ORIGINAL RESEARCH ARTICLE

Comparison of Ultrasonographic Grading of Fatty Liver with Liver Enzymes in Predicting Raised Total Serum Cholesterol

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ABSTRACT

Introduction: With better health care and imaging modalities, there is a rise in non-communicable diseases amongst the Indian population in the past four decades. In the present decade, non-alcoholic fatty liver disease (NAFLD) is emerging and gaining prominence in causing CLD. NAFLD is generally diagnosed as an incidental finding either through routine Trans abdominal ultrasonography as fatty liver, raised AST or ALT. In this study, we tried to compare the accuracy levels of the above mentioned in prediction of raised total serum cholesterol levels.

Material and methods: We examined 542 participants after applying the exclusion criteria. All the participants underwent general physical examination, trans-abdominal ultrasonography (USG) and examination of blood/serum parameters (liver function tests, fasting blood sugar levels and total cholesterol). The same radiologist examined all the 542 participants for fatty liver, whilst being blinded to the results of the serum parameters. The results of each test were compared for statistical significance taking serum total cholesterol as the gold standard. In addition, we divided the grades of fatty liver into two groups of mild (grade 0 and 1) and grade (2 and 3) to check for statistical significance in the prediction of steato-hepatitis.

Results: USG had better diagnostic accuracy (69.37%) in comparison to other serum parameters with a positive and negative likelihood ratio of 2.11 and 0.4 in predicting raised serum total cholesterol. In the blood/serum parameters, fasting blood sugar was the second best in predicting raised total serum cholesterol levels and amongst the parameters in LFT, Alanine transaminase(ALT) had the best results. In our study, we show that grade 2 and 3 of fatty infiltration of liver is a good predictor of steato-hepatitis with an odds ratio of 7.9 and p-value of <0.0001.

Conclusion: We conclude in our study, that USG has a role in general screening of population in predicting serum cholesterol levels. Hence, also improving the early detection of the spectrum of non-alcoholic fatty liver disease (NAFLD). USG is an easy to learn, operator dependent, inexpensive, easily available and non-invasive modality. USG also in our study has proven to be a good screening modality to detect steato-hepatitis. With our results and its advantages, USG clearly has a major role to play in screening and detection of NAFLD.

Key words: Trans-abdominal Ultrasonography (USG), Non-alcoholic fatty liver disease (NAFLD), Non-Alcoholic Steato-Hepatitis (NASH), Liver Function Test (LFT).

INTRODUCTION

With better health care and imaging modalities, there is a rise in non-communicable diseases amongst the Indian population in the past four decades. This holds true for chronic liver disease(CLD), where, in the past four decades viral was the main etiological factor for causing CLD, which was later taken over by chronic alcohol consumption.[1] In the present decade, non-alcoholic fatty liver disease is emerging and gaining prominence in causing CLD.[1–3] The prevalence of NAFLD is approximately 10-30% in India (General Population)[3,4], highest in urban Chennai and lowest in rural West Bengal.[1] Indians are at greater risk of developing NAFLD due to higher incidence insulin resistance among them.[1] NAFLD is considered by some to be a spectrum, the mild form non-alcoholic fatty liver (NAFL) and the severe form Non-alcoholic steatohepatitis (NASH).[5] NAFLD is also known to cause hepatic cirrhosis, hepatocellular carcinoma and failure.[2,5–7] NAFLD is generally diagnosed as an incidental finding either through routine Trans abdominal ultrasonography as fatty liver[6], raised AST or ALT[1], however liver biopsy is the gold standard for diagnosing it, but is an invasive technique.[1,2,5,7,8] Other techniques such as computed tomography (CT)[4,8] and Magnetic resonant(MR)/USG elastography[4,8], proton MR spectroscopy[4,8] are known to diagnose the condition, but the disadvantages include radiation hazards, expensive, expertise and limited availability.[1,5] In this study, we tried to compare the accuracy levels of USG with that of serum

parameters in prediction of raised total serum cholesterol levels.

MATERIAL AND METHODS

In this cross-sectional study, data was collected from health check-up patients visiting Father Mullers Medical College Hospital in the department of Radio-Diagnosis. The study was done over a period of two months in December 2016-January 2017.

Sample size was calculated to be a minimum of 357 for statistical significance, using $n = Z\alpha^2 p (1-p) / e^2$, as formula where n = sample size, Zα = 1.96 at 95% confidence interval and e = allowable error. The mean prevalence was calculated from previous studies done.

Ethical clearance was obtained from the institution ethical committee and informed consent was obtained from all participants in the language best understandable to them.

Study aimed to determine the accuracy of trans abdominal ultrasonography (USG) in comparison to that of serum parameters in predicting raised total serum cholesterol levels and to predict steato-hepatitis by classifying grades of fatty liver into mild (grade 0 and 1) and severe (grade 2 and 3).

