ORIGINAL ARTICLE

Assessing the diagnostic accuracy of radiological and histological findings in the diagnosis of non-alcoholic fatty liver disease stages among patients in a tertiary hospital

Ekpe Edemekong L[1], Emanghe U[2], Ekpe EL[3], Obiora IC[4], Yemiode Itam[5], Akinmola OO[6]

[1]Department of Mass Communication, [2]Department of Medical Microbiology, [3]Department of Chemical Pathology and Immunology, University of Calabar, Calabar, Nigeria, [4]Department of Radiology, University of Calabar Teaching Hospital, Calabar, Nigeria, [5]Department of Biochemistry, University of Calabar, Calabar, Nigeria, [6]Department of Clinical Pathology, Lagos University Teaching Hospital, Lagos, Nigeria

Abstract

Background: Early screening, detection, and early intervention are life-saving modalities to lessen the impact and burden of non-communicable diseases. *Aim and Objectives:* To evaluate the diagnostic strength of ultrasound in the diagnosis of Non-alcoholic Fatty Liver Disease (NAFLD) stages. *Material and Methods:* Participants were recruited from patients with fatty liver who underwent liver biopsy and baseline ultrasound at the University of Calabar Teaching Hospital between January 2023 and December 2023. Ultrasonographic findings were correlated with the histological findings of liver biopsy which was considered the gold standard for the diagnosis of NAFLD. *Results:* One hundred and nine participants were recruited and participated in this study, of which 62 (56.9%) were females and 47(43.1%) were males, with the highest age bracket presenting at 56-65 years. The female-to-male ratio was 1:1.4 and their mean age was 55.5 ± 12.8 years (age range was 18-70 years). The ultrasonographic findings were correlated with histological data (considered as the gold standard). The sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were evaluated. The ultrasonography had a sensitivity of 90.4% (95% Confidence Interval (CI): 83.6-93.6) and a specificity of 72.5% (95% CI: 68.7-79.8). The PPV and NPV were 74.7% and 65.6% respectively. The area under the curve was 84.5%. The positive likelihood ratio was 1.5 (95 CI: 1.21-1.90), and the negative likelihood ratio was 0.30 (0.17-0.54). *Conclusion:* Ultrasound findings were highly significant and useful in detecting advanced or late-stage steatosis in patients with fatty liver. In the future, as technology advances, it is hoped that the need for liver biopsy may not be necessary as hi-tech radiological involvement may help patients with fatty liver without the involvement of any invasive procedure.

Keywords: Sensitivity, Ultrasound, Steatosis, Fatty Liver, Biopsy

Introduction

Non-alcoholic Fatty Liver Disease (NAFLD) is the most common cause of chronic liver disease and is considered to have a global prevalence of 25% [1-2]. It is an emerging Noncommunicable Disease (NCD) [3]. According to the World Health Organization (WHO), mortality rate accounted for by NCDs was 41 million (74%) of all deaths globally in 2019 [4]. Seventy-seven percent (77%) of these deaths occurred in low-and middle-income countries [4]. Early screening, detection, and early intervention are life-saving modalities to lessen the impact and burden of NCD. NAFLD is one of the

common NCDs known for its terminal sequelae, which could be life-threatening. As the name implies, NAFLD is defined as a condition characterized by the presence of hepatic steatosis, not caused by alcohol intake [5]. It is one of the most common causes of chronic liver diseases, and leads to liver cirrhosis and other associated complications if prompt attention is not given to patients on time [6-7]. When examined histologically e.g., in a liver biopsy, excess accumulation of lipids (predominantly triglycerides) is usually evident within the hepatocytes [7]. In some cases, NAFLD may progress from steatosis to Non-alcoholic Steatohepatitis (NASH) (with evidence of inflammation and cell injury), cirrhosis (hepatic fibrosis), and ultimately, liver failure. The diagnosis of NAFLD is mainly derived by excluding alcohol-related hepato-pathology [6].

