Original Article

# Liver stiffness and liver function index in liver fibrosis patients afflicted with electrocardiographic abnormalities

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## Abstract

**Introduction:** Heart disorders are one of the causes of death in cirrhotic patients. **Objectives:** This study aimed to investigate liver stiffness and liver function indices in liver fibrosis patients afflicted with electrocardiographic abnormalities. **Patients and Methods:** Two hundred patients entered this cross-sectional study. First, all of the patients underwent liver elastography. They were then divided into four groups based on the results obtained. Patients in three of the total groups (I–III) had fibrosis and those in the fourth group (IV) had cirrhosis. Afterward, electrocardiograms were taken from the patients, and based on the existence of electrocardiographic abnormalities, the patients were divided into two groups (group 1, consisting of liver fibrosis patients with a heart disease and group 2, consisting of those without a heart disease). Finally, liver function index, liver stiffness, frequency of variables, and their relationship with the presence or absence of electrocardiographic (ECG) abnormalities were analyzed. **Results:** Forty-eight percent of the patients were afflicted with ECG abnormalities. The majority of the patients in each of the two groups were male. The differences between patients with and without electrocardiographic abnormalities as regards to liver stiffness, liver function index, and platelet count were found to be statistically significant ($P < 0.05$). However, the differences between the two groups with regard to serum transaminase levels did not appear to be statistically significant ($P > 0.05$). **Conclusion:** It seems that liver stiffness and liver function index are non-invasive factors for predicting the presence of accompanying heart disorders in patients suffering from liver fibrosis.

**Keywords:** Elastography, electrocardiography abnormality, liver fibrosis, liver function index, liver stiffness

## Introduction

Cardiovascular abnormalities have been reported to happen in patients with liver diseases and cirrhosis. These abnormalities worsen the cardiac symptoms of the patients and affect their liver function negatively.[1] Disturbance in liver function and portal hypertension lead to the dilation of visceral and systemic vessels. This, in turn, results in the development of hyperdynamic syndrome, which is characterized by increased cardiac output, higher heartbeat rate, reduced systemic peripheral resistance, and normal or lower arterial pressure.[2]

Hepatic steatosis is strongly associated with coronary heart disease (CHD) and is accompanied by its subclinical markers including carotid intima-media thickness and coronary artery calcification.[3] In adult cardiovascular diseases, liver stiffness is indicative of central venous pressure. However, the relationship between liver diseases and heart disorders is controversial.[4] Previous studies have mainly focused on hepatic steatosis, However, it is still unknown.[5,6]

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FibroScan shows the degree of liver fibrosis or liver stiffness based on the assessment of scans and collagen content.[7] It is a fast and highly precise non-invasive tool which can be used together with liver biopsy.[8] Studies have shown that there is a direct relationship between liver stiffness and fibrosis score.[9]

## Objectives

The aim of the present study was to investigate liver stiffness and liver function indices in patients with liver fibrosis who were suspected of having electrocardiographic abnormalities.

## Patients and Methods

### Study design

In this analytical cross-sectional study, 200 patients were investigated. After obtaining written consent from each of the patients, a checklist was used to record their demographic information, cause of liver disease, and results of liver function tests. First, the patients underwent liver elastography and a FibroScan was obtained for each of them based on the manufacturer's instructions (FibroScan 502, Model: Echosens, Paris, France). Based on the test results, the patients were then divided into four groups. Those in three of the groups (I–III) had fibrosis and those in the fourth group (IV) had cirrhosis. Liver function indices were calculated using the following formulae:

APRI = AST (IU/l)/(upper limit of normal)/platelet count ($\times 10^9$/L) × 100.

