Original Article

ISSN (0): 2347-338X; ISSN (P): 2347-3371

Grading Of Fatty Liver on Ultrasound and Its Correlation with Lipid Profile and Liver Enzymes

Anand K[1], Amulya Sundari V[1], Ashok Kumar[1]

[1]Department of Radio- diagnosis, Ramaiah Medical College, Bengaluru.

Abstract

Background: To correlate the grades of fatty liver on ultrasound with degree of alterations in lipid profile and liver enzymes. **Subjects and Methods:** The prospective, analytical observational study was conducted at a super specialty hospital based in south India in 122 patients diagnosed with fatty liver. The subjects underwent ultrasonography, and lipid profile and liver enzyme tests as a part of clinical evaluation. Those with positive viral markers and on drugs altering the various biochemical parameters were excluded. A radiologist graded the fatty liver into 3 grades- grade I, II and III using the visual grading system. Statistical analyses were carried out to determine the correlation between the grades of fatty liver and alterations in lipid profile and liver enzymes. **Results:** Out of the 122 selected participants, 51 subjects were categorizedas grade I, 63 as grade II and 8 as grade III fatty liver. There was statistically significant variation in AST, ALT and GGT among different grades (P value < 0.05).However, no significant variation in the BMI was found among patients with different grades of fatty liver. **Conclusion:** The increase in serum levels of AST, ALT, and GGT concentrations with the increase in the grades of fatty liver by ultrasonography might be useful in predicting the inflammation and progression of the disease. This preliminary finding may be useful for developing a non-invasive method for early diagnosis and predicting the disease prognosis.

Keywords: Fatty Liver, Lipid Profile, Ultrasound.

Corresponding Author: Dr. Anand K, Department Department of Radio- diagnosis, Ramaiah Medical College, Bengaluru.

Received: August 2019
Accepted: August 2019

Introduction

Fatty liver is a condition defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver (> 5% of hepatocytes histologically).[1] It comprises of a wide spectrum of conditions that involve accumulation of triglycerides in the cytoplasm of hepatocytes. A variety of clinical disorders is associated with diffuse fatty liver including obesity, malnutrition, diabetes mellitus, steroid use, alcoholic liver disease, pregnancy and hepatitis. It has emerged as a major health problem in developing as well as developed countries. Non-alcoholic fatty liver disease (NAFLD) has been identified as an independent risk factor for cirrhosis, hepatic cancer, chronic kidney disease, type 2 diabetes mellitus, cardiovascular disease and all-cause mortality. NAFLD is associated with substantial economic and healthcare burden.[2] Non-alcoholic steato hepatitis (NASH),a subtype of NAFLD, can progress to hepato cellular carcinoma, cirrhosis, liver transplantation, and mortality.[3,4]A 2010-2014 comprehensive estimate of 4 major liver diseases has reported fatty liver diseases as themajor cause for liver fibrosis in global north countries. In addition, an estimate of 15 years has demonstrated a substantial increase in the morbidity due to alcohol-associated liver disease in Europe and USA.[5] A 2017 study has reported a stark increase in global prevalence of NAFLD of around one billion, with Asian countries heading the rise.[6]

Early diagnosis and treatment of fatty liver is paramount to reduce the disease burden and associated morbidity. Though liver biopsy has been considered as the gold standard for diagnosing fatty liver, it is a painful and invasive procedure associated with the development of rare life-threatening complications like bleeding. Moreover, there is an ardent need for simple non-invasive markers of fatty liver disease, for the early diagnosis and prompt disease management.[7] The present study is intended to correlate and compare different grades of fatty liver on ultrasonography with degree of alterations in lipid profile and liver enzymes.

Subjects and Methods

The prospective, analytical observational study was carried out at a super specialty hospital based in south India between November 2014 to April 2016.Ethics committee approval was duly taken prior to the initiation of research. The study recruited patients undergoing ultrasound, lipid profile and liver enzyme tests as a part of their clinical evaluation for fatty liver. Patients with viral hepatitis and those on drugs (especially statins), which may alter lipid profile and liver enzyme levels, were excluded. A part from demographic characteristics and medication history, data pertaining to the following parameters were collected from all the participants: total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), as partate amino transferase (AST), alanine amino transferase (ALT)and gamma-glutamyl transferase (GGT).All the ultrasound examinations were performed on GE Voluson pro series, Philips HD 11, Siemens ACUSON 400 ultrasound using parasagittal, subcostal and intercostal transducer positions with a convex probe (3-5 MHz) and HI (harmonic imaging) in ON mode.[8] The diagnosis of fatty liver on ultrasound was made on the basis ofthe following characteristic sonographic features: increased echogenicity of liver, increased liver contrast compared to kidney, vascular blurring (mainly of portal veins),and attenuation of echogenic level in deep-seated area.[10,11]The following grading patterns were used by a radiologist for the classification of fatty liver on ultrasound:[1,4,9,10]

Grade 1

Fatty liver with increased liver echogenicity compared to the kidney.