Liver biopsy remains the gold standard for diagnosing hepatic steatosis however, this has its drawbacks [9]. Liver biopsy has two advantages; accurate diagnosis and its further ability to differentiate NASH from simple hepatic steatosis. Usually, histological diagnosis of fatty liver is graded into different types. However, liver biopsy is observer-dependent and invasive, conveying a non-negligible risk of significant morbidity and mortality among other serious medical complications. The relatively small core size of the biopsy also introduces sampling errors, especially as steatosis is known to be heterogeneous. Due to these limitations, liver biopsy becomes a suboptimal tool for screening, monitoring, and research. For this reason, imaging can be seen as an alternative to liver biopsy in the diagnosis and optimal management of patients with NAFLD. Basic and available conventional techniques for evaluating steatosis include ultrasound, Computed Tomography (CT), Magnetic Resonance (MR) spectroscopy, and Magnetic Resonance Imaging (MRI). This present study aimed to assess and outline the performance and clinical utility of ultrasonography with histological findings of patients with NAFLD presenting at the University of Calabar Teaching Hospital. Imaging and related non-imaging techniques could be used to precisely assess disease markers of liver steatosis and advanced liver fibrosis. The primary objective of this study was to explore adults with biopsy-proven NAFLD, the diagnostic performance, and reliability in comparison with abdominal ultrasonography for predicting histology-determined NAFLD using histologic grade as the reference standard. This study is relevant as there is limited data on the comparative assessment of NAFLD using histology and radiological approaches in our environment.

Furthermore, studies done in this regard have been on Caucasians with little or no emphasis on blacks. Based on these, it is necessary for clinicians to formulate measures to help curb the impact of NAFLD among persons at risk by initiating a local study in this regard. This research assessed the correlation between NAFLD patients diagnosed by ultrasound at the University of Calabar Teaching Hospital (UCTH) and compared with those diagnosed by histology.

Material and Methods

Ethical approval

Ethical approval was obtained from the Health Research Ethics Committee (HREC) of the UCTH (with NHREC/07/10/2012 as UCTH HREC Registration number and UCTH/HREC/33/Vol.111/123 as the HREC protocol assigned number) before carrying out the study. The study was carried out without coercion of participants and a signed

informed consent was obtained from patients and caregivers aged 18-70 years after duly explaining the purpose of the study in simple and clearly understood language.

Study design and population

This study was cross-sectional, with an analytical component. Every recruited subject who presented for this study had a liver biopsy done for histology, to assess those who had an accurate diagnosis of fatty liver. Histological diagnosis of the fatty liver following liver biopsy is considered the gold standard for diagnosis of fatty liver. Patients with absent liver biopsy results were excluded. Furthermore, patients with jaundice, ascites, and altered blood profiles were also excluded if the biopsy was performed for focal lesions or autoimmune liver disease.

Study setting

The study was done in the Radiology and Pathology departments of the UCTH from January 2023 to December 2023. All patients sent to the Radiology Department of UCTH for ultrasound-guided liver biopsy and matching the inclusion and exclusion criteria were included. Relevant socio-demographic data and clinical information from a semi-structured questionnaire were filled in by the researcher or research assistants. The participants then had a complete physical examination. Data was collected about their duration of illness (diabetes mellitus / NAFLD), treatment details, and other related health information. Patients' confidentiality was maintained and held in high esteem.

Anthropometric measurements were taken for each participant and included weight, height (and by extension BMI), and blood pressure. Weight was taken for all categories of patients with fatty liver-lean, normal, or obese participants.

Sample size determination

Sample size was calculated using the Cochran formula for calculating sample size, for a known prevalence rate.

$$n = \frac{Z^2 PQ}{d^2}$$

Where:

n = the desired sample size

z = the standard normal deviation usually set at 1.96 which corresponds to a 95 percent confidence level

p = 0.064 (the proportion in the target population estimated to have Type 2 DM in Nigeria) [10]

q = 0.936 (1-p)

d = degree of accuracy set at 0.05

$$n = \frac{(1.96)^2 \times 0.064 \times 0.936}{0.05^2} = \frac{0.23012}{0.0025} = 95$$

Although the minimum sample size required was 95, we recruited a total of 109 participants for this study.