Fibrosis 4 Score = (Age × AST)/(Platelet count × √ALT)

After that, an electrocardiogram was taken from each of the patients. The electrocardiograms were then examined by a cardiologist for possible arrhythmia (atrial fibrillation and flutter, left and right bundle branch block, and other heart blocks) and cardiac ischemia. The patients were divided into two groups based on the results of elastography and electrocardiography. Patients who had fibrosis together with heart disease were assigned to one group and those who had fibrosis without any heart disease were assigned to another group. Finally, liver function index, liver stiffness, the frequency of variables and their relationship with the presence or absence of electrocardiographic abnormalities were investigated.

The criteria for participating in the study were signing a written informed consent and being in the age range of 20–60 years. The exclusion criteria, on the other hand, were having acute infection, septicemia, autoimmune disease, and cancer, as well as consuming corticosteroid and anti-inflammatory drugs.

### Statistical analysis

The normality of the data was tested using Kolmogorov–Smirnov test. For the analysis of the data with normal distribution, a parametric test (i.e., independent *t*-test) was used, and for the analysis of the data with non-normal distribution, a non-parametric test (i.e., Mann–Whitney *U* test) was employed. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 20. In all tests, the significance level was set at $P < 0.05$.

## Results

In this study, 200 patients were investigated. From among these patients, 96 cases (48%) had electrocardiographic abnormalities while 104 cases (52%) did not have such abnormalities [Table 1]. The mean age of the patients with electrocardiographic abnormalities was 52.22 ± 9.18 years and that of the patients without such abnormalities was 48.32 ± 10.31 years. Of the total patients under investigation, 124 cases (62%) were male and 76 cases (38%) were female. In the group of patients with electrocardiographic abnormalities, 62 cases were male and 42 cases were female, while in the group of patients without such abnormalities, 62 cases were male and 34 cases were female. In this study, nonalcoholic steatohepatitis (NASH) was found to be the most common cause of liver fibrosis: it gave rise to liver fibrosis in 44 patients (22%) [Table 1].

Based on the FibroScan results, the patients were divided into four groups; the cases in three of these groups (I–III) had liver

**Table 1: Frequency of cardiac and hepatic disorders with severity of hepatic fibrosis**

| variable | Type of disorder | Number (%) |
|---|---|---|
| Electrocardiography | Normal | 96 (48) |
| | Fibrillation | 16 (8) |
| | Floater | 4 (2) |
| | Heart block | 29 (14.5) |
| | Cardiac ischemia | 5 (2.5) |
| | Cardiac arrhythmia | 44 (22) |
| | Cardiac hypertrophy | 6 (3) |
| Cause of hepatic fibrosis | Non-alcoholic steatohepatitis (NASH) | 44 (22) |
| | Primary biliary cholangitis (PBC) | 1 (0.5) |
| | IgG4-related disease | 6 (3) |
| | Cryptogenic | 11 (5.5) |
| | Biliary cirrhosis | 5 (2.5) |
| | Hemochromatosis | 2 (1) |
| | Wilson | 2 (1) |
| | Hepatitis C | 38 (19) |
| | Hepatitis B | 28 (14) |
| | Alcoholic Hepatitis | 15 (7.5) |
| | Autoimmune hepatitis (AIH) | 13 (6.5) |
| | Non-alcoholic fatty liver disease (NAFLD) | 29 (14.5) |
| | Primary sclerosing cholangitis (PSC) | 6 (3) |
| Severity of hepatic fibrosis | Grade I | 20 (10) |
| | Grade II | 25 (12.5) |
| | Grade III | 30 (15) |
| | Cirrhosis | 125 (62.5) |

**Table 2: Frequency of electrocardiographic abnormalities in different stages of liver fibrosis**

| Fibrosis | Electrocardiography | | | | | | |
|---|---|---|---|---|---|---|---|
| | Normal | Fibrillation | Floater | Heart block | Cardiac ischemia | Cardiac arrhythmia | Cardiac hypertrophy |
| Grade I | 17 | 0 | 0 | 1 | 0 | 2 | 0 |
| Grade II | 15 | 0 | 0 | 1 | 0 | 9 | 0 |
| Grade III | 14 | 6 | 0 | 2 | 0 | 8 | 0 |
| Cirrhosis | 50 | 10 | 4 | 25 | 5 | 25 | 6 |

