

# Association between high-sensitivity-CRP and liver elastography and cardiac ischemic diseases in patients with fatty liver

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## ABSTRACT

**Objective:** Inflammatory markers are among the possible contributing factors with a proposed role in hepatic and ischemic heart disease. The present study aimed to determine the association between high-sensitivity-C-reactive protein (hs-CRP), liver elastography, and cardiac ischemic diseases in patients with fatty liver. **Methods:** In this cross-sectional comparative study, 103 consecutive patients with fatty liver were enrolled to undergo angiography. They were divided into groups with and without cardiac ischemia. **Results:** The results demonstrated that the mean hs-CRP was 2.3 and 10.9 mg/L in normal and ischemic angiography groups, respectively ( $P = 0.001$ ). According to the receiver operating characteristic (ROC) analysis, the predictive role for hs-CRP was 94.5% that had sensitivity and specificity of 95.2% and 90%, respectively, with a cut-off point of 3.1. **Conclusion:** This study showed that there is an association between the fatty liver, cardiac ischemia, and hs-CRP level.

**Keywords:** Cardiac ischemia, elastography, fatty liver, hs-CRP, hepatic fibrosis

## Introduction

Fatty liver is a common hepatic disease that may originate from alcohol use (ALD) or diets (NAFLD).<sup>[1]</sup> The first stage in NAFLD is hepatic steatosis with the accumulation of triglyceride in hepatocytes.<sup>[2]</sup> The presence of triglyceride more than 5% in hepatocytes and about 55 g in hepatic tissue (g) is considered steatosis.<sup>[3]</sup> It may be stable or progressive to non-alcoholic steatohepatitis (NASH), recognized by collagen

accumulation and fibrosis with the possibility of progression to cirrhosis.<sup>[4]</sup> Also, cirrhosis may lead to hepatic cancer in 4 to 27% of cases.<sup>[5]</sup>

Ultrasound-based transient elastography is an important method to determine hepatic fibrosis with a further rate in harder and more elastic tissues.<sup>[6,7]</sup> NAFLD is also accompanied by a higher risk of cardiovascular diseases.<sup>[8]</sup> As reported by the World Health Organization (WHO), nearly 17 million deaths have occurred due to cardiovascular diseases.<sup>[9]</sup> Older age, male gender, family history, smoking, high cholesterol and triglyceride, low physical activity, and abdominal obesity are contributing factors.<sup>[10]</sup> Also, inflammation may result in the instability of atherosclerotic plaques leading to cardiovascular events.<sup>[7]</sup> C-reactive protein (CRP) is an important biomarker of inflammation, that is, a predictor of ischemic heart disease.<sup>[11,12]</sup>

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CRP is an acute-phase reactant produced in the liver in response to inflammation and both CRP and hepatic fibrosis are related to interleukin-6.<sup>[13]</sup> CRP may conversely be decreased in myocardial infarction or even overproduced.<sup>[14]</sup> High-sensitivity-CRP (hs-CRP) is a non-specific and sensitive marker for inflammation, infection, and tissue injury.<sup>[15]</sup> CRP has stability for the long-term without diurnal alterations, high sensitivity, low cost, and maybe predictive for the risk of cardiovascular diseases.<sup>[16]</sup> Some studies have shown both intermediate and risk factor roles for hs-CRP.<sup>[17-22]</sup> It may also be affected by clinical, genetic, biochemical, and environmental factors.<sup>[23]</sup> Although some studies have demonstrated that CRP cannot be affected by aspirin in healthy subjects and patients;<sup>[21,22]</sup> it can be increased in cirrhosis patients.<sup>[24]</sup> Previous studies have shown the association between CRP and fatty liver and also cardiovascular diseases; however, it is not assessed simultaneously. Moreover, different results may be obtained from various populations. Regarding some uncertainties in this area, this study aimed to determine the association between hs-CRP, liver elastography, and cardiac ischemic diseases in patients with fatty liver.

## Materials and Methods

In this cross-sectional comparative study, 103 consecutive patients with fatty liver attending Imam-Khomeini Hospital in 2018 were enrolled to undergo angiography. Inclusion criteria were patients with an age range from 20 to 70 years and fatty liver who signed informed consent. The exclusion criteria were patients with acute infection, septicemia, autoimmune disease, cancer, respiratory disease, the lack of informed consent, and who use anti-inflammatory drugs and steroid therapy. The study was carried out in accordance with the Helsinki Declaration Principles. This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical code number IR.AJUMS.REC.1397.928, Date: 2019-03-09).