Grade 2

Fatty liver in which echogenic liver obscures the echogenic walls of the portal venous branches.

Grade 3

Fatty liver in which the increased liver echogenicity obscures the diaphragmatic outline

Demographic characteristics, lipid profile and the liver enzymes of the subjects were correlated and compared with the grades of fatty liver. The data was analyzed using SPSS software version 18.0 (IBM, Somers, NY).

Analysis of variance (ANOVA) was performed for the co mparisons of BMI andKruskal Wallis test for comparing clinical parameters with different grades of fatty liver. ROC curve analysis was carried out to determine the sensitivity and specificity for the cut-off values of AST, ALT, and GGT in differentiating mild(grade I) and moderate to severe (grade II to III) fatty liver.

Results

The study involved 122 participants between the age group of 26 and 82 years, with a mean age of 49.9 years. The male to female ratio noted was 1: 0.03 with increased male preponderance across all the age groups. Maximum number of study participants belonged to the age group of 41-50 years. Hence, majority of the patient population who had undergone US for fatty liver were middle-aged adult males.

The number of subjects with grade I, II and III fatty liver were 51 (41.8%) 63 (51.6 %) and 8 (6.8 %) respectively. There was no significant variation in the distribution of grades among males, females and different age groups. The mean BMI noted in the respective groups were 26.4, 27.3 and 27.3. No significant variation in the BMI was noted among patients with different grades of fatty liver [Table 1].

Table 1: Mean, median and standard deviation noted for different clinical and demographic parameters across the three grades of fatty liver

USG GRADE		BMI	LIVERSIZE	AST	ALT	AST/ALT	GGT	ALP	HDL	LDL	VLDL	TG	TOT CHO	TOT CHO/HDL
I	Mean	26.88	14.28	25.5353	42.67	0.80	39.67	88.38	38.99	118.3	31.89	181.2	182.6	6.374
	Median	26.40	14.20	23.30	39.00	0.60	29.50	87.60	37.00	116.5	30.40	153.0	183.0	4.700
	Std. Deviation	3.745	1.48	12.83	23.82	1.09	26.86	30.82	10.62	31.20	14.00	106.5	50.42	11.06
	Minimum	22	11	8.60	12.00	0.20	14.30	39.00	18.30	42.00	0.00	65.00	89.10	1.40
	Maximum	41	18	81.20	162.9	6.00	159.7	223.0	79.00	213.0	69.00	670.0	411.0	83.00
II	Mean	27.46	14.35	34.26	65.73	0.56	46.0	95.8	38.2	118.2	27.29	170.8	182.6	5.07
	Median	27.30	14.30	26.80	51.40	0.50	37.00	95.00	37.20	115.8	26.00	146.0	176.0	4.70
	Std. Deviation	3.85	1.40	31.53	80.38	0.33	29.81	25.42	8.89	31.80	10.9	119.0	55.12	2.66
	Minimum	22	11	11.70	11.00	0.18	14.00	43.00	20.00	67.00	0.00	47.00	84.80	2.20
	Maximum	44	18	201.0	650.0	2.07	173.0	161.7	60.00	178.0	53.80	719.0	462.0	23.00
III	Mean	29.48	14.95	32.07	43.40	.50	52.31	89.15	36.57	115.4	25.97	159.7	167.4	4.73
	Median	27.35	14.55	32.20	46.95	0.49	46.90	87.30	35.30	113.8	29.60	150.5	167.5	4.450
	Std. Deviation	5.83	1.96	7.00	15.54	0.17	18.34	22.17	8.99	31.50	5.47	88.26	33.19	1.22

Due to the skewed distribution of various biochemical parameters, median was taken as standard for comparison among different ultrasound grades. Statistically significant difference was noted between the median values of AST, ALT and GGT across different grades [Table 2].