Inclusion criteria

- Patients presenting to Father Mullers Medical College Hospital availing the health package.

Exclusion criteria

- Known cases of cirrhosis
- Known cases of alcohol abuse/dependence (DSM-IV criteria)
- Hepatitis (autoimmune, viral, metabolic etc.) in the preceding six months.
- History of use of hepatotoxic drugs (present/past six months)
- HbsAg positive patients.

Study Design and patient selection: Patients availing the health check-up package, and upon willingness in participating in the study based on inclusion and exclusion criteria were selected in the study. They underwent a preliminary general physical examination. The following parameters were examined and recorded. The final study consisted of 542 patients.

Measurements

Body mass index: weight(kilograms), height (metres) were recorded and the body mass index (BMI) was calculated and grading according to the recommended (WHO) Asian stratification of BMI, ie <18.5 underweight, 18.5-22.9: normal, > 23 - 24.9: overweight, > 25: obese.[9]

Abdominal Ultrasonography: Patients underwent a trans-abdominal ultrasonography as part of the health check-up package. Features of liver disease such cirrhosis were excluded. The patients were then graded into grade 0: normal echotexture (with visualization of the walls of portal vein, diaphragm, and comparison of echogenicity of liver with that of kidney and spleen were similar), Grade 1: increased echogenicity in comparison to kidney and spleen with visualization of the walls of portal vein and diaphragm, Grade 2: increased echogenicity with non-visualization of the walls of portal vein with visualization of the diaphragm, grade 3: increased echogenicity with non-visualization of the walls of portal vein and diaphragm.[4] In addition to detecting liver echogenicity, liver size was also calculated and an abnormal value was set at >15 cm. All scans were done by the same radiologist.

Laboratory Investigations: All the participants would under FBS, total cholesterol and LFT (AST, ALT and ALP). The cut off values for AST >35 IU/L, ALT >45 IU/L, ALP >104 IU/L and Total cholesterol of >200 IU/L.

Approximately 20-30 patients were examined each day for the period of two months by the same radiologist, in order to eliminate the inter observer variability. The results of the serum parameters were blinded to the radiologist.

STATISTICAL ANALYSIS

Data was analysed by descriptive statistics and percentage frequency distribution, using the statistical package for social sciences (SPSS) 16.0 version. We calculated kappa to define the agreement of level of USG findings. Chi square test ($\chi 2$) was used to calculate the frequency of gender, age and BMI for normal and deranged total cholesterol levels.

By constructing a 2x2 table, sensitivity, specificity, positive and negative predictive values (PPV and NPV) and positive and negative likelihood ratios (LRs) were calculated. Odds ratios (ORs), relative risks (RRs), with their 95% confidence intervals (CIs) were calculated for each independent variable. Optimal cut-off values of the variables were calculated using receiver operating characteristic (ROC) curve analysis. We considered *P* value as <0.001 to be significant.

In addition, we divided the grades of fatty liver into two groups of mild (grade 0 and 1) and grade (2 and 3) to check for statistical significance in the prediction of steato-hepatitis.

RESULTS

The study was conducted in Father Mullers Medical College Hospital, a total of 575 patients were enrolled for the study. 20 cases were excluded in view of either being detected of being alcoholics as per history or cirrhosis of liver on ultrasonography. Another 13 cases were excluded, 9 in view of having viral hepatitis in the past 6 months, 4 in view of being on hepatotoxic drugs. After exclusion 542 patients were examined.

Demographics

Our study had a mean age of 38.7 (+/- 10.9). The patients were from the age group of 21 to 66 years, with highest in the age group of < 30 years (n=180,33.2%), (Table 1(a)). Highest number of patients with raised total serum cholesterol belonged to the 31-40 age group (n=71) constituting 27.3% of the participants with raised total cholesterol in our study (Figure/Table 1(a)). This was a male predominant study with male group constituting 91.9% (n=498) of the sample size (Figure/Table 1 (b)). Amongst the patients with raised cholesterol, male population again predominated with 91.5% (n=238).

Patients with BMI > 30 (ie obese class) had the highest number of patients raised cholesterol levels constituting approximately 60% (n=156) (Figure/Table 2(c)).

In comparison to the serum parameters USG grading of fatty

liver had the best accuracy with p-value of <0.001 and kappa agreement of 0.38. fasting blood sugar levels had the next best accuracy level of 55.9% with a p significant value of <0.001 with a kappa agreement of 0.132. the serum parameters and liver size in our study did not show to have significant p-values. Amongst the serum parameters, AST showed to have a better diagnostic accuracy of 55.1% (Figure/Table 2). The parameter with the best results was USG in our study with a positive and negative Likelihood Ratio of 2.11 and 0.4, Odds Ratio and Relative Risk of 5.3 and 2.1 when compared with other parameters (Figure/Table 2).

