81 NAFLD participants with an alpha level of 0.05. In order to account for exclusion due to incomplete information, the principal investigator decided to inflate 20% to the planned sample size which is 16 for NAFLD group. Hence, the total number of sample size are 97 NAFLD participants.

Sampling Technique

The systematic sample technique was utilized in the selection of 97 NAFLD participants with a regular interval of 2 [population size (198) divide by sample size (97)].

Inclusion/Exclusion Criteria

The principal investigator **included** those participants with the following criteria: Liver sonographic findings of fatty liver infiltration, and risk factors for NAFLD (*e.g. body mass index [BMI] ≥30 kg/m2, elevated level of ALT and AST and type 2 diabetes mellitus*).

The principal investigator **excluded** the participants who had fatty liver disease from identifiable cause such as an excessive alcohol consumption *(>20 g/day for women, > 30 g/day for men*), and other causes of liver enzyme elevation (*autoimmune hepatitis, viral hepatitis, Wilson's disease, alpha-1 antitrypsin deficiency, drug induced hepatitis, hemochromatosis and neoplasia*) based on specific clinical and physical findings.

In this study, data collected from three (3) NAFLD participants were not analyzed due to excessive alcohol consumption.

Withdrawal Criteria

Participant who has hemophobia and/or needle phobia may withdraw his or her consent to participate in the research investigation. Blood work-up which include determination of FBS, AST and ALT levels are needed in the computation of BARD Fibrosis score. In this study, there were no documented withdrawals from the NAFLD participants.

Research Instrument

Philips HD11 XE Ultrasound Machine with a low frequency transducer (3.5MHz)

The participant was diagnosed to have fatty liver disease when the echogenicity of the liver was increased than that of the renal cortex. The ultrasound procedure was done by the principal investigator. Sonography findings of fatty infiltration can vary, depending on the amount of fat and whether deposits are diffuse or focal[8]. Participant with evidence of fatty liver disease was assigned to have NAFLD and further subdivided according to grading of fatty liver disease (grade I, II, & III) on the basis of liver parenchymal echogenicity. Severity of the fatty liver was graded based on the US findings into: **Grade I (mild)** – if the echogenicity is slightly increased with normal visualization of the diaphragm and the intrahepatic vessel borders; **Grade II (moderate)** – if the echogenicity is moderately increased with slight impaired visualization of the diaphragm and the intrahepatic vessels and; **Grade III (severe)** – if the echogenicity is markedly increased with poor visualization of the diaphragm, intrahepatic vessels and posterior segment of the right lobe[5].

Other sonographic information documented include liver size (longitudinal diameter of the right hepatic lobe), and color Doppler parameters (using B-mode) such as: resistive index (RI), peak systolic velocity (PSV) and end diastolic velocity (EDV) of hepatic artery.

All sonographic findings assimilated by the principal investigator was verified by the Radiology Consultant on-duty who is a Fellow of Ultrasound Society of the Philippines.

During the entire course of the examination, the participant was instructed that he/she may feel a cold sensation on the abdominal region, which is a normal experience, and ascribed to the ultrasound gel placed on the ultrasound probe.

BARD Fibrosis Scoring System

BARD fibrosis score is a clinically validated scoring system and uses a simple clinical history and serum biomarkers to assess the risk of advanced liver fibrosis for patients with Non-alcoholic fatty liver disease[7]. It utilizes the following parameters: body mass index (BMI), AST/ALT ratio and FBS.

In this study, blood extraction was done for determination of ALT, AST and FBS levels. The participant was instructed that he/she may feel minimal pain or discomfort at the punctured site (mostly at the antecubital fossa), which is a normal sensation during the examination.

Body mass index (BMI) is determined through the standard formula of weight in kilograms divided by height in meters squared [kg/m2]. Computed value of BMI was used as one of the variables in determining fibrosis score.