Table 2: Comparison of various parameters across different fatty liver grades

Parameters	BMI	LIVER SIZE	AST	ALT	AST/ALT	GGT	ALP	HDL	VLDL	TG	TOT CHO	TOT CHO/HDL	LDL
P value	0.225	0.741	0.024	0.003	0.245	0.020	0.171	0.775	0.229	0.534	0.6	0.960	0.679

For subgroup analysis, the USG grades were revised and changed to ‘mild’, ‘moderate’ and ‘severe’ groups. The mild group consisted of participants with ‘mild’ fatty infiltration (grade 1) at ultrasonography and the ‘moderate to severe’ group consisted of those with either moderate or severe fatty infiltration (grade 2 or 3) at ultrasonography.
The optimal cutoff value was calculated through the contact point of the ROC curve and the line with slope equal to one in which the sum of sensitivity and specificity was the highest. The cutoff values of 25.5, 43.5.5, and 38.5 mg/dL for AST, ALT, and GGT demonstrated sensitivity of 60%, 63%, and 63% and specificity of 60%, 70% ,and 53% respectively in differentiating mild(grade I) and moderate to severe (grade II to III) fatty liver [Figure-1].

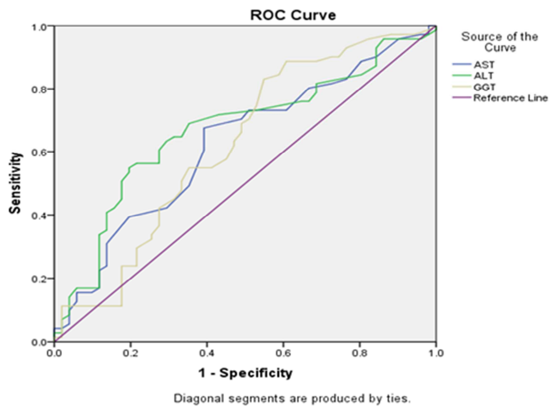

Figure 1: ROC curve demonstrating the sensitivity and specificity for the cut-off values of AST, ALT, and GGT

Discussion

Fatty liver has emerged as the most common liver problem worldwide and the disease prevalence in India is estimated to be as high as 15%-30%.[7]Despitethe increased prevalence, there is ambiguity regarding the biochemical profile of these patients. The current study, with an adequate sample size, has attempted to correlate serum parameters with grades of fatty liver at ultrasonography. Majority of the patient population, who had fatty liver on ultrasound, comprised of middle-aged adult males. This is in compliance with study by Leite et al., which has noted increased prevalence of fatty liver in middle-aged males[12,13]In the present study, mean BMI value did not vary significantly among different grades of fatty liver. The mean BMI noted for grade I, II and III were 26.4, 27.3 and 27.3 respectively. The median age of cohort of patients noted byDuseja et al. was 34 (17-58) years and the BMInoted was similar to the current study (26.7 (21.3-32.5) kg/$m^{2)}$ and 90% (46) were males.[14]
There is no clinically validated parameter, biomarker or panel marker for the diagnosis of fatty lever, especially during the early stages.[15]However, anthropometric measures like BMI and waist-to-hip ratio are foundto be useful by certain studies.[16] BMI was previously considered as an important determinant for the severity of insulin resistance. A 2011study involving 306 patients undergoing fat protocol CT scans has demonstrated a correlation between fatty infiltration of the liver and abdominal fat. The correlation was more significant with visceral fat than subcutaneous fat.[16]In stark contrast, the present study has not found any variation in BMI with different grades of fatty liver. Moreover, the study has not evaluated the association with total body fat content.
Ultrasonographic grading is based on the visual grading system and can identify the extent and severity of liver disease. This system has limitations and the major one is overlap between the ultrasonographic grades. Sometimes patients with borderline ultrasonographic findings of moderate or severe might be misclassified to either of the group.The results of the current study could be deemed as more accurate and reliable, since a radiologist performed the liver ultrasonography, and not a sonologist.
Sometimes the distribution of accumulated fat in the liver is not homogenous and a localized fatty change may masquerade as hepatic lesion. The sensitivity and specificity of ultrasonography in detecting fatty liver is comparatively lesser in obese patients. Ultrasound is operator dependent and has inability to detect small changesin liver fat content on serial scans.[14] In the present study, most of the patients had grade II fatty liver. Whereas, across-sectional study by Mohsen et al. has classified majority of the patients with NAFLD into grade I fatty liver (mild fatty liver disease). This difference could be attributed to the diversity in study population.[17]
In the presentstudy,15% of patients had lipid profile and liver enzyme values were within the normal limits. No correlation was found between lipid profile, serum ALP and the grades of fatty liver. Serum AST, ALT andGGT varied significantly with severity of fatty liver (among different grades) at ultrasonography. The present findings are similar tothestudy by Nimer et al. The most common enzyme abnormalities noted by the researchers were elevated serum ALT (47%) and GGT (45%). They also stated that majority of the patients with fatty liver had hypertriglyceridemia.[18]
Sanyal et al.have reported that fatty liver was significantly associated with higher ALT and GGT, but not ALP levels in patients with impaired glucose toleranceand T2DM. ALT and GGT were significant correlated with waist circumference, body mass index, fasting insulin, homeostatic model assessment- insulin resistance, fasting blood glucose, high density lipoprotein cholesterol, and triglyceride.[19]
Hamaguchi et al.have found that the abdominal ultrasonography scoring system was associated with the presence of metabolic syndrome components[20]Rafeey et al. have concluded that the severity of fatty liver at liver ultrasonography was correlated with elevated ALT, AST, and total cholesterol, and not with fasting blood sugarand TG.