In our study, we show that grade 2 and 3 of fatty infiltration of liver is a good predictor of steato-hepatitis with an odds ratio of 7.9 and p-value of <0.0001(Table 3(a)).

The optimal cut-off values of the various parameters used in our study to predict raised serum total cholesterol was calculated using ROC curve analysis. The cut-off values of USG, Liver size, AST, ALT, ALP, FBS was calculated to be Grade 1, 13.45 cm, 23.5, 29.5, 70.5 and 99.5-100.5 with a sensitivity of 74.2%, 55.8%,58.8%, 58.5%, 54.2, 65.4-62.3% and gave a sensitivity of 64.9%, 54.6%,52.2%, 53.5%, 53.2% and 62.8%-64.5% respectively (Table 3 (B)).

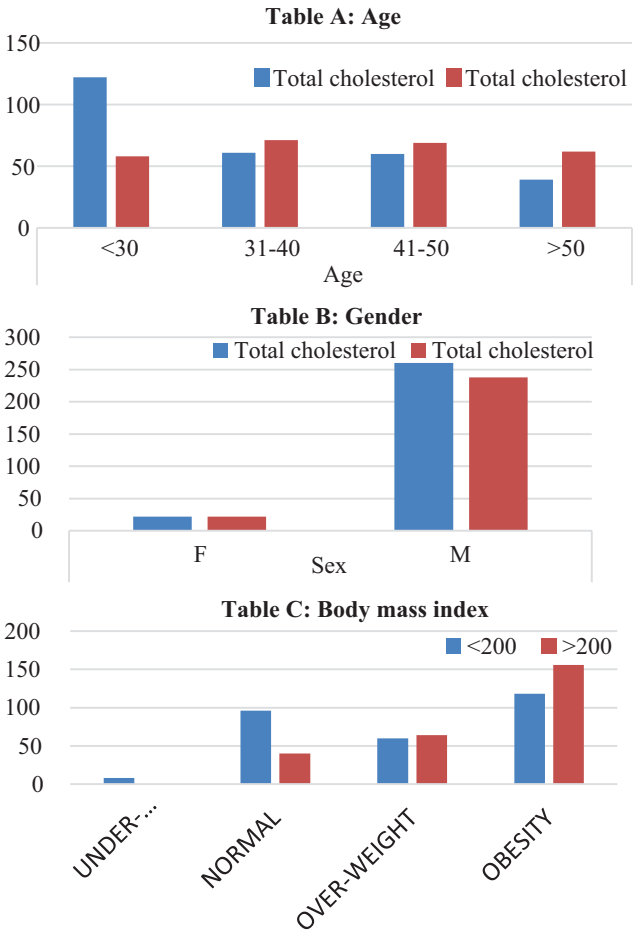

Figure-1A: Bar Chart Age* Total Cholesterol; **Figure-1B:** Bar Chart Gender*Total Cholesterol. **Figure-1C:** BMI * Total Cholesterol

Sensitivity	77.78%
Specificity	69.40%
Positive Likelihood Ratio	2.54
Negative Likelihood Ratio	0.32
Positive Predictive Value	64.34% (*)
Negative Predictive Value	81.48% (*)
Odds ratio	7.9381
95% CI:	5.3490 to 11.7806
Relative risk	3.4743
Significance level	P < 0.0001

Table-3(A): Prediction of grade 2 and 3 fatty infiltration of liver in predicting steato-hepatitis.

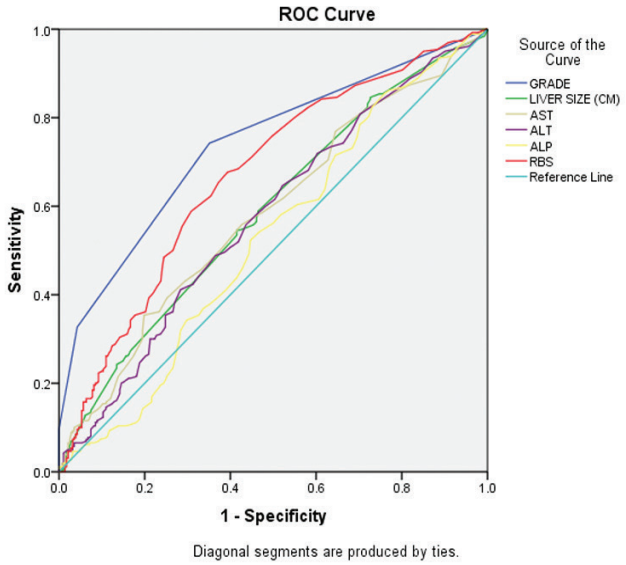

Figure-3B: Roc Curve Analysis For Area Under Curve (AUC)