Alcohol Consumption (grams/day) Questionnaire

A standard questionnaire by *Poikolainen and Vartiainen 1997* that determines the average daily alcohol consumption was applied in this study. The questionnaire was utilized to exclude those participants diagnosed to have fatty liver disease from identifiable cause and one of which is excessive alcohol consumption (>20 g/day for women, > 30 g/day for men). In this study, data collected from three (3) NAFLD participants were not analyzed due to chronic alcohol consumption.

Participant's Data Sheet

All gathered questionnaires, laboratory and ultrasound results are recorded in the subject data sheet formulated by the principal investigator for easy collection and access of participant's data (*See appendices*). Participants' recorded data sheet was kept on locked files at all time. At the end of the research investigation, all gathered data from the participants' data sheet was destroyed after it was analyzed.

Statistical Method

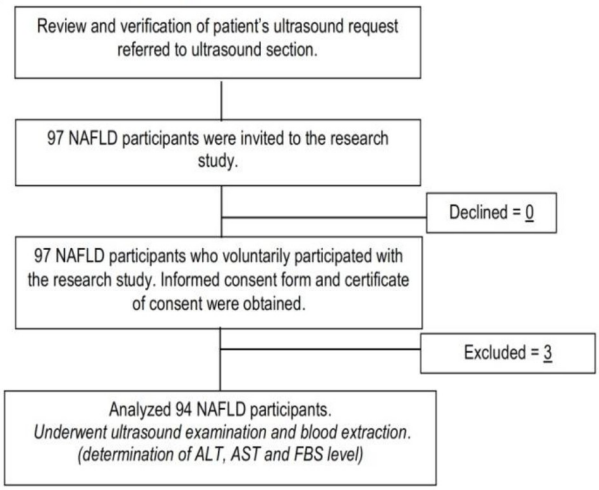
The number of retrieved, reviewed, selected and rejected clinical information was presented as a flowchart (Figure 1). The statistical analysis and tables were done using, Microsoft Excel Data Analysis ToolPak. The baseline characteristics of NAFLD participants are presented as tables of

frequencies, means and standard deviations. Determination of the concordance of the Hepatic Artery Resistive Index (HARI) with BARD Fibrosis score, both measured qualitatively was analyzed using correlation coefficient. Determination of the concordance across the different levels of severity of nonalcoholic fatty liver disease was done using analysis of variance. A statistically significant difference was considered if the p value is less than 0.05.

Cost Analysis

Cost for the procedure will depend on the request of the attending physician. It varies from liver, upper abdomen and whole abdomen ultrasound. The principal investigator's interest focused on the liver size, its corresponding echogenicity and Doppler Ultrasound parameters (RI, PSV, EDV) of hepatic artery, and the latter is not routinely included in the requested procedure. Hence, these additional parameters will not be charged to the participant. The principal investigator shouldered 50% as to the total cost of the ultrasound procedure of the NAFLD participant. Cost for laboratory (ALT, AST and FBS) was also shouldered by the principal investigator. The pricing of laboratory and ultrasound procedure fee was adopted from Quezon City General Hospital information system (HIS). Total cost of this study was highlighted on the appendices.

Figure 1. Flowchart of Data Collection



RESULTS

Baseline Characteristics of the NAFLD Participants

There is a total of 94 participants (66 males, 28 females) with mean age of 44.6 participated in the research investigation. The sample comprised of participants of both sexes aged 18 years and above who were diagnosed with nonalcoholic fatty liver disease (NAFLD) through sonographic features with no history of excessive alcohol consumption and other known history of liver enzyme elevation (eg. Hepatitis, drug-induced hepatitis, neoplasia, etc) based on clinical and physical examination. It was found that most of the participants with NAFLD had Grade II (moderate) fatty liver changes (51.1%), followed by Grade III (severe) fatty liver changes (26.6%), and Grade I (mild) fatty liver changes (22.3%) [Table 1]. The majority of the NAFLD participants have no history of alcohol consumption (67.0%) [Table 1]. Only 33.0% has a history of mild alcohol consumption with male preponderance (71.0%). Both sexes have an average daily alcohol consumption of 19.91 grams/day for male and 14.56 grams/day for female (Table 1). The age distribution and demographics of the participants is shown in Table 1. Most of the NAFLD participants are predominantly male (70.2 %). The mean age from both sexes is 44.6 and mostly in the 4th decade of life.

