ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 7, Issue – 2, April - 2024, Page No. : 28 – 35

Differential diagnosis between alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) by using ultrasonography (USG), ALD/ NAFLD index (ANI) and Gammaglutamyl transferase (GGT)

[1]Jyoti Shardhul, Ph.D. Student, Department of Biochemistry, D Y Patil Deemed to be University School of Medicine, Nerul, Navi Mumbai, India.

[2]Snehagandha Satale, Assistant Professor, Department of Radiology, Terna Medical College, Navi Mumbai.

[3]Sanjaykumar Satale, Consultant Physician, Fortis, Vashi, Kokilaben Ambani Hospital Koparkhairane and Apollo Hospital CBD Belapur, Navi Mumbai.

[4]Yash Madhavi, Student of MBBS, D Y Patil Deemed to be University School of Medicine, Navi Mumbai.

[5]Siddhi Dhamal, Student of Bachelor of MLT, D Y Patil Deemed to be University Navi Mumbai.

[6]Deepali Vidhate, Professor, Department of Biochemistry, D Y Patil Deemed to be University School of Medicine, Nerul, Navi Mumbai, India.

Corresponding Author: Deepali Vidhate, Professor, Department of Biochemistry, D Y Patil Deemed to be University School of Medicine, Nerul, Navi Mumbai, India.

How to citation this article: Jyoti Shardhul, Snehagandha Satale, Sanjaykumar Satale, Yash Madhavi, Siddhi Dhamal, Deepali Vidhate, "Differential diagnosis between alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) by using ultrasonography (USG), ALD/ NAFLD index (ANI) and Gammaglutamyl transferase (GGT)", IJMACR- April - 2024, Volume – 7, Issue - 2, P. No. 28 – 35.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Incidence of fatty liver is one of the alarming sign for global population. In India also it is increasing in all ages. Sedentary lifestyle, changed food habits and excessive intake of alcoholic beverages are some of the main causes. The differential diagnosis is one of the crucial factors in Fatty liver. The aim of the study is to evaluate responsiveness of the alcoholic liver disease (ALD)/non-alcoholic fatty liver disease (NAFLD) index (ANI) for differentiating the ALD in patients with liver steatosis from NAFLD, and to evaluate role of γ-glutamyl transferase (GGT) with ANI in enhancing the accuracy of diagnosis in Indian population.

Methods: A total 244 cases ALD (120) and NAFLD (124) were included in the current study. The ANI was calculated by using sex, height, weight, hepatic transaminases (AST, ALT) and mean corpuscular volume (MCV). These parameters and ANI indices were

statistically analyzed using IBM-SPSS 23, using appropriate statistical methods.

Results: The study observed a high value of ANI in patients with ALD as compared to NAFLD participants (11.58 ± 43.21/ –3.06± 1.45, $p < 0.001$). It was reported that transaminases (AST and ALT), MCV, and GGT were increased in ALD than NAFLD.

Conclusions: It was concluded that ANI was one of the better indicator for ALD diagnosis and further it was observed that when consideration serum GGT levels with ANI definitely improve its utility in differential diagnosis between ALD from NAFLD,

Keywords: ALD/NAFLD index, Gamma-glutamyl transferase, Liver diseases, alcoholic, Non-alcoholic fatty liver disease.

Introduction

Excessive hepatic fat buildup is a characteristic of nonalcoholic fatty liver disease. Without fatty liver ultrasound pictures or other abnormal liver enzyme values, increased gamma-glutamyl transferase (GGT) levels. It's unclear, though, if these people have a higher chance of getting fatty liver. We examined the risk variables and rates of fatty liver change between people with regularly increased GGT concentration annd with normal levels of GGT.

Excessive deposition of hepatic fat, as determined by imaging following the proper exclusion of other liver illnesses, such as alcoholic liver disease, is the hallmark of non-alcoholic fatty liver disease (NAFLD). Modification in lifestyle has caused a sharp rise in the prevalence of obesity and related disorders, which in turn raised the chances of non-alcoholic fatty liver disease [1, 2, 3]. Changes in the fatty liver are a significant indicator of non-alcoholic fatty liver disease (NAFLD), a group of liver illnesses that includes occurrence of inflammatory changes and sometimes may develop the fibrotic or nonalcoholic steatohepatitis (NASH) disease. Further these may result in liver cirrhosisas well as hepatocellular carcinoma [3, 4].

