

## Relationship between Different Ultrasonographic Grades of Fatty Liver and Serum Alanine Aminotransferase Levels in Asymptomatic Individuals

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### ABSTRACT

**Objective:** to determine the relationship between different ultrasonographic grades of fatty liver with serum Alanine aminotransferase levels in asymptomatic individuals.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** OPD, Radiology Department in collaboration with the Department of Pathology, District Headquarters Hospital, Sargodha Pakistan, from Jan to Oct 2021.

**Methodology:** One-thirty-eight asymptomatic individuals with fatty livers were included in the study. Fatty livers were graded as mild, moderate and severe fatty change. Serum ALT was also determined in these individuals.

**Results:** Out of 138 cases, moderate 61(44.2%) grade of fatty liver was the commonest grade seen after mild 49(35.5%) and severe 28(20.2%) grades. Abnormal serum ALT was commonest in severe grade 27(96.4%), followed by moderate grade 45(73.7%) and mild grade 10(20.4%). On comparison of means of serum ALT levels in different grades of fatty liver, it was found to have a significant relationship with a grade of the fatty liver ( $p$ -value <0.001).

**Conclusion:** Fatty liver should be graded into three grades rather than reported as fatty liver. Finding the severe and moderate grades of fatty liver should warrant further investigations for NAFLD/NASH, provided that common alternative chronic liver diseases are excluded.

**Keywords:** Alcohol, Alanine transaminase, Fatty liver, Non-alcoholic liver disease, Ultrasonography.

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### INTRODUCTION

Fatty liver is a term applied to a wide spectrum of conditions characterized histologically by the accumulation of triglycerides within the cytoplasm of hepatocytes.<sup>1,2</sup> Common conditions are viral hepatitis and alcoholic and non-alcoholic fatty liver disease (NAFLD).<sup>3</sup>

Ultrasound is a non-invasive radiological modality and is extensively used in daily practice.<sup>4</sup> Ultrasound abdomen is the common radiological investigation requested by clinicians but is not graded in routine practice. On ultrasonography, fatty liver is graded as mild when there is increased liver echogenicity; moderate when there are obscured hepatic and portal vein walls; and severe when there is posterior attenuation of the ultrasound beam.<sup>1,5</sup> Fatty liver can be diagnosed by ultrasound, having a sensitivity of 83%-94%, specificity of 84%-100%, a positive predictive value of 89%-100% and negative predictive value of 94%.<sup>5,6</sup>

The worldwide prevalence of NAFLD is around 25.24%, with variations worldwide. For example, ultrasound-based studies have documented a prevalence of around 30% in the Middle East and South American countries. In contrast, the limited number of African studies report a much lower prevalence of 13%,<sup>7,8</sup> while in India, it is 9%.<sup>9</sup>

Serum alanine aminotransferase (ALT) is a screening tool for non-alcoholic fatty liver disease (NAFLD).<sup>10</sup> Raised ALT is associated with fatty liver in 18.9- 26.7% of cases. The study aimed to determine the importance of grading fatty liver as a screening tool for NAFLD in asymptomatic individuals. In addition, the finding of a particular grade of fatty liver on ultrasound will warrant further invasive investigations in otherwise asymptomatic individuals.

### METHODOLOGY

This cross-sectional study was conducted at the Outpatient Department of Radiology, District Headquarters Hospital, Sargodha Pakistan, from January to October 2021. Permission from the Hospital Ethical Review Committee from District Head Quarters Hospital Sargodha was taken (Ltr no. 1972 DHQ/SMC

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dated 19<sup>th</sup> Nov 2021). The sample size was calculated using the WHO sample size calculator, taking a confidence level of 95%, a margin of error of 5%, reported prevalence of NAFLD was 9%.<sup>11</sup> The estimated sample size came out to be 138 Patients.

The non-probability consecutive sampling of asymptomatic individuals was employed. All individuals were subjected to abdominal ultrasound after informed written consent.

**Inclusion Criteria:** All the cases with fatty liver, irrespective of age and gender, were included in the study.

**Exclusion Criteria:** Those cases of fatty liver with any history of illnesses affecting the liver were excluded from the study, e.g. acute or chronic hepatitis (B and C), rare disorders (haemochromatosis, thalassemia,  $\alpha$ -1 antitrypsin deficiency etc.), other liver pathologies (liver abscess or hydatid disease), and cases with a history of alcohol intake, diabetes mellitus, malignancy or any prolonged drug intake were excluded from the study.