Table 1 also showed the risk factors for NAFLD. Majority of the participants are overweight (61.7%) followed by obese group (8.5%). It was also observed that 31.9% has pre-existing or newly diagnosed with diabetes mellitus (DM) type II who is currently taking oral anti-diabetic medications (29.7%). Upon checking their fasting blood sugar (FBS) level, it showed that 76.7 % of the NAFLD participants with pre-existing diabetes are compliant with maintenance medication since their FBS are within normal level (≤125 mg/dl) with a mean value of 110.2 mg/dl (Table 2). However, 50.0 % of the NAFLD participants who are undetected with DM or having an unknown status of FBS level, showed elevated (>125 mg/dl) level with a mean value of 128.5 mg/dl (Table 2).

Sonographic features of the liver with NAFLD are reported in Table 1. It was found that 42.6% of the participants with NAFLD have a longitudinal liver diameter (midclavicular) ranging from 14.0-14.9 cm (42.6 %) followed by 15.0-15.9 cm (23.4%) with a mean liver size of 14.46 cm and 15.38 cm, respectively. Using the B-mode scan of Philips HD11 XE ultrasound machine, hepatic artery resistive index (HARI) was calculated among NAFLD participants and found that 45.7 % had a normal HARI value followed by 44.7% who have low value, with mean HARI of 0.68 and 0.45, respectively.

Markers used for BARD fibrosis scoring system are also shown in Table 1. It showed that 72.3% of the NAFLD participants have increased (>0.80) in AST/ALT ratio with mean value of 0.88. The fasting blood sugar (FBS) level was also determined and showed that 55.3% has increased (>125 mg/dl) in FBS level with mean value of 128.24 mg/dl.

HARI of NAFLD participants with different BARD Fibrosis scores

Table 3 shows the correlation of HARI and BARD fibrosis score. The correlation coefficient was -0.84 which showed strong negative relationship between the Hepatic Artery Resistive Index and Bard Fibrosis Score. This indicates that yielding a higher BARD Fibrosis score, the HARI equates to a lower value. The HARI of NAFLD with BARD Fibrosis scores of 1 and 2 ranges from 0.80 to 0.88 and 0.69 to 0.88 with an average index of 0.84 and 0.75, respectively. The HARI of NAFLD with BARD Fibrosis scores of 3 and 4 ranges from 0.42 to 0.69 and 0.39 to 0.70 with an average index of 0.54 and 0.52, respectively. Thus, Table 3 showed that there is an unwavering inverse correlation between HARI to BARD Fibrosis scoring system.

HARI and BARD Fibrosis score across different severity of NAFLD

Based on the p-values under Table 4 using analysis of variance, Hepatic Artery Resistive Index (HARI), EDV (cm/s), Bard Fibrosis Score, BMI (kg/m2), and AST/ALT Ratio have significant difference across the different severity or grading of NAFLD participants. Meanwhile, PSV (cm/s) and FBS (mg/dl) do not indicate any significant difference among the grading of fatty liver disease.

Grade III (severe) nonalcoholic fatty liver disease has the lowest mean HARI at 0.53 followed by grade II (moderate) at 0.76 and grade I (mild) at 0.81. Mean HARI value for grades I (mild) and grade III (severe) are not within the normal limits. Correspondingly, the BARD Fibrosis Score showed inverse ranking pattern across the different severity of NAFLD, grade I (mild) has the lowest score followed by grade II (moderate) and grade III (severe), which yielded having a mean score of 1.00, 3.29 and 3.56, respectively.

Table 4 showed that across the different severity of NAFLD, those who had grade III (severe) fatty liver disease commensurate to a higher BARD Fibrosis score and lowest Hepatic artery resistive index (HARI). And those who had grade I (mild) fatty liver disease corresponds with lower BARD Fibrosis score and highest HARI.