Because liver function tests and abdominal ultrasonography are included in routine checkups, NAFLD can be identified with ease. According to statistical data available, NAFLD has been identified by ultrasonography in 9–30% of adults [4].

Increased serum gamma-glutamyl transferase (GGT) concentration without any clear liver enzyme abnormalities or fatty liver appearances on ultrasonography. Hepatocytes and intra-hepatic bile duct epithelial cells produce the hepatic and biliary enzyme GGT [5, 6]. Increased serum GGT enzymatic activity is linked to ROS generation [9, 10], atherosclerosis, and chronic renal disease [11, 12]. It is also a strong predictor of the metabolic syndrome [7, 8]. Furthermore, high GGT levels have been reported in cases of fatty liver [13, 14]. Higher serums GGT are likely exhibiting symptoms of a liver disease, although it is unclear if these symptoms fasten the development of fatty liver.

The current research was designed to compare the differential diagnosis of ALD and NFALD alterations and its association with USG, ANI and GGT.

The records into two study groups in order to concentrate on the relationship between high serum GGT levels and deposition of fat in liver. During the observation period, NAFLD (n = 120) had no elevated serum GGT values found, whereas the other ALD group had higher serum GGT levels.

In Alcoholic liver diseases ultrasound is one of the most convenient and cost effective imaging technique for the assessment purpose. Ultrasound is an effective imaging tool for detection of hepatic steatosis of all grades with a

good sensitivity of 60–94% and a specificity of 88–95%. It was also observed that its accuracy is higher when hepatic steatosis of > 30% [15,16]. However, there is significant variability in the subjective evaluation of gray-scale ultrasonography findings indicating steatosis [17]. It is challenging to distinguish between different grades of steatosis, detect mild steatosis, and assess minute changes over time using conventional ultrasonography [18]. To circumvent subjective evaluation, a quantitative hepatorenal index has been devised; nevertheless, operator experience, measurement depth, and vendor algorithm variability all impact it. Recently, quantitative ultrasonic measures, such as attenuation, back scatter coefficient, and sound speed, were created for the assessment of hepatic fat. The most popular of them is the controlled attenuation parameter (CAP) [19].

Hepatic steatosis of all grades, ultrasound has a sensitivity of 60–94% and a specificity of 88–95%; accuracy is higher when steatosis of greater than 30% is detected [15]. In patients with ALD, CAP demonstrated good diagnostic accuracy of 0.77, 0.78, and 0.82 for mild, moderate, and severe steatosis [20].

ANI was one of the better indicator for ALD diagnosis. AST, ALT, MCV, gender, height, and weight in the determination of ANI. For better understanding and differential diagnosis so e additional parameters can also be correlated with ANI and further it was observed that when consideration serum GGT levels with ANI definitely improve its utility in differential diagnosis between ALD from NAFLD.

Methodology: A total 244 cases ALD (120) and NAFLD (124) were included in the current study. Anthropometric parameter, biochemical investigations and USG data was collected. The ANI was calculated by using sex, height, weight, hepatic transaminases (AST, ALT) and mean corpuscular volume (MCV). The statistical analysis of the data was done using IBM SPSS software version 23 using appropriate statistical methods.

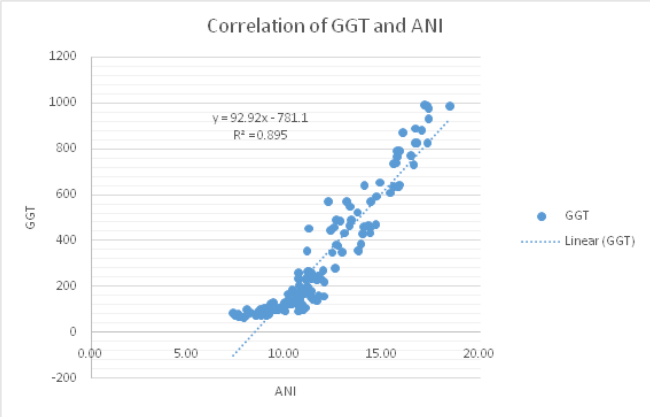
Results:

The study observed high values of ANI in patients with ALD as compared to NAFLD participants (11.58 ± 43.21/ –3.06± 1.45, p < 0.001). It was reported that transaminases (AST and ALT), MCV, and GGT were increased in ALD than NAFLD.

