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# Correlation between nonalcoholic fatty liver disease by ultrasound with hepatic veins spectral doppler and aminotransferases

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***Abstract*---**Background: Nonalcoholic fatty liver disease is a common cause of chronic liver diseases in developed countries. Ultrasound imaging is widely used in evaluation of liver disease. The alanine transaminase and aspartate transaminase are common laboratory investigations in diagnosing liver diseases. Methodology: A cross sectional study was conducted at the Rizgary and Hawler teaching hospitals from March to 2021 to April 2022 on sample of one hundred and fifty adult patients with non-alcoholic liver fatty disease. After excluding other cause of increasing liver echogenicity, patients were diagnosed as having NAFLD if they have elevated liver enzymes with a report of fatty liver in sonographic evaluation. Results: Mean ALT of patients was (88.3 U/L); 3% of them had normal ALT, 34% of them had ALT of 57-80 U/L, 45.3% of them had ALT of 81-100 U/L and 18.7% of patients had ALT of more than 100 U/L. while and mean AST of NAFLD patients was (28.5 U/L); 10% of them had high AST. The result shows a highly significant association between increasing of ALT level and advanced grading of NAFLD. Our study also showed a highly significant association between each of monopolistic and reverse hepatic vein flow with advanced grading of NAFLD. Conclusions: There is an obvious correlation between increased ALT and AST levels with advanced grading of non-alcoholic fatty liver disease assessed by Doppler ultrasound hepatic vein flow patterns.

***Keywords*---**Non-alcoholic fatty liver disease, hepatic veins Doppler, Ultrasound, Aminotransferases.

## Introduction

Nonalcoholic fatty liver disease (NAFLD) is among the most common causes of chronic liver diseases in Western countries, occurring in approximately 30% of the entire population [1, 2]. Non-alcoholic fatty liver disease (NAFLD) is defined as the excessive and abnormal intracellular accumulation of lipid in the liver, primarily in the form of triglycerides [3, 4]. NAFLD is present when the deposit of lipids, particularly triglycerides, exceeds 5% of total weight [5, 6]. NAFLD consists of a spectrum of diseases, can be ranged from simple steatosis, nonalcoholic steatohepatitis (NASH), liver fibrosis, and liver cirrhosis [7, 8]. Progression from simple hepatic steatosis to advanced stages of nonalcoholic fatty liver disease has not clear risk factor or incidence, However, the progression of simple hepatic steatosis to cirrhosis through the development of nonalcoholic steatohepatitis (NASH) and fibrosis has been established [2, 9, 10]. The pathogenesis of NAFLD is not completely understood; however, a few mechanisms were proposed to explain the liver injury associated with metabolic syndrome. Identification of these mechanisms has therapeutic importance, because targeted therapies might prevent the progression of NAFLD to fibrosis and cirrhosis [9]. Insulin resistance plays a central role in NASH pathogenesis. Insulin resistance is the main feature of metabolic syndrome, which embodies obesity, hypertension, diabetes, and dyslipidemia [10]. Traditionally, liver biopsy has been the gold standard technique for the diagnosis and quantification of hepatic steatosis, and the only reliable method for differentiating NASH from simple steatosis [11]. liver biopsy is an invasive procedure with its own complication such, bleeding as well as procedure related mortality although the morality rate associated with liver biopsy is quite low. Small sample volume of liver parenchyma and reproducibility of assessment among the different pathologists could be another limitation of liver biopsy [12].

Ultrasound (US) has several virtues over other imaging modalities including computerized tomography scan and magnetic resonance imaging: US is widely available, and there is no need of radiation exposure in doing US examination. Therefore, US has been widely used as primary imaging modality for the evaluation of liver disease. Evaluation of hepatic steatosis using US is based on the echo change in hepatic parenchyma. As intracellular accumulation of fat vacuoles reflects the ultrasound beam, hepatic steatosis appears as a diffuse increased hepatic parenchymal echogenicity, or “bright liver” on US [11]. High diagnostic accuracy can be achieved by the ultrasound when sonographic features unique to NAFLD are standardized and used to aid in diagnosis. Bright hepatic echoes, increased hepatorenal echogenicity and vascular blurring of portal or hepatic vein have been classified as unique sonographic features of NAFLD. In a prospective study by Dasarathy et al [13] real time ultrasound was performed followed by a liver biopsy to evaluate the accuracy of ultrasound in hepatic steatosis. When steatosis was greater than 20% on biopsy, these sonographic features were able to predict the presence of NAFLD with greater than 90% sensitivity. Lower levels of fat content resulted in reduction of sensitivity [13].