Table 1. Baseline Characteristics of the NAFLD participants (*n*=94)

	Frequency (%)	Mean	*SD*
CHARACTERISTICS			
Sex			
Male	70.2 %	NA	*NA*
Female	29.8 %	NA	*NA*
Age (years)		**44.670**	***9.24***
18-29	3.4 %	26.00	*4.20*
30-39	18.1 %	34.82	*2.92*
40-49	47.8 %	44.51	*2.49*
50-59	23.4 %	54.27	*3.40*
60-69	4.3 %	63.5	*3.08*
BMI (kg/m2)**		**27.254**	***2.95***
>40 kg/m2 (Extremely obese)	0	NA	*NA*
30-39.9 kg/m2 (Obese)	8.5 %	30.15	*0.14*
25-29.9 kg/m2 (Overweight)	61.7 %	28.92	*0.56*
18.5-24.9 kg/m2 (Normal)	29.7 %	22.98	*1.42*
<18.5 kg/m2 (Underweight)	0	NA	*NA*
Alcohol consumption			
None	67.0 % (63/94)		
With history of mild to moderate alcohol consumption	33.0% (31/94)		
Male	71.0 %	NA	*NA*
Female	29.0 %	NA	*NA*
Average mild-moderate alcohol consumption (g/day)***		**6.054**	*9.15*
Male	NA	19.91	*5.21*
Female	NA	14.56	*2.18*
Pre-existing or newly diagnosed DM	**31.9 %**	NA	*NA*
Pre-existing or newly diagnosed HPN	**11.7 %**	NA	*NA*
Medication History			
1. No medication intake	60.6 %	NA	*NA*
2. Multivitamins	21.3 %	NA	*NA*
3. Anti-hypertensive (*Losartan, Amlodipine, others*)	10.6 %	NA	*NA*
4. Anti-diabetic (*Metformin, others*)	29.7 %	NA	*NA*
5. Anti-dyslipidemic (*Rosuvastatin, others*)	14.9 %	NA	*NA*
Physical activity (with exercise)	**34.0 %**	-	*NA*

ULTRASOUND PARAMETER			
Liver size (cm)		**14.25**	*0.96*
10.0-10.9	0	NA	*NA*
11.0-11.9	1.1 %	11.90	*NA*
12.0-12.9	12.8 %	12.66	*0.17*
13.0-13.9	19.1 %	13.52	*0.28*
14.0-14.9	42.6 %	14.46	*0.30*
15.0-15.9	23.4 %	15.38	*0.27*
16.0-16.9	1.1 %	16.00	*NA*
HARI			
>0.80	9.6 %	0.84	***0.02***
0.55 – 0.80	45.7 %	0.68	***0.08***
<0.55	44.7 %	0.45	*0.05*
LABORATORY TESTS			
AST (U/L)	*NA*	37.794	*5.86*
ALT (U/L)	*NA*	46.165	*8.27*
AST/ALT ratio	*NA*	0.833	*0.12*
≤ 0.80	27.7 %	0.70	*0.07*
>0.80	72.3 %	0.88	*0.09*
FBS (mg/dl)****	-	117.330	*11.12*
< 125	44.7 %	109.00	*7.22*
> 125	55.3 %	128.24	*2.24*

NAFLD non-alcoholic fatty liver disease; *BMI* Body mass index; *AST* aspartate aminotransferase; *ALT* alanine aminotransferase; *FBS* fasting blood sugar; *HARI* hepatic artery resistive index; *SD* standard deviation; DM *diabetes mellitus;* HPN *hypertension;*
**significant values at α = 0.05 are shown in bold text*
***Average Body Mass Index for both sexes*
****Average mild to moderate alcohol consumption for both sexes*
*****FBS of all NAFLD participants*

Table 2. FBS among NAFLD participants with Pre-existing or newly diagnosed DM and undiagnosed DM