	Fatty liver	AST	ALT	ALP
True negative	183	243	218	262
True positive	193	56	80	17
False negative	67	204	180	243
False positive	99	39	64	20
Sensitivity	74.20%	21.50%	30.80%	6.50%
Specificity	64.90%	86.20%	77.30%	92.90%
Positive predictive value	66.10%	58.90%	55.60%	45.90%
Negative predictive value	73.20%	54.40%	54.80%	51.90%
Diagnostic accuracy	69.37%	55.17%	54.98%	51.48%
Kappa statistics	0.389	0.079	0.082	-0.006
P value	<0.001	0.023	0.041	0.865

Table-2: Sensitivity specificity and PPV with NPV with the given cut offs: along with kappa agreement statistics

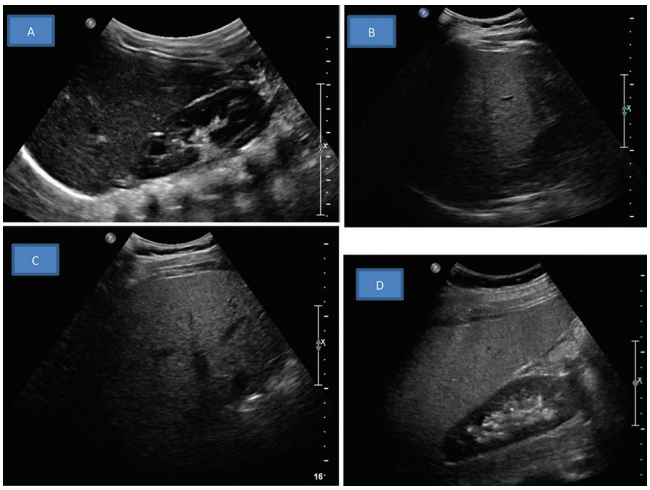

Figure-4A: Grade 0: Normal Appearing Liver Echogenecity. **Figure-4B:** Grade 1: Grqade I Fatty Infiltration of Liver; **Figure-4C:** Grade II: Grqade I Fatty Infiltration of Liver. **Figure-4D:** Grade III: Grqade I Fatty Infiltration of Liver

DISCUSSION

This study was a male predominant study, and shows that USG is a better screening modality in comparison to the other serum parameters in predicting raised serum total cholesterol levels. USG is shown to have a diagnostic accuracy of 69.37%. USG is also an invaluable, non-invasive, easy, inexpensive (in comparison to MR elastography), however it is operator dependent and in inexperienced hands can over/under predict cases of fatty infiltration of liver. In our study, we over-predicted 99 cases and under predicted 67 cases in the diagnosis of fatty infiltration of liver when we compared to the gold standard i.e. total serum cholesterol levels. However, follow up of patients with over prediction is ideal as to whether they consequently would develop raised total cholesterol levels.

The sensitivity and specificity of USG in our study was 74.2% and 64.9%. In comparison with similar studies our specificity was noted to be lower.[3,4,6] This could be due to operator in-experience.

However, in our study, we show that AST, ALT and FBS had a correlation with that of raised serum total cholesterol levels, with USG having the better diagnostic accuracy in comparison to the rest.

The gold standard for diagnosis of NAFLD is liver biopsy. However, to perform liver biopsy for every suspected patient is not feasible, hence the need for a cost effective, non-invasive technique is the need of the hour.

With our study, we show USG can provide the answer for it and provides basic screening modality for raised total cholesterol levels and therefore NAFLD.

USG, in addition to predicting raised total serum cholesterol levels, USG also in our study is shown to be a good predictor of steato-hepatitis especially grade 2 and 3.

Liver enzymes have shown to have lower diagnostic accuracy in our study, is also an invasive technique which in comparison to USG requires more time for processing its values.

Limitations

We did not include waist to hip ratio in our study. USG is operator dependent and there is always a possibility of inter and intra-observer variability. Fasting lipid profiles were not used in this particular study due to non-availability in the particular health check-up package availed.

CONCLUSION

We conclude in our study, that USG has a role in general screening of population in predicting serum cholesterol levels. Hence, also improving the early detection of the spectrum of non-alcoholic fatty liver disease (NAFLD). USG is an easy to learn, operator dependent, inexpensive, easily available and non-invasive modality. With our results and its advantages, USG clearly has a major role to play in screening and detection of NAFLD. Our study shows that USG has the highest diagnostic accuracy in comparison to serum parameters. In addition, USG also has a high sensitivity, PPV and NPV value. In addition, USG in our study has proven to be a sensitive modality in detecting hepatitis in patients for screening of NAFLD. However, USG is an operator dependent modality, which could explain the lower specificity in our study. We also state that with experience and an easy learning curve the specificity can be improved with or without taking clinical parameters (BMI, WHR) into consideration. For better health-care outcome for the patient, LFT can be performed if USG detects fatty infiltration of liver, thus, avoiding unnecessary patient discomfort.

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