[21]The controversy in the association of USG staging with serum parameters in some of the previous studies might be due to inter-observer variability bias or limitations of the visual scaling system in grading the severity of liver involvement at ultrasonography.

Subgroup analysis (post-hoc tests) in the present study showed no statistically significant difference between the laboratory values of various components of lipid profile upon comparing the different ultrasound grades. Large body of evidence indicate that increased TG and decreased HDL levels are associated with severity of fatty liver. However, in the present study, the USG grades of fatty liver did not correlate with increased levels of TG and decreased levels of HDL.

Serum ALP was not associated with the severity of f atty infiltration at ultrasonography. This finding was in line with the results of Altlparmak et al.[22] Total cholesterol and LDL alone cannot be considered as indicators of insulin resistance, whereas oxidized LDL is proposed to be a better measure. Considering this fact, correlation between ultrasonographic grading and total cholesterol and LDL noted in this study is justifiable. High sensitivity C-reactive protein, pentraxin 3, interleukin 6, cytokeratin 18 and tissue polypeptide-specific antigen are the recently unveiled serum biomarkers that may assist in diagnosis and predicting the response to treatment for fatty liver.[23]

The present study has several limitations. Though the required sample size was achieved, total number of cases evaluated was lesser than some of the other reported studies. Distribution of patients in this study among various grades was non-uniform with only 8 cases having grade III fatty liver. Despite using appropriate tests for statistical analysis to overcome this limitation (non-parametric distribution), the probability of bias cannot be ruled out. Visual grading of fatty liver is subjective with overlap between the grades. The lack of liver biopsy is another main limitation of this study and the findings could not be confirmed histologically.

In conclusion, serum AST, ALT, and GGT concentra tions showed statistically significant increase with increasing grade of fatty liver. Since AST and ALT are intracellular enzymes, their increase might predict the progression of disease in patient with fatty liver. Further investigations are recommended for the development of non-invasive methods like newer laboratory biomarkers and advanced imaging techniques to determine the extent of fatty liver disease and the early diagnosis of the disease, which may alter the natural course of the disease and halt progression.

Conclusion

This study showed a significant positive correlation between transrectal ultrasound prostate volume measurements and serum prostate specific antigen concentration in patients with prostate enlargement.

Therefore, in the absence of reliable direct biochemical measurement of serum prostate specific antigen concentration, sonographic measurement of transrectal prostate volume is a very valuable tool