**Table 3: Liver stiffness and liver function index in patients with electrocardiographic abnormalities**

| Variable | Electrocardiography | | | | | | |
|---|---|---|---|---|---|---|---|
| | Normal | Fibrillation | Floater | Heart block | Cardiac ischemia | Cardiac arrhythmia | Cardiac hypertrophy |
| Liver stiffness | 3.22±2.55 | 5.47±2.78 | 7.10±1.68 | 4.22±2.95 | 6.57±3.76 | 3.76±2.16 | 3.24±0.21 |
| Liver function index | 45.83±33.63 | 66.84±47.48 | 67.5±23.67 | 55.62±36.26 | 84.00±43.60 | 51.13±32.70 | 37.65±2.11 |

**Table 4: Comparison of liver function index and liver stiffness in patients with and without electrocardiographic abnormalities**

| Variable | ECG | Mean±SD | *P* |
|---|---|---|---|
| Liver function index | Normal | 45.84±33.63 | 0.037 |
| | Abnormal | 56.23±36.25 | |
| Liver stiffness | Normal | 3.21±2.55 | 0.003 |
| | Abnormal | 4.33±2.68 | |

**Table 5: Hematological parameters under investigation in patients with and without electrocardiographic abnormalities**

| Variable | ECG | Mean±SD | *P* |
|---|---|---|---|
| Alanine aminotransferase (ALT) | Normal | 40 | 0.198 |
| | Abnormal | 48 | |
| Aspartate aminotransferase (AST) | Normal | 47.5 | 0.065 |
| | Abnormal | 66 | |
| Platelets | Normal | 130,000 | 0.033 |
| | Abnormal | 115,000 | |

fibrosis and in those in the fourth group (IV) had cirrhosis. Cirrhosis was the most prevalent condition, which was observed in 62.5% of the cases [Table 1]. Also, the highest frequency of electrocardiographic abnormalities was observed in patients with liver cirrhosis [Table 2].

The patients' liver stiffness was examined based on the FibroScan results. The patients' mean liver stiffness was 3.79 ± 2.68. Furthermore, their mean liver function index was 51.24 ± 35.31 [Table 3].

The difference between patients with and without electrocardiographic abnormalities as regards to the liver function index was statistically significant ($P = 0.037$). Moreover, the difference between these two groups of patients regarding liver stiffness was also significant ($P = 0.003$) [Table 4].

The results of the Mann–Whitney *U* test revealed that there were no significant differences between patients with and without electrocardiographic abnormalities as regards to serum ALT and serum AST levels. However, the two groups of patients turned out to be significantly different in terms of platelet count ($P = 0.033$) [Table 5].

## Discussion

Most of the patients afflicted with cirrhosis have some degree of cardiovascular disorders which usually emerge following great stresses such as liver transplant and, in some cases, can lead to death. There is a direct relationship between the severity of cirrhosis and the progress of cardiac disorders.[10] These disorders can emerge as either systolic or diastolic dysfunction. Different humoral and hemodynamic mechanisms which cause cardiac disorders in patients with cirrhosis can affect the prognosis of patients with advanced cirrhosis. The increase of circulating blood volume in patients with advanced cirrhosis leads to a constant increase in cardiac output and the load imposed on the heart which, in turn, can lead to the reduction of afterload, resistance of heart failure, and cirrhotic cardiomyopathy. Peripheral arteries in cirrhotic patients can hide heart failure.[11] In general, based on the findings of the present study, the differences between patients with and without electrocardiographic abnormalities as regards to liver stiffness, liver function index, and platelet count were statistically significant, while their differences regarding serum ALT and serum AST levels were not statistically significant ($P > 0.05$).