The severity of hepatic steatosis on ultrasound in the presence of metabolic syndrome is an exceptional non-invasive tool for observing liver disease than liver enzymes [14]. Laboratory abnormalities often are the only sign of non-alcoholic fatty

liver disease. The most common abnormal laboratory test results are elevated alanine transaminase (ALT) and aspartate transaminase (AST), usually one to four times the upper limits of normal [15]. However, patients with nonalcoholic fatty liver disease may have normal transaminase levels. The ratio of AST/ALT usually is less than 1 (in alcoholic liver disease, this ratio typically will be greater than 2) but may increase as the severity of the liver damage increases [16].

Alkaline phosphatase may be elevated up to twice the upper limit of normal; γ-glutamyl transferase (GGT) also may be elevated. Normal alanine aminotransferase (ALT) level alone was not sufficient for exclusions of significant hepatic steatosis [17]. As change occurs in aminotransferases, there is usually increased alanine transferase (ALT), while aspartate aminotransferase (AST) levels remain normal or slightly elevated values. Meanwhile, nearly 80% of patients have normal ALT levels. The use of ALT for diagnosis is controversial to detect severity of NAFLD [18-20]. Those had advanced fibrosis on liver biopsy has been found that Aspartate aminotransferase (AST)/ALT ratio greater than 1 [21].

Another noninvasive mechanism for evaluation of hepatic vasculature and certain hepatic parenchymal diseases is duplex doppler ultrasonography which is an important diagnostic approach [22]. Recent articles suggest that NAFLD can change the waveform pattern of hepatic veins [23]. Hepatic vein pulsatility is also flattened in obese patients, correlating with the grade of hepatosteatosis. The body habitus itself does not have an independent effect on hepatic venous waveform [24]. The aim of this study was to evaluate hepatic doppler ultrasound indices in liver steatosis diagnosis and grading in correlation to aminotransferases.

**Methodology**

The design of present study was a cross sectional study implemented in the Rizgary teaching hospital and Hawler teaching hospitals in Erbil, Kurdistan/Iraq, through the period of one year from 1st of June 2021, to 31st of May 2022. The studied population was all patients with non-alcoholic fatty liver disease (NAFLD) presented to ultrasound unit of Rizgary teaching hospital and Hawler teaching hospitals. Inclusion criteria were adults patients irrespective than gender with NAFLD attending ultrasound unit for abdominal ultrasound. Patients with a history of alcohol consumption more than 20 g/day were excluded. Subjects using potential steatosis- inducing drugs such as prednisolone, corticosterone, amiodarone, calcium channel blockers, tamoxifen, and methotrexate were also excluded. Likewise, positive viral hepatitis serum markers indicating chronic viral hepatitis, critically ill patients, hemodynamically unstable patients, patients not willing for the study and patients with morbid obesity posting difficulty in doppler measurement were among exclusion criteria. Those with a history of gastric bypass surgery, quick weight loss, or cachexia were also excluded. The study ethics were implemented in regard to Helsinki Declaration by documented approval of Ethical Committee of Hawler Medical University, oral consent of patients and management of any complications accordingly. A convenient sample of 150 patients with NAFLD detachment was enrolled in present study. The sample size is calculated according to statistical software EPI-info program.

Information of patients was collected directly by researcher through a prepared questionnaire designed by the researchers. The questionnaire included general characteristics of patients with NAFLD (age, gender, smoking and body mass index), dietary patterns and lifestyle of NAFLD patients (meals per day, eating fast food, times of eating fast food per day, performing exercise and current symptoms) and investigations findings and grading of NAFLD patients (ALT, AST, liver span, ultrasound grading of fatty liver and hepatic vein flow pattern). Patients who had ultrasound characteristics of non-alcoholic fatty liver disease (moderate or severe), detailed medical history, was taken and subjected to specific investigations to exclude alcoholic liver disease, viral hepatitis. After excluding other cause of increasing liver echogenicity, patients were diagnosed as having NAFLD if they have elevated liver enzymes (usually if AST / ALT ratio less than 1 simple steatosis will be suggested but if AST /ALT ratio greater than 1 fibrosis will be suggested) with a report of fatty liver in sonographic evaluation, because NAFLD resembles alcoholic liver disease but occurs in people who drink little or no alcohol.