References

1. LaBrecque D, Abbas Z, Anania F, Ferenci P, Khan A, Goh K et al. World Gastroenterology Organisation Global Guidelines. Journal of Clinical Gastroenterology. J Clin Gastroenterol. 2014 Jul;48(6):467-73.
2. Health and Economic Burden of Nonalcoholic Fatty Liver Disease in the United States and Its Impact on Veterans [Internet]. [cited 2019 Jun 7]. Available from: https://www.mdedge.com/fedprac/article/192463/mixed topics/health-and-economic-burden-nonalcoholic-fatty-liver-disease
3. Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. J Hepatol. 2019 Mar;70(3):531–44.
4. Gao B and Bataller R. Re Alcoholic Liver Disease: Pathogenesis and New Therapeutic Targets views in basic and clinical gastroenterology and hepatology; Gastroenterology. 2011 Nov; 141(5): 1572–1585.
5. Ndugga N, Lightbourne TG, Javaherian K, Cabezas J, Verma N, Barritt AS. Disparities between research attention and burden in liver diseases: implications on uneven advances in pharmacological therapies in Europe and the USA. BMJ Open. 2017; 7(3): e013620.
6. Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A5. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J Gastroenterol. 2017 Dec 21;23(47):8263-8276
7. Mahaling DU, Basavaraj MM, Bika AJ. Comparison of lipid profile in different grades of non-alcoholic fatty liver disease diagnosed on ultrasound. Asian Pac J Trop Biomed. 2013 Nov;3(11):907–12.
8. Dietrich CF, Serra C, JedrzejczyM3. Ultrasound of the liver; European Course Book. [cited 2019 June 6]. Available from: http://www.kosmos-host.co.uk/efsumb-ecb/coursebook-ultrasoundliver_ch02.pdf
9. Ultrasound of liver protocol. Ultrasoundpaedia. [Internet]. [cited 2019 Jun 7]. Available from: https://www.ultrasoundpaedia.com/normal-liver2/ Lupşor-Platon M, Stefănescu H, Mureşan D, Florea M, Szász ME, Maniu A, Badea R. Noninvasive assessment of liver steatosis using ultrasound methods; Med Ultrason 2014, Vol. 16, no. 3, 236-245
10. Singh D, Das CJ, Baruah MP. Imaging of non alcoholic fatty liver disease: A road less travelled; Indian Journal of Endocrinology and Metabolism / Nov-Dec 2013 / Vol 17 | Issue 6
11. Mottin CC, Moretto M, Padoin AV, Swarowsky AM, Toneto MG, Glock L, et al. The role of ultrasound in the diagnosis of hepatic st eatosis in morbidly obese patients. Obes Surg 2004;14:635-637.
12. Leite NC, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. Liver Int 2009;29:113-119.
13. Duseja A. Nonalcoholic fatty liver disease in India a lot done, yet more required. Indian J Gastroenterol. 2010 Nov;29(6):217-25
14. Obika M and Noguchi H. Diagnosis and Evaluation of Nonalcoholic Fatty Liver Disease. Exp Diabetes Res. 2012; 2012: 145754.
15. Jang S, Lee CH, Choi KM, Lee J, Choi JW, Kim KA. Correlation of fatty liver and abdominal fat distribution using a simple fat computed tomography protocol. World J Gastroenterol. 2011 Jul 28; 17(28): 3335–3341.
16. Razavizade M, Jamali R, Arj A, Talari H. Serum parameters predict the severity of ultrasonographic findings in non-alcoholic fatty liver disease. HepatobiliaryPancreat Dis Int. 2012 Oct;11(5):513-20.
17. Assy N, Kaita K, Mymin D, Levy C, Rosser B, Minuk G. Fatty Infiltration of Liver in Hyperlipidemic Patients. Dig Dis Sci. 2000 Oct;45(10):1929-34.
18. Sanyal D, Mukherjee P, Raychaudhuri M, Ghosh S, Mukherjee S, Chowdhury S. Profile of liver enzymes in non-alcoholic fatty liver disease in patients with impaired glucose tolerance and newly detected untreated type 2 diabetes. Indian Journal of Endocrinology and Metabolism. 2015;19(5):597-601.

19. Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, et al. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol 2007;102:2708-2715.
20. Rafeey M, Mortazavi F, Mogaddasi N, Robabeh G, Ghaffari S, Has ani A. Fatty liver in children. The Clin Risk Manag 2009;5:371-374.
21. Altlparmak E, Koklu S, Yalinkilic M, Yuksel O, Cicek B, Kayacetin E, et al. Viral and host causes of fatty liver in chronic hepatitis B. World J Gastroenterol 2005;11:3056-3059.
22. Joy D, Thava VR, Scott BB. Diagnosis of fatty liver disease: is bio psy necessary? Eur J Gastroenterol Hepatol 2003;15:539- 543.

How to cite this article: Anand K, Sundari AV, Kumar A. Grading Of Fatty Liver on Ultrasound and Its Correlation with Lipid Profile and Liver Enzymes. Asian J. Med. Radiol. Res. 2019;7(2):61-65.
DOI: dx.doi.org/10.21276/ajmrr.2019.7.2.14

Source of Support: Nil, **Conflict of Interest:** None declared.