FBS (mg/dl)	Pre-existing or newly diagnosed (*n=30*)		Undiagnosed (*n=64*)	
	Frequency (%)	Mean	Frequency (%)	Mean
>125	23.3 %	128.43	50.0 %	128.50
≤125	76.7 %	110.26	50.0 %	109.59

NAFLD non-alcoholic fatty liver disease; *FBS* fasting blood sugar; DM *diabetes mellitus*

Table 3. Correlation of Hepatic Artery Resistive Index (HARI) and Bard Fibrosis Score

BARD Fibrosis Score	Hepatic Artery Resistive Index (HARI) Average index	*Lowest index*	*Highest index*
1	0.84	0.80	0.88
2	0.75	0.69	0.82
3	0.54	0.42	0.69
4	0.52	0.39	0.70
Correlation Coefficient is **-0.84**			

Table 4. Hepatic artery resistive index (HARI) and BARD Fibrosis Score across different severity of Non-Alcoholic Fatty Liver Disease (NAFLD) (*n* = 94, means ± SD)

	Different severity of Non-Alcoholic Fatty Liver Disease						*p**
	Grade I (Mild) (*n* = 21)		Grade II (Moderate) (*n* = 48)		Grade III (Severe) (*n* = 25)		
Hepatic Artery Resistive Index (HARI)	0.81	(±0.058)	0.76	(±0.106)	0.53	(±0.098)	**0.000**
PSV (cm/s)	54.92	(±12.212)	57.97	(±12.786)	55.86	(±13.755)	0.607
EDV (cm/s)	11.42	(±4.22)	12.44	(±5.112)	23.33	(±5.503)	**0.000**
Bard Fibrosis Score	1.00	(±0.755)	3.29	(±0.865)	3.56	(±0.571)	**0.000**
BMI (kg/m2)	24.62	(±3.022)	28.21	(±2.351)	27.62	(±2.541)	**0.000**
FBS (mg/dl)	117.33	(±9.843)	116.95	(±11.25)	119.04	(±11.515)	0.748
AST/ALT Ratio	0.72	(±0.088)	0.81	(±0.069)	0.94	(±0.121)	**0.000**

PSV peak systolic velocity, *EDV* end diastolic velocity, *BMI* Body mass index, *FBS* fasting blood sugar, *AST* aspartate aminotransferase; *ALT* alanine aminotransferase
**significant values at α = 0.05 are shown in bold text*

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

Non-alcoholic fatty liver disease (NAFLD) is characterized by imaging or histological evidence of steatosis in patients with predisposing factors such as obesity, diabetes, hypertension, and hypercholesterolemia. NAFLD patients should have no specific etiology of liver disease such as hepatitis or excessive alcohol abuse. Instrumental evaluation of NAFLD is made with conventional ultrasound (US), with 94% sensitivity and 95% specificity in the detecting of fatty liver disease [21]. Because of its low cost, simple and rapid performance by skilled radiologist, it is more commonly requested imaging procedure in diagnosing NAFLD. Though histopathology is considered the gold standard for the diagnosis of NAFLD, it is not practically possible to perform biopsy for the colossal population of NAFLD and taking consideration of its various complication.

Baseline Characteristics of the NAFLD Participants

Among 94 participants diagnosed with non-alcoholic fatty liver disease (NAFLD), the study showed 70.2% cases were found in males. Similar results found by some investigators (Shivram Prasad, *et al.*, and Jen Jung Pen *et al.*,) who found that it has a male predominance among patients with NAFLD. In the article of Jen Jung Pen *et.al.*, this was attributable to the difference in body fat composition, lifestyle, and sex hormone metabolism.

It was also found in this study that the mean age for both sexes diagnosed with NAFLD is 44.6 years old. One study (Dhumal *et al.*,) showed similar findings where the prevalent fraction of people with fatty liver was in the age group of 4th to 5th decade. This is also showed in this study where 47.8% of the NAFLD participants belonged to the age group of 4th to 5th decade with a prevalence of 47.8% and 23.4%, respectively. This can possibly be attributed to the sedentary lifestyle and less engagement in physical activity in this age group[27].