Liver biopsy and histological examination

Each patient for this study had a liver biopsy done to make a diagnosis of fatty liver based on histology. The liver biopsy was performed under ultrasound guidance by an experienced consultant radiologist, and the findings were interpreted by a hepato-pathologist who was oblivious to the clinical history and presentation of the patient. Non-targeted percutaneous biopsies of the right liver lobe were performed for clinical care using a 16- or 18-gauge needle by hepatologists.

Although biopsies were performed for clinical care, histology slides were reviewed by an expert hepato-pathologist for this research. A consultant pathologist carried out the histological examination of all liver biopsies suspected to have fatty liver.

Blinded to clinical and radiologic data, this hepatopathologist scored steatosis at low-to-medium power using a 4-point ordinal score, as defined by the Nonalcoholic Steatohepatitis Clinical Research Network scoring system. Our study included only patients with biopsy-proven NAFLD and only three steatosis grades (1, 2, and 3) were observed in the study cohort.

Imaging

Patients were asked to fast for a minimum of 4 hours before imaging. Ultrasound examinations were performed on the same day if possible. The same patients who had liver biopsies were made to have an abdominal ultrasound to assess for the presence of fatty liver based on imaging. The essence was to correlate the imaging findings and diagnoses with the histological diagnoses. Though liver biopsy is the gold standard for making a diagnosis of fatty liver, however, because of its associated complications and high cost, it is a lot easier and cheaper to consider radio-imaging for the same diagnostic purpose. Ultrasonography was performed by an experienced radiologist using a 3.5MHz probe Siemens G60S scanning machine, who looked for radiological evidence of hepatic steatosis in each recruited participant. This was further confirmed by another consultant radiologist to ensure certainty of diagnosis with a curved vector array transducer. This transducer has a nominal frequency range of 1–4.5 MHz (in this case 3.5Hz). Scanning was done with the patient in the dorsal decubitus position with the right arm at maximum abduction. The transducer was placed at 90^0 to the liver capsule through the right intercostal approach. The ultrasound beam scattering by fat droplets in steatosis caused more echo signals to return to the transducer, creating the appearance of a "bright" or hyperechoic liver.

Furthermore, fat also attenuates the beam which decreases beam penetration into tissue. This attenuation leads to poor visualization of structures within the steatotic liver parenchyma-such as intrahepatic vessels, bile ducts, and in some cases liver lesions and structures deep into the liver, such as the diaphragm. Thus, the presence of steatosis can be inferred if the liver is too bright and/or if liver structures are blurry or poorly visualized radiologically.

Data analysis

Data were analyzed using SPSS version 20 (Chicago, USA). Quantitative variables like age, height, and BMI had mean and standard deviation calculated. Also, sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were noted for ultrasonographic findings of fatty liver whose diagnosis was already made on histology, which is considered the gold standard.

Results

A total of 109 participants were recruited and participated in this study, of which 62 (56.9%) were females and 47 (43.1%) were males with the highest age bracket presenting at 56-65 years. The female-to-male ratio was 1:1.4 and their mean age was 55.5 ± 12.8 years (age range was 18-70 years). The ultrasonographic findings were correlated with histological data (considered as the gold standard). The ultrasonography had a sensitivity of 85.4% (95% CI: 83.6-93.6) and specificity of 72.5% (95% CI: 68.7-79.8) (Figure 1). The PPV and NPV were 74.7% and 65.6% respectively. The area under the curve was 84.5%. The positive likelihood ratio was 1.5 (95CI:1.21-1.90), and the negative likelihood ratio was 0.30 (0.17-0.54).