Ultrasound examinations was performed by a single system Phlipis machine a 3.5 MHz convex transducer, Liver gray scale and vascular Doppler US was performed by the researcher at entry. After 8-12 hour of fasting to report grades of fatty liver, hepatic vein waveform (HVW). The ALT and AST investigations were implemented in Laboratory of teaching hospitals. These data was categorized as normal level, high and low level according to laboratory normal ranges. The NAFLD patients' information were entered and interpreted statistically by SPSS program-26. Suitable statistical tests (Chi square and Fishers exact tests) for data were implemented accordingly and p value of ≤0.05 was significant.

**Results**

This study included one hundred and fifty patients with non-alcoholic liver fatty disease (NAFLD) presented with mean age of (49.2 years); 32.7% of them were at age group of 50-59 years and 31.3% of them were at age group of 60-69 years. The male gender NAFLD patients were more than females (55.3% vs. 44.7%). Current smoking was represented by 58% of NAFLD patients and ex-smoking was represented by 18.7% of them. The body mass index of NAFLD patients was divided into overweight (68%) and obese (32%). (***Table 1***)

Table 1: General characteristics of NAFLD patients.

| **Variable** | **No.** | **%** |
|---|---|---|
| **Age** mean±SD (49.2±18.5 years) | | |
| 20-29 years | 7 | 4.7 |
| 30-39 years | 11 | 7.3 |
| 40-49 years | 15 | 10.0 |
| 50-59 years | 49 | 32.7 |
| 60-69 years | 47 | 31.3 |
| ≥70 years | 21 | 14.0 |
| **Gender** | | |
| Male | 83 | 55.3 |
| Female | 67 | 44.7 |

| | | |
|---|---|---|
| **Smoking** | | |
| Current smoking | 87 | 58.0 |
| Ex-smoking | 28 | 18.7 |
| No smoking | 35 | 23.3 |
| **Body mass index** | | |
| Overweight | 102 | 68.0 |
| Obese | 48 | 32.0 |
| **Total** | **150** | **100.0** |

Most (78.7%) of NAFLD patients ate three meals per day, while 62% of NAFLD patients ate fast food; one time/week (53.8%), 2-3 times/week (33.3%) and more than three times/week (12.9%). Less than half (46%) of NAFLD performed exercise; 58% of them performed exercise twice weekly. Common current symptom of NAFLD was upper abdominal pain (84.8%), followed by; no related symptoms (15.2%). (***Table 2***)

Table 2: Dietary patterns and lifestyle of NAFLD patients.

| **Variable** | **No.** | **%** |
|---|---|---|
| **Meals per day** | | |
| Two meals | 20 | 13.3 |
| Three meals | 118 | 78.7 |
| More than three meals | 12 | 8.0 |
| **Eating fast food** | | |
| Yes | 93 | 62.0 |
| No | 57 | 38.0 |
| **Times of eating fast food per week** | | |
| One time | 50 | 53.8 |
| 2-3 times | 31 | 33.3 |
| >3 times | 12 | 12.9 |
| **Performing exercise** | | |
| Yes | 69 | 46.0 |
| No | 81 | 54.0 |
| **If yes, times of exercise** | | |
| Everyday | 1 | 1.4 |
| Once a week | 28 | 40.6 |
| Twice a week | 40 | 58.0 |
| **Current symptom** | | |
| Upper abdominal pain | 123 | 84.8 |
| No related symptoms | 22 | 15.2 |
| **Total** | **150** | **100.0** |

Mean ALT of NAFLD patients was (88.3 U/L); 3% of them had normal ALT, 34% of them had ALT of 57-80 U/L, 45.3% of them had ALT of 81-100 U/L and 18.7% of patients had ALT of more than 100 U/L. while and mean AST of NAFLD patients was (28.5 U/L); 10% of them had high AST. Mean liver span of NAFLD patients was (14.1 cm); 62% of them had liver span of 12-14 cm and 38% of them had span of 15- 16 cm. Grading of NAFLD was distributed as followings; grade I (53.3%), grade II (40%) and grade III (6.7%). The hepatic vein flow patterns were monopolistic in 9.3%

of NAFLD patients, biphasic in 61.3% of patients, triphasic in 28% of patients and reverse in 1.3% of patients. (***Table 3***)