In this study, only 29.7% had normal body mass index (BMI), 61.7% are overweight, and 8.5% are obese. In the study of Ghobad *et al.*, showed that most of the NAFLD patients are overweight and obese. In the study done by Mohammad Aleem *et*

al., showed that increasing weight was associated with increasing grades or severity of fatty liver.

Sonographic liver size of 75.6% NAFLD participants are within normal limits, on which 42.6% ranges from 14.0-14.9 cm with mean size of 14.46 cm. On the contrary, 24.5% is considered to have slight hepatomegaly, on which 23.4% ranges from 15.0-15.9 cm with mean size of 15.38 cm. The average sonographic liver size through midclavicular line is 10.0-12.5 cm in craniocaudal length. A liver that is longer than 15.5-16.0 cm in the midclavicular line (MCL) is considered enlarged [25]. There is lack of consensus on standard reference values for sonographic measurement of the liver [37]. There have been quite a few previous reports giving the standard sizes of liver through ultrasound in general adult population, but none has been done in Asian populace, and in particular with NAFLD patient. In this study, the liver span of the NAFLD patient was found to be significantly higher or within the upper margin when compared with the average liver size. In the study of Khanal, *et al*., showed increasing grades of NAFLD were significantly associated with increasing levels of serum cholesterol, LDL, *liver size* and BMI. There is moderate positive correlation seen between increasing severity of fatty liver and increasing liver size (r=0.405). In the study of Tana *et al*., the possible explanation would be as the severity of the fatty infiltration increases there is more deposition of fat in the liver, causing increase in the liver span. It is plausible that when NAFLD patients with reduced liver span, the clinician must suspect and must adequately evaluate to rule out the possibility of fibrous tissue accumulation. However, due to paucity of literature regarding liver span in various severity of NAFLD (histologically diagnosed), validation of our remark needs furthermore studies in this concern.

Concordance of HARI and BARD Fibrosis score across different severity of NAFLD

Although ultrasound can demonstrate fatty liver, however its reliability to predict fibrous tissue in NAFLD is not well established. The recent development of novel techniques, such as elastography, has led to great advances in the assessment of liver fibrosis, but these methods are not readily available, are expensive, need additional US equipment and have significant limitations in obese patients[5,6,7]. The failure rate is 2-10% of patients with BMI >30 kg/m^2 [2, 7]. Liver biopsy remains the gold standard in the assessment of advanced liver fibrosis in the course of NAFLD; therefore, identification of these patients is with prodigious importance[14]. Various simple, non-invasive methods have been established as an alternative to liver biopsy. Among the serological tests that could be expedient, the BARD fibrosis scoring system, a simple, readily available and, has been corroborated in several studies which give auspicious results.

The BARD fibrosis score is easily calculated, and requires clinical and laboratory parameters such as BMI, fasting blood sugar and AST/ALT ratio. It represents a simple method of assessing the presence of advanced liver fibrosis in NALFD patients [6]. The BARD Fibrosis scoring system has been validated by liver biopsy. A recent study found that the BARD fibrosis score has a negative predictive value (NPV) of 94% [15]. Similar study validated 126 patients with biopsy proven NALFD reported the sensitivity, specificity, PPV and NPV of 88.89, 88.89, 68.57 and 96.70%, respectively [8]. The total possible score ranges from 0-4. In this study, it revealed contrasting BARD fibrosis score across different severity of NAFLD with mean scores of 1.0, 3.3 and 3.6 for grades I (mild), II (moderate) and III (severe) fatty liver disease, respectively. In the study of Harrison *et al*., found high values of NPV (96%) in patients with low BARD score (0-1), which enabled identification of patients without advanced liver fibrosis and a higher score (2–4) was associated with advanced liver fibrosis. The findings of this study are similar with the study of Hussein Ageely, *et al*., which revealed that grade 3 fatty liver disease is associated with high BARD fibrosis score, and hence correlated significantly with advanced fibrosis. Thus, it can deduce in this study that those with grade III fatty liver disease having BARD fibrosis scores of 3-4 are associated with advanced liver fibrosis. The result gathered can be a parameter in the primary health care, since it provides positive data necessary for identification of those patients with NAFLD who require liver biopsy for histologic diagnosis of advanced liver fibrosis and assessment of its severity. Liver biopsy is the most sensitive and specific to establish and assess the degree of inflammatory activity (grading) and extent of fibrosis (staging), but in general it