Data were gathered by questionnaire, biochemical and angiography analysis, and elastography findings. After signing the informed consent, patients were asked to attend the experiment after fasting for 12–14 h. All patients fulfilled the WHO MONICA questionnaire. Blood sampling (5 mL) was carried out for biochemical analysis and it was put at room temperature for 10 min. Then, the clot was removed, serum was obtained by centrifugation at 4000 rpm for 10 min, and stored at  $-20^{\circ}\text{C}$ . The CRP was measured using a commercial Human CRP ELISA Kit (DCRP00, R&D Systems Inc., USA). The patients underwent a physical examination by a cardiologist and resting electrocardiography was recorded. Patients underwent angiography and were accordingly divided into groups with and without cardiac ischemia (codes 1.1 and 1.2 as myocardial infarction, codes 4.1–4.4, 1.3, 5.1–5.3, and 7.1 as cardiac ischemia). Also, the liver ultrasonography and elastography were done by a single device (Fibroscan, model 502; Echosens, Paris, France) and the same operator. The subjects were subdivided into groups with fibrosis (I, II, and III) and cirrhosis (IV).<sup>[25]</sup>

The hs-CRP level was compared across the groups with the consideration of elastography grades and ultrasound fatty liver grades.

Data analysis was done using the SPSS software. The association of CRP levels as dependent variables with independent factors including cardiac disease severity and the intensity of liver disease was evaluated by two-way analysis of variance (ANOVA) to determine the effect of severity of these disorders on the CRP level. Also, ROC analysis and independent-sample *t*-tests were used. *P* values under 0.05 were considered significant.

## Results

Patients were female in 24.2% and 31.7% in those with abnormal and normal angiography results, respectively ( $P > 0.05$ ). According to Table 1, age and obesity did not have a significant effect on angiography ( $P > 0.05$ ). On the contrary, individuals with normal and abnormal angiography were different in background disease ( $P = 0.001$ ) and drug history ( $P = 0.008$ ). The involved vessels were left anterior descending (LAD), right coronary artery (RCA), left circumflex artery (LCX), left anterior descending artery + right coronary artery (LAD plus RCA), left anterior descending artery + left circumflex artery (LAD plus LCX), right coronary artery + left circumflex artery (RCA plus LCX), and three-vessel in 37.1%, 3.2%, 6.5%, 19.4%, 16.1%, 3.2%, and 14.5%, respectively.

The fibrosis and fatty liver grades are shown in Table 2. Although higher fibrosis grades were observed in patients with abnormal angiography ( $P = 0.001$ ), there was no significant difference between normal and abnormal angiography groups in terms of fatty liver grade ( $P > 0.05$ ).

**Table 1: Background variables across the groups**

Variable	ANL angiography	NL angiography	<i>P</i>
Elderly age	10 (16.1%)	3 (7.3%)	>0.05
Overweight/obesity	54 (87.1%)	29 (70.7%)	>0.05
Background disease*	43 (69.4%)	12 (29.3%)	0.001
Drug history**	36 (58.1%)	11 (26.8%)	0.008

\*including diabetes, hyperlipidemia, hypertension. \*\*including anti-hypertensive, anti-hyperlipidemia, glucose-lowering, and cardiotoxic drugs

**Table 2: Fibrosis and fatty liver grades across the groups**

Variable	ANL angiography	NL angiography	<i>P</i>
Fibrosis grade			
0	1 (1.6%)	3 (7.3%)	0.001
1	1 (1.6%)	27 (65.9%)	
2	26 (41.9%)	9 (22.0%)	
3	30 (48.4%)	2 (4.9%)	
4	4 (6.5%)	---	
Fatty liver grade			
1	20 (32.3%)	15 (36.6%)	>0.05
2	32 (51.6%)	18 (43.9%)	
3	10 (16.1%)	8 (19.5%)	

Mean (standard deviation [SD]) hs-CRP was 2.3 [2.1] and 10.9 [5.3] mg/L in normal and ischemic angiography groups ( $P = 0.0001$ ), respectively. According to the ROC analysis, the predictive role for hs-CRP was 94.5% (confidence interval [CI] 95% between 0.891 and 0.998) that had sensitivity and specificity of 95.2% and 90%, respectively, with a cut-off point of 3.1. According to Table 3, the comparison of mean hs-CRP between normal and abnormal angiography in patients with fatty liver was not differed ( $P > 0.05$ ); however, this difference was observed in patients with hepatic fibrosis ( $P = 0.001$ ). This difference (hs-CRP level in NL and ANL angiography groups with fibrosis) was observed in both individuals with no background diseases and individuals with background diseases (diabetes mellitus [DM], hyperlipidemia [HLP]; hypertension [HT]). In addition to individuals with no drug history, there was no significant difference in hs-CRP levels between groups (NL and ANL angiography) with fatty liver and drug history ( $P > 0.05$ ).