In their study, Kasper *et al.*[12] investigated the relationship between liver fibrosis and the risk of CHD in patients afflicted with non-alcoholic fatty liver disease (NAFLD). Their findings showed that the assessment of liver fibrosis could be useful for classifying the risk of CHD, which is consistent with our findings in the current study.

In another study, Ostovaneh *et al.*[2] investigated the relationship between liver fibrosis and cardiovascular diseases. They found that liver fibrosis was associated with heart failure, atrial fibrillation, left bundle branch block (LBBB), right bundle branch block (RBBB), and CHD. The existence of a relationship between

liver fibrosis and CHD can be due to atherosclerosis, which is in line with the finding of the present study. We too observed that liver stiffness and advanced stages of liver fibrosis were more prevalent among patients with more electrocardiographic abnormalities.

In another study, Friedrich-Rust *et al.*[13] indicated that although NAFLD was significantly more prevalent among patients with atherosclerosis, there was no significant difference between NAFLD and advanced fibrosis, which is in line with the findings of the present study. They also showed that cardiac ischemia was considerable in patients afflicted with NAFLD.

In their study, Ismaiel *et al.*[14] investigated heart arrhythmias and electrocardiographic variations in patients afflicted with NAFLD. They found that hepatic steatosis and cirrhosis were independently associated with the increased risk of atrial fibrillation, flutter, and other arrhythmias in NAFLD and cirrhotic patients, which is in line with our findings. They observed that atrial fibrillation was the most prevalent arrhythmia. They also observed that the severity and frequency of electrocardiographic abnormalities were directly related to the severity of liver fibrosis.

Two studies demonstrated that hepatic steatosis caused various types of heart block due to QTc prolongation. Four studies supported the existence of a relationship between cardiac conduction abnormalities on the one hand and NAFLD and cirrhosis on the other. They concluded that NAFLD and cirrhosis were independently associated with atrial fibrillation, QTc prolongation, and multiple heart blocks. Diabetic patients with NAFLD were also found to be at a higher risk of being afflicted with ventricular arrhythmia.[14] The findings reported in all of these studies are consistent with our findings in this study.

In the study conducted by Matin *et al.*,[15] heart failure in patients with cirrhosis was investigated. Results revealed that the prognosis of patients afflicted with cirrhotic cardiomyopathy was affected by heart failure. In the current study too, the severity of fibrosis was found to be higher in patients with left ventricular hypertrophy (LVH).

In another study, You *et al.*[16] investigated the FibroScan results of 285 patients with the aim of determining the relationship between coronary atherosclerosis and liver fibrosis. They indicated that higher coronary artery calcification score was independently associated with liver stiffness in patients afflicted with NAFLD. This relationship was also observed in the current study in the form of severe electrocardiographic abnormalities in patients afflicted with NAFLD.

## Conclusion

The findings of this study indicated that with an increase in the severity of liver fibrosis, the frequency and severity of the various types of heart disorders increase. Moreover, significant differences were observed between patients with and without electrocardiographic abnormalities as regards to liver stiffness, liver function index, and platelet count. It seems that liver stiffness and liver function index can be used as non-invasive factors for predicting the presence of heart disorders. This prediction can lead to the detection of patients at high risk of heart diseases, and providing appropriate therapeutic interventions can reduce the mortality of these patients.

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## Limitations of the study

Limitations of the study are the small number of patients and monocentric design, which might limit its generalization.

## Authors' contribution

EH, PA and ASD were the principal investigators of the study. SJH, AP, AK, EH and ASD were included in preparing the concept and design. EH and ASD revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

## Ethical issues

The research was conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved the study. The institutional ethical committee at Ahvaz Jundishapur University of Medical Sciences accepted all study protocols (IR.AJUMS.HGOLESTAN.REC.1400.003). Accordingly, written consent was taken from all participants before any intervention. This study was extracted from MSc thesis of Ahmad Shokr Darghahi at this university (Thesis #4259).

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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