should be weighed against the small, but not negligible, risk of a various complication. Hence, imaging modalities (ie. Ultrasonogram, computed tomography, magnetic resonance imaging) are now becoming reasonable and acceptable alternative for diagnosing NAFLD.

Literature shown that as the disease progresses from isolated fatty liver disease to NAFLD to cirrhosis, the hemodynamics of the vascular components passing thru the portal triad (portal vein and hepatic artery) also changes, the resistance to the blood flow in these vessels increases secondary to changes occurring in the liver (ex. inflammation, fatty accumulation, inflammation with or without fibrosis) [16-19]. Of the total hepatic blood flow, one third is supplied by the hepatic artery and about two thirds is supplied by portal venous blood [30]. Erdogmus *et al*., and Balci *et al*., hypothesized that the fatty liver infiltration causes increased resistance to the portal vein flow thereby reducing the portal blood flow to the liver. However, some studies disputed this hypothesis. In the study of Oguzkurt *et al*., reported no correlation between the degree of fat infiltration and the hepatic vein waveform pattern. Ehsan Solhjoo *et al*., found no correlation between the severity of fat deposition and portal vein pulsatility index (VPI), Mean flow velocity (MPF), or rate of abnormal hepatic vein waveform patterns. Because of these contrasting findings, the present study opted not to utilize portal vein indices as a variable for assessment of advance liver fibrosis. Interestingly, there are only few studies have correlated the hepatic artery indices with the different grades of severity of the NAFLD. Hence, this study was done to observe whether there is significant hemodynamic changes in the HARI of NAFLD patients and whether the hemodynamic changes correlates with the different severity assessed thru US grading.

In this study, it showed that there is a significant difference in the HARI across different severity of NAFLD. The study revealed that grade III (severe) NAFLD has the lowest mean HARI value (0.53±0.09) when compared to grades II (moderate) and I (mild) yielding 0.76 and 0.81, respectively. Similar findings reported by Tana, *et al*., and Padhmini B, *et al*., showed variations in HARI value of patients with different severity of NAFLD, diagnosed based on ultrasonography. The research investigators concluded that HARI was found to be significantly lower in the NAFLD when compared to healthy group. When compared to the different grading of NAFLD, they found that Grade III (severe) fatty liver disease has the lowest HARI value followed by grade II (moderate) and grade I (mild), on which similar ranking pattern is established to this present study[2, 4]. The usual range of HARI in normal, as well as post-transplant patient, is between 0.55 and 0.80[22]. Surprisingly, among the two studies mentioned previously, this present study documented the lowest HARI value for grade III (severe) NAFLD (vs 0.61±0.10 and 0.61±0.05, respectively). This study when compared to the investigation done by Padhmini B, *et al*. documented a strong negative relationship (r=-0.84) between the Hepatic Artery Resistive Index and Fibrosis Score (vs r=-0.51). The lower value of HARI can be attributed that as the fatty infiltration progresses, it causes increase in resistance to blood flow and as a compensatory, the hepatic artery blood flow increases thereby reducing its HARI[20,23,24]. In this study, the total hepatic blood volume is not estimated because of the intricate visualization of other arteries (ex. Common hepatic artery).

Concordance of HARI and BARD Fibrosis Score in the Assessment of Advanced Liver Fibrosis Among NAFLD Patients

With the use of HARI value thru B-mode technique on ultrasonography, the assessment of advanced liver fibrosis in the course of NAFLD can be established readily. Although its accuracy is not well established because there are no reports that correlated HARI value with the biopsy proven advanced liver fibrosis in the course of NAFLD. Since the BARD Fibrosis scoring system has been validated by liver biopsy, the present study correlated the HARI value with the BARD Fibrosis score in the assessment of advanced fibrosis among NAFLD patients.