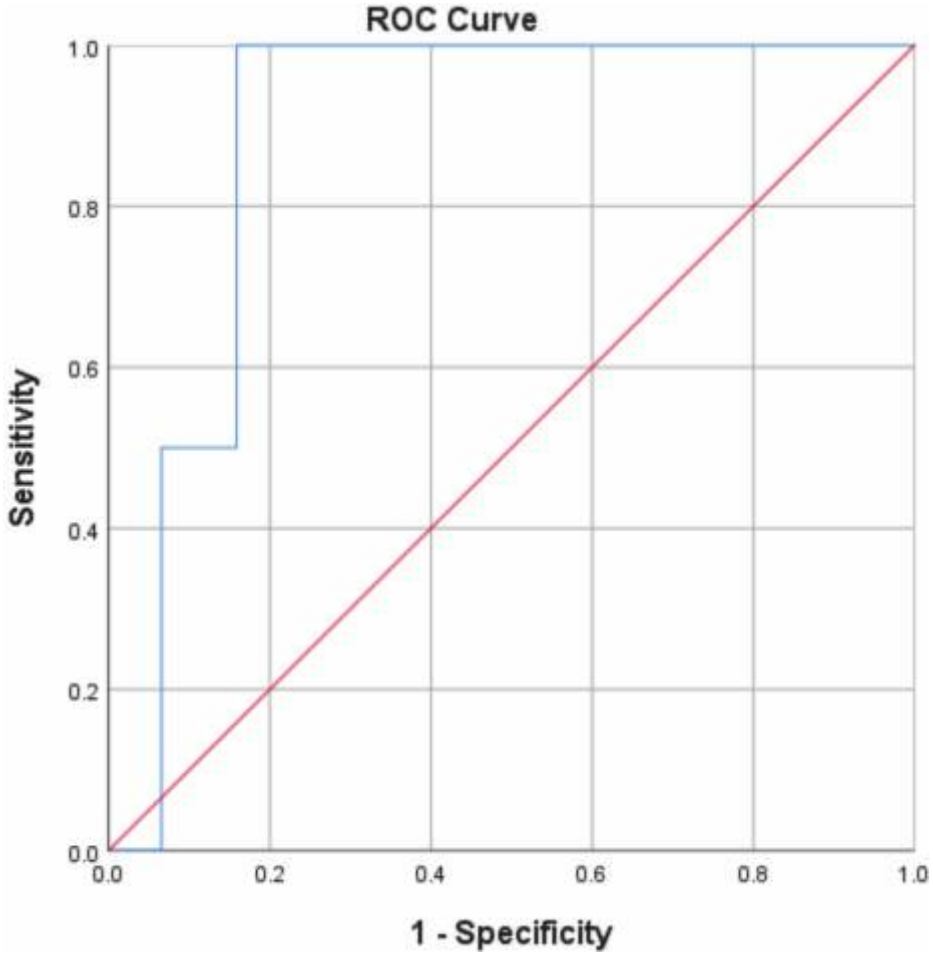

Figure 1: Receiver operating characteristic (ROC) curve for ultrasonography

Discussion

NAFLD is the most common cause of chronic liver disease in Western countries with prevalence ranging from 20% to 40% [2, 5, 11-12]. It encompasses a histological spectrum that ranges from simple steatosis to steatohepatitis, which can progress to cirrhosis in up to 20% of patients. The diagnosis of fatty liver is usually a diagnosis of exclusion. NAFLD is diagnosed by the presence of steatosis in ⩾ 5% of the hepatocytes in the absence of other liver diseases. Other causes of hepatic steatosis, systemic diseases, pancreatic diseases, effects of drugs, congenital abnormalities, and iatrogenic causes have to be ruled out [13-15]. The diagnosis of NAFLD is confirmed by the presence of hepatic steatosis seen on abdominal ultrasound assessment and the exclusion of significant alcohol (defined as alcohol intake less than 30 g/day in men and less than 20 g/day in women ingestion in susceptible patients) and the presence of hepatic steatosis on ultrasound evaluation [16].

Liver biopsy is also the hallmark for assessing the severity of the NAFLD. Grades of fatty liver severity can be assessed by liver biopsy under histological examination. However, radiological findings

are unable to express features that suggest similar diagnoses with high sensitivity as evidenced in this and other research [17].

Sadly, accurate non-invasive modalities for diagnosing NASH and monitoring disease progression or regression are rare to come by. This has placed liver biopsy to remain the gold standard in diagnosing NAFLD. This procedure is not without associated risks and sampling errors. Since liver biopsy cannot be performed as a screening method to detect NAFLD in the general population, abdominal ultrasonography as a noninvasive modality has been widely used. Abdominal ultrasonography has been shown to have a sensitivity of 60-94% and specificity of 84-95% for detecting fatty liver. This study obtained a high sensitivity which tallies with the works of other researchers who found 92% sensitivity and 100% specificity [18-20]. High diagnostic accuracy in correlating ultrasonography with histology has been obtained from various other studies [21-23]. The inability of ultrasonography to distinguish different forms of NAFLD and staging hepatic fibrosis limits the use of ultrasonography as a stand-alone investigation for detecting NAFLD [24-25].