Fatty liver was Graded<sup>1,5</sup> by a radiologist on ultrasonography. Clotted blood was taken after the ultrasound, and serum ALT level was estimated. The cut-off value of ALT for male patients was considered less than 43U/L, and for females, it was less than 32U/L. The radiologist performing the ultrasound was not informed about the results of serum ALT levels to overcome the possibility of any future bias.

Data was entered in Statistical Package for the Social Sciences (SPSS) version 22. Descriptive statistics were used to describe the data. Analysis of variance (ANOVA) was used to compare the ALT levels in different grades of fatty liver. The *p*-value  $\leq 0.05$  was considered significant.

**RESULTS**

The present study, 138 cases were selected, fulfilling the inclusion and exclusion criteria. Male patients 72(52.17%) slightly outnumbered female patients 66(47.82%). Age ranged from 19-71 with a mean age of 47.00 $\pm$ 12.46 years.

Fatty liver was graded according to already defined criteria. Moderate grade 61(44.2%) was the commonest grade of fatty liver, followed by mild grade 49(35.5%) of fatty liver, while severe grade 28(20.3%) of fatty liver was the least common one.

Serum ALT level was raised in 82(59.4%) cases. However, different levels were seen in different grades of fatty liver. Overall, it ranged from 19-103U/L, with a mean of 43.70 $\pm$ 16.70. The range of serum ALT levels was slightly higher in the mild grade of the fatty liver compared to the moderate grade, but the mean value was higher in the moderate grade with a higher number of cases with deranged ALT levels (Table).

The mean ALT level for the male gender (n=72) in all grades of fatty liver was 46.89 $\pm$ 17.04U/L. The mean ALT level for female cases (n=66) in all the grades of fatty liver was 40.21 $\pm$ 15.71U/L.

The largest number of patients was seen to have a moderate grade of fatty liver, and the smallest was a severe grade of fatty liver. Out of all cases included in the present study, according to specified criteria for normal ALT levels, 56 patients, 26 had normal serum ALT levels, and 40 had deranged serum ALT levels. In comparing means of serum ALT levels in different grades of fatty liver, serum ALT levels had a significant relationship with the grade of the fatty liver (*p*-value less than 0.001).

**DISCUSSION**

Liver steatosis can be quantified using different radiological modalities like ultrasound, CT scan and MRI. The ability of these techniques to detect steatosis is limited in cases where fatty change is <15–30%. Magnetic resonance imaging is considered far superior to ultrasound, and computed tomography (CT) scans detect <30% of fat content.<sup>12</sup> Liver biopsy is considered a reliable tool in distinguishing non-alcoholic steatohepatitis from fatty liver, but it is an invasive procedure associated with complications and high sample variability.<sup>13,14</sup> Quantitative ultrasound is more accurate and precise with a good interobserver agreement than

**Table: Comparison of means of serum ALT levels in different grades of fatty liver (n=138)**

Grades of Fatty Liver		Cases with Normal ALT Level (U/L)	Cases with Abnormal ALT Level (U/L)	Highest ALT Level (U/L)	Lowest ALT Level (U/L)	Mean $\pm$ SD ALT Levels (U/L)
Mild grade (n=49)	Male (n=25)	19 (76%)	6 (24%)	69	19	34.68 $\pm$ 12.93
	Female (n=24)	21 (87.5%)	3 (12.5%)	41	21	26.75 $\pm$ 6.69
Moderate grade (n=61)	Male (n=30)	10 (33.3%)	20 (66.7%)	62	34	47.40 $\pm$ 7.40
	Female (n=31)	5 (16.1%)	26 (83.9%)	70	21	44.03 $\pm$ 11.81
Severe grade (n=28)	Male (n=17)	1 (5.8%)	16 (94.1%)	103	38	63.94 $\pm$ 19.11
	Female (n=11)	0	11 (100%)	87	47	58.82 $\pm$ 14.90

conventional ultrasound.<sup>15</sup> Innovative statistical methods and quantitative ultrasound-based approaches are promising new technologies to assess liver steatosis non-invasively.<sup>16</sup> In the present study, fatty change of the liver has been graded into three grades based on criteria used by Palmentieri *et al.*<sup>5</sup>

Needleman *et al.*<sup>17</sup> had considered only an abnormal liver to have increased echogenicity, and liver biopsy was used as a gold standard. Moderate and severe grades of the liver were detected with good sensitivity rather than mild grades. Only undetected cases were in mild grades, and the detection was difficult compared to moderate and severe grades. The criteria for grading the liver fatty were not as well defined as in the present study. The present study also had some limitations on the grey zones between mild and moderate grade; and moderate and severe grade.