## Discussion

The association of CRP with the severity of fatty liver and cardiovascular diseases was assessed separately in previous studies, and these variables were simultaneously evaluated for the first time. This study was carried out to investigate the possible association between these variables, introduce a common biomarker among them, and consequently diagnose and probably prevent these diseases in their early stages. The mean hs-CRP was 10.9 and 2.3 mg/L in those with normal and abnormal angiography showing significant differences. Moreover, the cut-off was 3.1 with a sensitivity and specificity of 95 and 90%, respectively. However, there was a significant difference in the level of hs-CRP according to elastography fibrosis grade but not based on ultrasound fatty liver grade.

Ischemic heart disease or coronary heart disease happens when the blood vessels are narrowed due to an inflammatory disease, namely atherosclerosis. Recent studies showed that the atherosclerotic process occurs along with an increase in the

markers of inflammation, for example, acute-phase protein and cytokines.<sup>[26]</sup> CRP is considered the first line of defense against pathogens and may contribute to atherosclerosis because it decreases the expression of nitric oxide synthase and prostacyclin synthase. However, this molecule induces macrophages to uptake LDL-C, an important step in atherosclerosis.<sup>[27]</sup> The mean level of this protein is 0.8 mg/L in healthy individuals and 50 µg to more than 500 mg/L in patients with inflammatory diseases.<sup>[28]</sup> Fatty liver diseases and coronary heart diseases are associated with each other through multiple pathophysiological mechanisms such as systemic inflammation, endothelial dysfunction, hepatic insulin resistance, oxidative stress, and altered lipid metabolism.<sup>[29]</sup> Fatty liver disease can progress to fibrosis and cirrhosis and the degree of liver fibrosis contributes to cardiovascular risk.<sup>[30]</sup> Despite lacking a comprehensive study to evaluate the association between fatty liver disease, CRP, and ischemic heart disease, several studies have assessed these factors separately. Shah *et al.*<sup>[31]</sup> revealed that higher severity of hepatic fibrosis was related to higher IL-6 levels; however, the increased IL-6 conversely decreased the CRP level. Tohidi *et al.*<sup>[17]</sup> reported a significant association between hs-CRP and ischemic heart disease, and CRP measurement was advised in patients with medium-level risk for cardiovascular diseases. However, their study was done in a restricted age range and needed more participants. Lee *et al.*<sup>[18]</sup> showed that the risk of NAFLD increased with higher CRP among men aging from 30 to 59 years. Forooghi *et al.*<sup>[19]</sup> found that there was a significant association between hs-CRP and fatty liver disease in 55 patients. Yeniova *et al.*<sup>[20]</sup> showed that hs-CRP may be a useful biomarker for fatty liver disease. However, Dumitrascu *et al.*<sup>[26]</sup> showed that there is no serum marker, for example, hs-CRP, that has a good predictive role for cardiac involvement in patients with fatty liver. Similarly, the current study showed no significant association between hs-CRP and the results of elastography. One of the limitations of the present study was the use of a relatively small sample population. Also, this study was done in a referral tertiary health care center leading to less generalization potency.

The detailed mechanism linking fatty liver disease and ischemic heart disease is initiated from the process of atherosclerosis and dysfunction of the endothelium. Nitric oxide synthesis has an endogenous antagonist called asymmetric dimethylarginine, whose level increases in fatty liver patients.<sup>[31]</sup> Moreover, the level of homocysteine is also increased in fatty liver patients, which increases intrahepatic vascular resistance and consequently leads to impaired nitric oxide formation. However, oxidative stress can be originated from increased homocysteine, leading to increased platelet activation.<sup>[32]</sup> The increased systemic inflammation markers (e.g., hs-CRP and interleukin 6) also occur in fatty liver patients. These inflammation events can increase endothelial dysfunction, change the vascular tone, and enhance vascular plaque formation.<sup>[29]</sup> Thus, as shown in the present study, the level of hs-CRP had a significant difference between liver fibrosis patients (a severe form of the fatty liver) with abnormal and normal angiography.

**Table 3: hs-CRP in groups according to medical and drug history**

Variable	ANL angiography	NL angiography	P
Fibrosis grade			
None	8.2±4.8	2.1±1.3	0.001
DM	27.8±33.4	-----	
HLP	5.9±2.4	4.5±6.0	
HTN	7.6±5.6	1.9±0.6	
>1	14.7±22.2	1.3±0.0	
Others	5.2±0.0	2.6±0.0	
Fatty liver grade			
None	7.4±4.4	2.1±1.3	>0.05
Anti-HTN	3.9±0.9	1.9±0.7	
Anti-HLP	7±2.2	5.7±6.7	
Cardiotonic	2.9±1.3	1.7±0.0	
Glucose lowering	2.8±1.4	1.3±0.0	
>1	3.3±0.8	2.6±0.0	

## Conclusion

Generally, this study showed that there is an association between the fatty liver, cardiac ischemia, and hs-CRP level. However, it seems that this association is only correct for the severe form of fatty liver (fibrosis) and not in its mild form.

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## 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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