Although liver biopsy remains the gold standard for diagnosis, its limitations have already been stressed necessitating the use of imaging modalities. However, a major limitation of radiological diagnosis is the inability to distinguish between simple steatosis and steatohepatitis. In the future, serum markers together with advancements in imaging modalities may potentially diminish or obviate the need for liver biopsy. It is hoped that the best diagnostic approach for patients with NAFLD may be abdominal ultrasonography and potentially replace the necessity for liver biopsy in most patients just as other researchers [26-30]. In this study, it was observed that the weight of the individual patients (lean, obese, or normal) did not affect the final result outcome. This study differs from other studies in that this study was done among blacks with fatty livers as against those done in Caucasians. More so, this study further stressed the fact that the histological grade of the liver pathology determines its ability to be picked up on radiological imaging as agreed by other researchers [18, 25-27]. So, ultrasonography is an important non-invasive tool in the assessment of NAFLD.

Normal or grade 1 hepatic echogenicity can soundly exclude histological NAFLD and obviate the need for liver biopsy.

Limitations

Ultrasound performs best at detecting liver steatosis when there are no other associated liver diseases; however, it remains relatively insensitive to the detection of fatty liver at the early stage. Despite its many limitations, it may be reasonable to use ultrasound in the appropriate clinical setting as an initial screen for steatosis, though it is not suitable for clinical trials.

Conclusion

The use of ultrasonography of the liver to assess for NAFLD has high diagnostic accuracy as a valuable diagnostic tool in resource-poor environments. It makes the process of diagnosing NAFLD easier thereby bringing early attention of physicians. This may help in cutting off the anticipated delay usually occasioned by tissue processing demands from biopsy for histology.

References

1. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, *et al*. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; 40(6):1387-1395.
2. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; 64(1):73-84.
3. Suk KT, Kim DJ. Staging of liver fibrosis or cirrhosis: The role of hepatic venous pressure gradient measurement. *World J Hepatol* 2015; 7(3): 607-615.
4. WHO STEPS Surveillance Manual, Part 3, Data Collection, Section 5: Collecting Step 2 Data: Physical measurements (online) Available: http://cdn.who.int/media/docs/default-source/ncd-surveillance/steps/part3-section5.pdf?sfvn=a46653c72 [Accessed 28 April 2023]
5. Bhatt HB, Smith RJ. Fatty liver disease in diabetes mellitus. *Hepatobiliary Surg Nutr* 2015; 4(2):101-108.
6. Takahashi Y, Fukusato T. Histopathology of non-alcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol* 2014; 20(42):15539-15548.
7. Marušić M, Paić M, Knobloch M, LiberatiPršo AM. NAFLD, Insulin Resistance, and Diabetes Mellitus Type 2. *Can J Gastroenterol Hepatol* 2021;2021: 6613827.
8. Zhang JZ, Cai JJ, Yu Y, She ZG, Li H. Nonalcoholic fatty liver disease: An update on the diagnosis. *Gene Expr* 2019; 19(3):187-198.
9. Sumida Y, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol* 2014, 20(2):475-85.
10. Akinkugbe O.O(Ed.). The non-communicable diseases in Nigeria-Report of the National Survey, Ibadan, Nigeria: Intec printers;1997
11. Goyal A, Arora H, Arora S. Prevalence of fatty liver in metabolic syndrome *J Family Med Prim Care* 2020; 9(7):3246-3250.
12. Teng ML, Ng CH, Huang DQ, Chan KE, Tan DJ, Lim WH, *et al*. Global incidence and prevalence of nonalcoholic fatty liver disease. *Clin Mol Hepatol* 2023; 29(Suppl): S32-S42.
13. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; 34(3):274-285.
14. Liebe R, Esposito I, Bock HH, Vom Dahl S, Stindt J, Baumann U, *et al*. Diagnosis and management of secondary causes of steatohepatitis. *J Hepatol* 2021; 74(6):1455-1471.
15. Patel V, Sanyal AJ. Drug-induced steatohepatitis. *Clin Liver Dis* 2013;17(4):533-546
16. Nassir F, Rector RS, Hammoud GM, Ibdah JA. Pathogenesis and prevention of hepatic steatosis. *Gastroenterol Hepatol (N Y)* 2015; 11(3):167-175.
17. Obika M, Noguchi H. Diagnosis and evaluation of nonalcoholic fatty liver disease. *Exp Diabetes Res* 2012; 2012: 145754.
18. Chen YY, Yeh MM. Non-alcoholic fatty liver disease: A review with clinical and pathological correlation. *J Formos Med Assoc* 2021; 120(1 Pt 1):68-77.
19. Jang JK, Choi SH, Lee JS, Kim SY, Lee SS, Kim KW. Accuracy of the ultrasound attenuation coefficient for the evaluation of hepatic steatosis: a systematic review and meta-analysis of prospective studies. *Ultrasonography* 2022;41(1):83-92.
20. Martinou E, Pericleous M, Stefanova I, Kaur V, Angelidi AM. Diagnostic modalities of non-alcoholic fatty liver disease: From biochemical biomarkers to multi-omics non-invasive approaches. *Diagnostics (Basel)* 2022;12(2):407.
21. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, *et al*. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology* 2011; 54(3):1082-1090.
22. Paul J. Recent advances in non-invasive diagnosis and medical management of non-alcoholic fatty liver disease in adults. *Egypt Liver J* 2022;10(37).
23. Baisakh P, Baisakh MR, Kumari BS, Mohanty BB, Panda DK, Pradhan S. Diagnostic accuracy of ultrasonography-guided fine needle aspiration cytology in abdominopelvic masses: A prospective study. *Cureus* 2023;30:5(6): e41228.
24. Ahmed M, Diggory R. The correlation between ultrasonography and histology in the search for gallstones. *Ann R Coll Surg Engl* 2011; 93(1):81-83.