Bass *et al.*<sup>18</sup> graded fatty liver into three grades on ultrasonography, and serum ALT levels were also done in addition to other biomarkers. The male-to-female ratio was 2.36:1 which is quite different from the present study, where the male-to-female ratio is 1.09:1. The age range was comparable in both studies. Grade-2 steatosis was the commonest in the present study. In contrast, the mild grade was the most frequently observed grade of fatty liver found by Bass *et al.* There was a significant relationship between the grade and serum ALT levels, which corresponds to the present study.

In a study by Andrabi *et al.*<sup>19</sup> fatty liver was graded by ultrasonography into three grades. Grade-1 (40%) was the commonest, followed by Grade-3 (30%) and Grade-2 (24%), while 6% of the cases showed normal ultrasound. Similarly, in another study by Ejaz *et al.*<sup>20</sup> 138 patients were graded on ultrasound. Grade-1 (60.9%) was the commonest, followed by Grade-2 fatty liver (37.7%) and Grade-3 (1.4%). While in the present study, moderate grade (44.2%) was the commonest grade of the fatty liver, followed by mild grade (35.5%), while severe grade (20.3%) was the least common one. Cases with normal liver were not included in the present study. The difference may be on account of differences in inclusion and exclusion criteria which were not precisely mentioned by Ejaz *et al.*<sup>20</sup>

Alteration in liver enzymes may be an unexpected finding on routine biochemical profiling/screening and may pose a challenge to finding out the reason. The spectrum of fatty liver disease is a common cause of an unidentified rise in liver enzymes. In the present study, the percentages of cases with normal and

abnormal ALT levels change markedly from one grade to another. Normal ALT level was seen in the highest proportion in the mild grade of fatty liver, least in the severe grade of fatty liver and in between in the moderate grade of fatty liver. However, this proportion reversed for abnormal ALT levels, i.e., the highest proportion of abnormal ALT levels was seen in the severe grade and lowest in the mild grade, with a moderate grade in between. This phenomenon was found to be independent of gender or age.

Jawarchan *et al.*<sup>21</sup> found that ultrasonological grades of the fatty liver are directly related to serum ALT levels. Fatty liver was graded into two grades rather than three in the present study. Serum ALT levels were higher in Grade-2 compared to Grade-1 of fatty liver. Compared to the present study, this study has limitations as the fatty liver was graded in two grades rather than three, and the authors did not mention exclusion and inclusion criteria for selecting cases.

Only limited data is available in the literature from Pakistan. Taseer *et al.*<sup>22</sup> conducted a study in Southern parts of Punjab. The main inclusion pre-requisite in the study was type 2 diabetes. Later, these 100 patients were subjected to ultrasound, and fatty liver was only seen in Fifty-one (51%) diabetic patients with fatty liver. Serum ALT was raised in only (6%) of total cases. The authors have not graded the fatty liver, and the main inclusion criteria were type-2 diabetes. The authors concluded that NAFLD is commonly associated with type-2 diabetes mellitus.

## CONCLUSION

Ultrasound diagnoses moderate and severe grades of fatty liver with good sensitivity and specificity. Therefore, fatty liver should be graded into three grades in routine radiological practice. Finding the severe and moderate grades of fatty liver should warrant further investigations for NAFLD/NASH, provided that common alternative chronic liver diseases are excluded. Patients not willing to further investigations and liver biopsy or to have contraindications of liver biopsy should resort to healthier lifestyle modifications, which will not only help to stop the disease progression or even reverse the changes. In addition, further studies should be conducted considering other factors of metabolic syndrome, body mass index, and other biochemical evidence to elucidate the factors affecting disease pathophysiology.

**Conflict of Interest:** None.

**Author's Contribution**

Following authors have made substantial contributions to the manuscript as under:

AK: Data acquisition, data analysis, critical review, drafting the manuscript, critical review, approval of the final version to be published.

AA & KS: Conception, Study design, drafting the manuscript, approval of the final version to be published.

RAG & MMK: Drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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