Table 3: Investigations findings and grading of NAFLD patients.

| **Variable** | **No.** | **%** |
|---|---|---|
| **ALT** mean±SD (88.3±18.1 U/L) | | |
| <57 U/L | 3 | 2.0 |
| 57-80 U/L | 51 | 34.0 |
| 81-100 U/L | 68 | 45.3 |
| >100 U/L | 28 | 18.7 |
| **AST** mean±SD (28.5±10.1 U/L) | | |
| Normal | 135 | 90.0 |
| High | 15 | 10.0 |
| **Liver span** mean±SD (14.1±0.8 cm) | | |
| 12-14 cm | 93 | 62.0 |
| 15-16 cm | 57 | 38.0 |
| **Grade of fatty liver** | | |
| Grade I | 80 | 53.3 |
| Grade II | 60 | 40.0 |
| Grade III | 10 | 6.7 |
| **Hepatic vein flow pattern** | | |
| Monopolistic | 14 | 9.3 |
| Biphasic | 92 | 61.3 |
| Triphasic | 42 | 28.0 |
| Flatten | 0 | - |
| Reverse | 2 | 1.3 |
| **Total** | **150** | **100.0** |

No significant differences were observed between NAFLD patients with different grades regarding age (p=0.73) and gender (p=0.55). There was a significant association between obesity of NAFLD patients and advanced grading of NAFLD (p=0.004). (***Table 4***)

Table 4: Distribution of patients' general characteristics according to NAFLD grading.

| ***Variable Grades of fatty liver*** | ***Grade I*** | | ***Grade II*** | | ***Grade III*** | | |
|---|---|---|---|---|---|---|---|
| | **No.** | **%** | **No.** | **%** | **No.** | **%** | |
| **Age** | | | | | | | 0.73 NS |
| 20-29 years | 6 | 7.5 | 1 | 1.7 | 0 | - | |
| 30-39 years | 6 | 7.5 | 5 | 8.3 | 0 | - | |
| 40-49 years | 9 | 11.3 | 5 | 8.3 | 1 | 10.0 | |
| 50-59 years | 27 | 33.8 | 19 | 31.7 | 3 | 30.0 | |
| 60-69 years | 20 | 25.0 | 23 | 38.3 | 4 | 40.0 | |
| ≥70 years | 12 | 15.0 | 7 | 11.7 | 2 | 20.0 | |
| **Gender** | | | | | | | 0.55 NS |
| Male | 42 | 52.5 | 34 | 56.7 | 7 | 70.0 | |
| Female | 38 | 47.5 | 26 | 43.3 | 3 | 30.0 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Smoking** | | | | | | | 0.38 NS |
| Current smoking | | 57.5 | 37 | 61.7 | 4 | 40.0 | |
| Ex-smoking | | 15.0 | 13 | 21.7 | 3 | 30.0 | |
| No smoking | | 27.5 | 10 | 16.7 | 3 | 30.0 | |
| **Body mass index** | | | | | | | **0.004** S |
| Overweight | 62 | 77.5 | 37 | 61.7 | 3 | 30.0 | |
| Obese | 18 | 22.5 | 23 | 38.3 | 7 | 70.0 | |

*NS=Not significant, S=Significant.*

No significant differences were observed between NAFLD patients with different grades regarding meals per day (p=0.42), eating fast food (p=0.26), times of eating fast food per week (p=0.73) and times of exercise (p=0.78). There was a significant association between not performing exercise by patients and advanced grading of NAFLD (p=0.02). A significant association was observed between patients with no related symptoms and advanced grading of NAFLD (p=0.02). (***Table 5***)

Table 5: Distribution of dietary patterns and lifestyle according to NAFLD grading.