Table 1: Comparison of various parameters between ALD and NAFLD

Characteristic	ALD (n = 120)	NAFLD (n = 124)	P Value
Demographic Parameters			
Age (years)	48.42 ± 11.56	49.37 ± 16.20	NS
Anthropometric Parameters			
BMI, kg/m2	23.49 ± 3.48	27.23 (3.89)	< 0.001
WC, cm	88.34 ± 8.55	94.57 ± 11.22	< 0.001
Biochemical Parameters			
TG, mgl/dl	1.92 (1.74)	1.78 (1.21)	>0.001
AST/ALT	1.78(1.28)	0.58 (0.28)	< 0.001
MCV, fl	98.30 ± 8.72	89.38 ± 6.11	< 0.001
ANI	11.58 ± 3.21	-3.06± 1.45	< 0.001
GGT, IU/L	252.0 (423.50)	62.0 (38.20)	< 0.001
Ultrasound Accuracy	78 (90.68)	70 (94.34)	>0.001

Fig.1: Correlation of GGT with ANI in ALD patients



The present study results showed that the ANI values in the ALD group were higher than that of NAFLD group, with significant statistical difference between these two groups respectively (11.58 ± 3.21 vs. –3.06 ± 1.45, $p < 0.001$). The study further observed that a significant correlation (R^2=0.89) between the serum GGT levels and ANI, which suggest GGT is one of the important parameter if considered with ANI.

Discussion

Identification of the cause of liver steatosis as ALD or NAFLD is crucial as the management usually depends on it. Further the etiology of liver disease is also important for liver transplantation and organ allocation. Biomarkers have been used for the diagnosis of ALD or NAFLD,but there is a limitation for their insufficient sensitivity and specificity [21-23]. Hernaez et al. showed in a meta analysis that ultrasound is an accurate, reliable imaging technique for the detection of fatty liver, with a limitation that it could not differentiate between the etiology of steatosis [24]. The CAP as a parameter which can detect hepatic steatosis. Some researchers have identified its high diagnostic utility with a good accuracy in the detection of hepatic steatosis [19, 20].

Dunn et al. provided an index, ALD/NAFLD Index (ANI) [25] and it was observed that it has a high accuracy which can also distinguish between ALD and NAFLD. Various parameters were used like AST, ALT, MCV, gender, height, and weight in the determination of ANI. The present study used this model and evaluated other parameters or risk factors for obesity and alcohol intake.

Gastric alcohol dehydrogenase activity is low in women due to comparatively more body fat than men. Hence females are prone to develop the hepatotoxicity by alcohol intake [26]. But globally ALD is more common in men as compared to females, because men's alcohol consumption is comparatively very high than the females [27]. The present study included only male population as rate of ALD in men was much higher in men compared to women.

Various anthropometric parameters were shown a close association between the NAFLD. In addition to anthropometric parameters of obesity other conditions like IR, HTN, and deranged lipid profile, and is considered to be associated with syndrome X [28]. Visceral obesity, high waist hip ratios are important risk factors for NAFLD [29]. In this study it was observed that the BMI of NAFLD study group was significantly high with high than ALD study group ($p < 0.001$).

The increased MCV is an indicator of the direct toxic effects of alcohol on hematopoietic stem cells, along-with the reduced intake of balanced food or malabsorption of certain vitamins like cobalamine and folate [30-32].

Not only for MCV, but the circulatory levels of transaminases can be deranged by the toxic effects of alcohol. Many researchers reported that AST/ALT is an independent predictor of ALD [33]. It was also observed that elevated levels of serum ALT than AST signifies the liver damage. But in ALD patients it was reported that

often AST levels were increased mainly. As AST is a mitochondrial enzyme, which produces some toxic end products like acetaldehyde and intermediates (such as free radicals). These can lead to generation of ROS and lipid peroxidation, which can cause mitochondrial injury and results in increase in the serum AST levels. Further, chronic alcoholism can lead to peridoxal phosphate (PLP) deficiency which can rise AST and ALT. As PLP is the major co enzyme for ALT, its deficiency alters the AST/ALT ratio [34,35]. The study findings were consistent with these findings. Hence AST/ALT is also calculated and used with ANI scoring system along-with MCV for distinguishing between diagnosis of ALD and NAFLD.