25. Petzold G. Role of ultrasound methods for the assessment of NAFLD. *J Clin Med* 2012; 11(15):4581.
26. Polukchi TV, Slavo YA. Assessment of cognitive impairment in patients with chronic viral hepatitis. *J Krishna Inst Med Sci Univ* 2023; 12(2):65-73.
27. Dwivedi A, Choudhary S, Trehan V, Yadav N, Kanth L. Large pseudocyst of the adrenal gland radiological pathological correlation. *J Krishna Inst Med Sci Univ* 2017; 6(1):112-116.
28. Sachdeo M, Devi NP, Vijayalaskmi D, Prabhu E, Shanmugam, Shankar R. High prevalence of metabolic syndrome among outpatients in tertiary care. *J Krishna Inst Med Sci Univ* 2019; 8(1): 52-60.
29. Ravibabu K, Prakash JR, Adepu V. Association of the risk factors with insulin resistance/severity biomarkers among manufacturing industry workers. *J Krishna Inst Med Sci Univ* 2020; 9(2): 9-21.
30. Basumatary TK, Begum RH, Bose M, Kalita MP, Bose SS. Alcohol metabolizing gene polymorphisms as genetic biomarkers of alcoholic liver disease susceptibility and severity: A Northeast India patient-based study. *J Krishna Inst Med Sci Univ* 2017; 8(1): 62-75.

Author for Correspondence:
Dr. Ekpe Edemekong L, Department of Mass Communication, University of Calabar, Calabar, Nigeria
Email: edemekong@unical.edu.ng
Cell: +2348036022953

How to cite this article:
Ekpe EL, Emanghe U, Ekpe EL, Obiora IC, Yemiode I, Akinmola OO. Assessing the diagnostic accuracy of radiological and histological findings in the diagnosis of non-alcoholic fatty liver diseases stages among patients in a tertiary hospital. *J Krishna Inst Med Sci Univ* 2024; 13(3):90-97.

Submitted: *10-Apr-2024* ***Accepted:*** *10-June-2024* ***Published:*** *01-July-2024*