| ***Variable Grades of fatty liver*** | | | ***P Grade I*** | | ***Grade II*** | | ***Grade III*** |
|---|---|---|---|---|---|---|---|
| | **No.** | **%** | **No.** | **%** | **No.** | **%** | |
| **Meals per day** | | | | | | | 0.42 |
| Two meals | 10 | 12.5 | 10 | 16.7 | 0 | - | |
| Three meals | 62 | 77.5 | 46 | 76.7 | 10 | 100.0 | |
| More than three meals | 8 | 10.0 | 4 | 6.7 | 0 | - | |
| **Eating fast food** | | | | | | | 0.26 NS |
| Yes | 49 | 61.3 | 40 | 66.7 | 4 | 40.0 | |
| No | 31 | 38.8 | 20 | 33.3 | 6 | 60.0 | |
| **Times of eating fast food per week** | | | | | | | 0.73 NS |
| One time | 28 | 57.1 | 20 | 50.0 | 2 | 50.0 | |
| 2-3 times | 16 | 32.7 | 13 | 32.5 | 2 | 50.0 | |
| >3 times | 5 | 10.2 | 7 | 17.5 | 0 | - | |
| **Performing exercise** | | | | | | | **0.02** S |
| Yes | 35 | 43.8 | 33 | 55.0 | 1 | 10.0 | |
| No | 45 | 56.3 | 27 | 45.0 | 9 | 90.0 | |
| **If yes, times of exercise** | | | | | | | 0.78 NS |
| Everyday | 1 | 2.9 | 0 | - | 0 | - | |
| Once a week | 14 | 40.0 | 14 | 42.4 | 0 | - | |
| Twice a week | 20 | 57.1 | 19 | 57.6 | 1 | 100.0 | |
| **Current symptom** | | | | | | | **0.02** S |
| Upper abdominal pain | 70 | 89.7 | 48 | 82.8 | 5 | 55.6 | |
| No related symptoms | 8 | 10.3 | 10 | 17.2 | 4 | 44.4 | |

*S=Significant, NS=Not significant.*

There was a highly significant association between each of monopolistic and reverse hepatic vein flow with advanced grading of NAFLD (p<0.001). A highly significant association was observed between increasing of ALT level and advanced grading of NAFLD (p<0.001). Means of ALT and AST were significantly increased with advanced grading of NAFLD (p<0.001). No significant differences

were observed between NAFLD patients with different grades regarding liver span (p=0.57). (***Table 6***)

Table 6: Distribution of investigations findings according to NAFLD grading.

| ***Variable*** | ***Grades of fatty liver*** | | ***P*** | ***Grade I*** | | ***Grade II*** | | ***Grade III*** | |
|---|---|---|---|---|---|---|---|---|---|
| **No.** | | **%** | | **No.** | **%** | **No.** | **%** | | |
| **Hepatic vein flow pattern** | | | | | | | | **<0.001** | S |
| Monopolistic | 0 | - | | 7 | 11.7 | 7 | 70.0 | | |
| Biphasic | 51 | 63.8 | | 40 | 66.7 | 1 | 10.0 | | |
| Triphasic | 29 | 36.3 | | 13 | 21.7 | 0 | - | | |
| Reverse | 0 | - | | 0 | - | 2 | 20.0 | | |
| **ALT groups** | | | | | | | | **<0.001** | S |
| <57 U/L | 3 | 3.8 | | 0 | - | 0 | - | | |
| 57-80 U/L | 50 | 62.5 | | 1 | 1.7 | 0 | - | | |
| 81-100 U/L | 25 | 31.3 | | 41 | 68.3 | 2 | 20.0 | | |
| >100 U/L | 2 | 2.5 | | 18 | 30.0 | 8 | 80.0 | | |
| **ALT mean** | | | | | | | | **<0.001** | S |
| Mean±SD (U/L) | 76.5±13.5 | | | 98.9±9.6 | | 118.1±14 | | | |
| **AST** | | | | | | | | **<0.001** | S |
| Mean±SD (U/L) | 24.4±7.2 | | | 29.2±4.7 | | 56.5±7.7 | | | |
| **Liver span** | | | | | | | | 0.57 | NS |
| Mean±SD (cm) | 14±0.8 | | | 14.1±0.7 | | 14.1±0.8 | | | |