GGT is a transmembrane protein present in the micro some which is also associated with the uptake of amino acid at cellular level [36]. In alcoholic persons alcohol abuse cause liver cell damage which results in release of GGT from microsomes into the circulation [37,38]. Previous literature have shown that GGT is a marker of alcoholism and has a high predictive value of ALD [39,40].

ANI is identified as a novel index to differentiate between ALD and NAFLD. It was observed that ANI has a good sensitivity (83.1%) and specificity (94.3%) in accurate differential identification of of ALD/ NAFLD. Dunn et al. [25] observed that ANI > 0, the ALD is can be diagnosed , and ANI < 0 is likely to be associated with the occurrence of NAFLD, which were not reflected in the current study. So it was clear that instead of just GGT inclusion of ANI can provide a distinguishing diagnosis between ALD and NAFLD.

Still some limitations are there even after inclusion of ANI. Hence a detailed understanding of the of ANI scoring system can provide a better utility of this parameter in future. It was also observed that the short-term removal of alcohol has no impact on ANI.

Conclusion: ALD/NAFLD index (ANI) is an effective parameter to improve the diagnosing power of ALD and NAFLD, but it comes with certain limitations which makes its clinical approach subjected to certain restrictions. When combined with some other predictive parameter like serum GGT, its utility in differential diagnosis between ALD and NAFLD will be further improved.

References

1. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346:1221–31.
2. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67:328–57.
3. Sberna AL, Bouillet B, Rouland A, Brindisi MC, Nguyen A, Mouillot T, et al. European Association for the Study of the liver (EASL), European Association for the Study of diabetes (EASD) and European Association for the Study of obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with type 2 diabetes. Diabet Med. 2018;35:368–75.
4. Watanabe S, Hashimoto E, Ikejima K, Uto H, Ono M, Sumida Y, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. J Gastroenterol. 2015;50:364–77.
5. Ruttenburg AM, Goldbarg JA, Pineda EP. Serum gamma-glutamyl transpeptidase activity in

hepatobiliary pancreatic disease. Gastroenterology. 1963;45:43–8.

6. Nemesánszky E, Lott JA. Gamma-glutamyltransferase and its isoenzymes: progress and problems. Clin Chem. 1985;31:797–803.
7. Liu CF, Zhou WN, Fang NY. Gamma-glutamyltransferase levels and risk of metabolic syndrome: a meta-analysis of prospective cohort studies. Int J Clin Pract. 2012;66:692–8.
8. Kunutsor SK, Apekey TA, Seddoh D. Gamma glutamyltransferase and metabolic syndrome risk: a systematic review and dose–response meta-analysis. Int J Clin Pract. 2015;69:136–44.
9. Lee DH, Blomhoff R, Jacobs DR. Is serum gamma glutamyltransferase a marker of oxidative stress? Free Radic Res. 2004;38:535–9.
10. Lim JS, Yang JH, Chun BY, Kam S, Jacobs DR, Lee DH. Is serum gamma-glutamyltransferase inversely associated with serum antioxidants as a marker of oxidative stress? Free Radic Biol Med. 2004;37:1018–23.
11. Arasteh S, Moohebati M, Avan A, Esmaeili H, Ghazizadeh H, Mahdizadeh A, et al. Serum level of gamma-glutamyl transferase as a biomarker for predicting stenosis severity in patients with coronary artery disease. Indian Heart J. 2018;70:788–92.
12. Shen ZW, Xing J, Wang QL, Faheem A, Ji X, Li J, et al. Association between serum γ-glutamyltransferase and chronic kidney disease in urban Han Chinese: a prospective cohort study. Int Urol Nephrol. 2017;49:303–12.
13. Ikai E, Honda R, Yamada Y. Serum gamma-glutamyl transpeptidase level and blood pressure in nondrinkers: a possible pathogenetic role of fatty liver in obesity-related hypertension. J Hum Hypertens. 1994;8:95–100.
14. Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology. 2006;44:865–73.
15. Joseph AE, Saverymuttu SH. al-Sam S, cook MG, Maxwell JD. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. Clin Radiol. 1991;43:26–31.
16. Haring R, Wallaschofski H, Nauck M, Dörr M, Baumeister SE, Völzke H. Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. Hepatology. 2009;50:1403–11.
17. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011;54:1082–1090.
18. Yao SK, Gao C. Differential diagnosis between alcoholic liver disease and nonalcoholic fatty liver disease. World Chin J Dig. 2010;18:1456–1460. [Google Scholar]
19. Kumar M, Rastogi A, Singh T, et al. Controlled attenuation parameter for non-invasive assessment of hepatic steatosis: does etiology affect performance? J Gastroenterol Hepatol. 2013;28:1194–1201.
20. de Ledinghen V, Vergniol J, Foucher J, Merrouche W, le Bail B. Non-invasive diagnosis of liver steatosis using controlled attenuation parameter (CAP) and transient elastography. Liver Int. 2012;32:911–918.
21. Becker U, Deis A, Sorensen TI, et al. Prediction of risk of liver disease by alcohol intake, sex, and age:

a prospective population study. Hepatology. 1996;23:1025–1029.

22. Mandayam S, Jamal MM, Morgan TR. Epidemiology of alcoholic liver disease. Semin Liver Dis. 2004;24:217–232.
23. Loomba R, Abraham M, Unalp A, et al. Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis. Hepatology. 2012;56:943–951.
24. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011;54:1082–1090.
25. Dunn W, Angulo P, Sanderson S, et al. Utility of a new model to diagnose an alcohol basis for steatohepatitis. Gastroenterology. 2006;131:1057–1063.
26. Becker U, Deis A, Sorensen TI, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology. 1996;23:1025–1029.
27. Mandayam S, Jamal MM, Morgan TR. Epidemiology of alcoholic liver disease. Semin Liver Dis. 2004;24:217–232.
28. Loomba R, Abraham M, Unalp A, et al. Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis. Hepatology. 2012;56:943–951.
29. Lomonaco R, Ortiz-Lopez C, Orsak B, et al. Effect of adipose tissue insulin resistance on metabolic parameters and liver histology in obese patients with nonalcoholic fatty liver disease. Hepatology. 2012;55:1389–1397.
30. Das SK, Mukherjee S, Vasudevan DM, Balakrishnan V. Comparison of haematological parameters in patients with non-alcoholic fatty liver disease and alcoholic liver disease. Singapore Med J. 2011;52:175–181.
31. Cylwik B, Naklicki M, Gruszewska E, Szmitkowski M, Chrostek L. The distribution of serum folate concentration and red blood cell indices in alcoholics. J Nutr Sci Vitaminol (Tokyo) 2013;59:1–8.
32. Fragasso A, Mannarella C, Ciancio A, Sacco A. Functional vitamin B12 deficiency in alcoholics: an intriguing finding in a retrospective study of megaloblastic anemic patients. Eur J Intern Med. 2010;21:97–100.
33. Cohen JA, Kaplan MM. The SGOT/SGPT ratio: an indicator of alcoholic liver disease. Dig Dis Sci. 1979;24:835–838.
34. Sorbi D, Boynton J, Lindor KD. The ratio of aspartate aminotransferase to alanine aminotransferase: potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. Am J Gastroenterol. 1999;94:1018–1022.
35. Ono K, Ono T, Matsumata T. The pathogenesis of decreased aspartate aminotransferase and alanine aminotransferase activity in the plasma of hemodialysis patients: the role of vitamin B6 deficiency. Clin Nephrol. 1995;43:405–408.
36. Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci. 2001;38:263–355.
37. van Beek JH, de Moor MH, Geels LM, et al. The association of alcohol intake with gamma-glutamyl transferase (GGT) levels: evidence for correlated genetic effects. Drug Alcohol Depend. 2014;134:99–105.
38. Robles-Diaz M, Garcia-Cortes M, Medina-Caliz I, et al. The value of serum spartate aminotransferase

and gamma-glutamyl transpetidase as biomarkers in hepatotoxicity. Liver Int. 2015;35:2474–2482.

39. Anton RF, Lieber C, Tabakoff B, CDTect Study Group Carbohydrate-deficient transferrin and gamma-glutamyltransferase for the detection and monitoring of alcohol use: results from a multisite study. Alcohol Clin Exp Res. 2002;26:1215–1222.
40. Litten RZ, Bradley AM, Moss HB. Alcohol biomarkers in applied settings: recent advances and future research opportunities. Alcohol Clin Exp Res. 2010; 34:955–967.