This study showed inverse correlation between HARI and BARD fibrosis score (r=-0.84). The HARI of NAFLD in this study with BARD Fibrosis score of 1 to 4 has an average index of 0.84, 0.75, 0.54 and 0.52, respectively. This indicates that yielding a higher BARD Fibrosis score, the HARI equates to a lower value. According to the study of Ageely et.al, a BARD Fibrosis score of 2-4 points

indicate significant liver fibrosis[5]. In this study, the mean HARI value of grade III (severe) NAFLD is 0.53±0.09 with a mean BARD fibrosis score of 3.56. These finding suggest fibrous tissue accumulation and maybe attributed in increased arterial rigidity, and that the different tissue composition of the liver (adipose or fibrous) can influence HARI [2, 4]. The HARI has demonstrated a significant negative correlation with advanced liver fibrosis when correlated with BARD fibrosis score.

The cutoff HARI values may be helpful in the selection of NAFLD patients to undergo liver biopsy for histologic diagnosis of advanced liver fibrosis. Another major benefit of noninvasive ultrasound HARI determination is that the examinations can be readily repeated; a method helpful for the long-term monitoring of liver fibrosis.

Lastly, the study also supports the hypothesis that there are different physiopathological mechanisms influencing the hepatic arterial resistance in the different severity of NAFLD [2, 4]. Thus, this study showed that the conventional Doppler US with hepatic artery indices and laboratory variables can be helpful to detect fibrous tissue accumulation in the course of NAFLD.

LIMITATIONS OF THE STUDY

The present study has three limitations. First, the sample may not be a representation of NAFLD population of the Philippines, since it was conducted in only one tertiary government hospital in Quezon City, Metro Manila, Philippines. This study should be corroborated by larger NAFLD population from other hospital to estimate the prevalence of NAFLD in the country. Second, assessment of fibrous tissue accumulation was done through correlation between HARI and BARD fibrosis score, parameters determined on clinical, laboratory and imaging variables, and not with the histopatholic results. If correlated with the biopsy proven advance liver fibrosis in the course of NAFLD, the cutoff HARI value can be a sole indicator and may integrate in the clinical practice guideline as a non-invasive alterative imaging technique in the assessment for advanced hepatic fibrosis. Thus, treatment plan can be planned to prevent from progression into liver cirrhosis and evaluation of its effectiveness. Lastly, the diagnosis of NAFLD was based on correlation of clinical and ultrasonographic findings. The grading gives an indirect estimation of the quantification of fat deposition in the liver [27]. Radiologist observation is a major variability of US, however, it has been shown to have satisfactory sensitivity and specificity for identifying moderate to severe hepatic steatosis. Though it was not confirmed by liver biopsy, ultrasonography is by far the most common imaging modality of diagnosis NAFLD in clinical practice. Quantification of fat content using CT scan or MRI may be more reliable for estimation of fat deposition in the liver. Quantification of fat using CT and MRI with lipid correlation can be done in the future.

RECOMMENDATIONS

The present study has the following recommendations: First, further studies to look for the exact physiopathological event on hemodynamic changes (ie. Hepatic artery resistive index) like positive feedback mechanism and role of possible mediators, which might be tangled in the proposed increase in hepatic arterial blood flow. These changes might be important for prognosticating advanced hepatic fibrosis in the course of NAFLD because if the cutoff of HARI value when used alone, or in combination with other fibrosis score can detect early cirrhosis with a higher sensitivity and specificity, then it will be a better noninvasive and cost effective method for risk assessment. Second, further studies to look whether medication intake, lifestyle modifications and exercise affects the hemodynamic changes (ie. Hepatic artery resistive index) in hepatic arterial blood flow. HARI can be used as a noninvasive diagnostic value for monitoring treatment response.

Declaration of Conflict of Interests

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