*S=Significant, NS=Not significant.*

**Discussion**

The non-alcoholic fatty liver disease (NAFLD) is prevalent all over the world. Severity of NAFLD is various from mild to nonalcoholic steatohepatitis (NASH) or liver cirrhosis. The alanine transaminase (ALT) and aspartate aminotransferase (AST) are predictors of hepatocellular injury [25]. The current study showed that all NAFLD patients had high ALT level with 45.3% of patients had ALT of 81-100 U/L and 18.7% of patients had ALT of more than 100 U/L. These findings are in agreement with results in many literatures such as Hadizadeh et al [26] review study in Iran and Obika et al [27] review study in Japan which all documented a significant association between increased ALT levels in cases of NAFLD. Our study found that 10% of NAFLD patients had high AST level. This finding is similar to results of Zou et al [28] population based study in China which reported the significance of ALT and ALT to AST ratio in diagnosis and severity assessment of NAFLD with less importance of AST alone in diagnosis of NAFLD. In our study, mean liver span of NAFLD patients was (14.1 cm); 62% of them had liver span of 12-14 cm and 38% of them had span of 15-16 cm. However all of the cases have normal liver span but other signs of hepatomegaly were not excluded like extension of the right lobe inferior to the lower pole of the right kidney and rounding of the hepatic inferior border. Our study revealed that grading of NAFLD was distributed as followings; grade I (53.3%), grade II (40%) and grade III (6.7%). This finding is close to results of Alrubaie et al [29] study in Iraq on 192 patients with NAFLD which reported that more than half of patients had grade I NAFLD. The current study showed that hepatic vein flow patterns were monopolistic in 9.3% of NAFLD patients, biphasic in 61.3% of patients, triphasic in 28% of

patients and reverse in 1.3% of patients. This finding coincides with results of Rangankar et al [30] study in India which stated that incidence of biphasic hepatic vein waveforms increased as severity of fatty liver increased.

The present study showed a highly significant association was observed between increasing of ALT level and advanced grading of NAFLD ($p<0.001$) and means of ALT were significantly increased with advanced grading of NAFLD ($p<0.001$). This finding is consistent with results of Verma et al [31] study in USA on 222 patients with NAFLD which showed a higher specificity of increased ALT values in prediction of fibrosis, NASH and advanced grading of NAFLD. Another prospective hospital based study conducted in Nepal on 85 NAFLD patients by Jwarchan et al [32] found that increased ALT level is correlated significantly with advanced ultrasound grading of NAFLD. Many authors reported normal ALT levels in NAFLD patients with abnormal histological features and progressive disease [19, 33]. Moreover, some authors discussed a new ALT upper limit for a healthy individual (≤ 40 U/L) in both genders. However, increased ALT levels are mostly accompanied by underlying NAFLD [34]. Present study found that Mean of AST was significantly increased with advanced grading of NAFLD ($p<0.001$). This finding coincides with reports of Stål study in Sweden [35]. Our study also showed a highly significant association between each of monopolistic and reverse hepatic vein flow with advanced grading of NAFLD ($p<0.001$). This finding is parallel to results of Sabry et al [36] study in Egypt which stated that hepatic vein flow pattern is changed in accordance to grades of NAFLD.

In present study, there was a significant association between obesity of NAFLD patients and advanced grading of NAFLD ($p=0.004$). Similarly, Polysoz et al [37] study in USA reported the significant correlation between obesity and advanced grading of NAFLD. Our study found a significant association between not performing exercise by patients and advanced grading of NAFLD ($p=0.02$). This finding is consistent with results of Golabi et al [38] study in USA which reported that physical inactivity lead to sarcopenia and advanced grading of NAFLD with high mortality. In our study, a significant association was observed between patients with no related symptoms and advanced grading of NAFLD ($p=0.02$). Consistently, Armstrong et al [39] study in UK revealed that high proportion of patients with advanced grading of NAFLD were asymptomatic.

This study concluded an obvious correlation between increased ALT and AST levels with advanced grading of non-alcoholic fatty liver disease assessed by Doppler ultrasound hepatic vein flow patterns. Higher levels of ALT are significantly correlated with advanced grades of non-alcoholic fatty liver disease. Obesity, physical inactivity and asymptomatic presentation are highly related to advanced grades of non-alcoholic fatty liver disease. This study recommended adopting aminotransferases measurement as a routine screening tool in population at high risk of non-alcoholic fatty liver disease.

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