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**Research Article**

# SERUM MARKERS OF APOPTOSIS AND INFLAMMATION IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS

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**ABSTRACT**

**Background**: Our study aimed to elucidate the possible relationship between apoptosis, inflammation, and fibrosis in hepatitis C virus (HCV) patients.
**Methods**: Patients aged 18 to 60 years with HCV were included and underwent clinical and pathological examinations. Patients with chronic renal failure, malignancies, alcohol abuse, or pregnancy and/or those who were taking immunosuppressant agents were excluded. Body mass index, glucose, insulin, HOMA-IR, lipid profile, and the extent of fibrosis (METAVIR) were determined, as were the serum levels of CK-18 (M30-Apoptosense, ELISA - Lausen, Switzerland), Fas, Fas-L, I-CAM, V-CAM, MIF, and PAI (HSEP-63k, Milliplex, Millipore, Copenhagen, Denmark).
**Results**: Of the 55 patients, 23 were treatment-naïve, 15 demonstrated a sustained virologic response (SVR) and 17 were non-responders (NR). The levels of CK-18 did not differ between the groups. Inflammation, as assessed by sVCAM, was directly associated with advanced fibrosis ($p = 0.009$). sFas-L and sVCAM were increased in the SVR group compared with the treatment-naïve group ($p = 0.006$ and 0.019, respectively). sVCAM was associated with both sFas-L ($r_s = 0.778$, $p < 0.001$) and MIF ($r_s = 0.621$, $p < 0.001$). MIF and sFas-L were also correlated ($r_s = 0.526$, $p = 0.001$).
**Conclusions**: Advanced fibrosis was positively correlated with inflammation according to the levels of sVCAM. Furthermore, apoptosis, as assessed by the levels of sFas-L, and inflammation, as determined by sVCAM, were increased in the patients who achieved viral clearance compared with the treatment-naïve patients. The patients with advanced fibrosis were also more likely to present with higher levels of MIF.



## INTRODUCTION

It is estimated that approximately 170 million people are chronically infected with hepatitis C virus (HCV) [1], which represents approximately 2-3% of the world population. In Brazil, few studies have assessed the prevalence of HCV. A recent population-based study conducted by the Brazilian Ministry of Health that included 19,634 individuals revealed that the prevalence of anti-HCV antibodies was 1.38% [2]. Several factors may influence the natural history of hepatitis C with respect to its progression to liver cirrhosis. Approximately 5% to 20% of patients with moderate to severe liver inflammation will develop cirrhosis after 20-30 years of disease [3]. Some of the factors that are related to the accelerated progression of fibrosis are male gender, age at infection, alcoholism, co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), and the presence of steatosis or steatohepatitis [4]. The age at which patients are infected with HCV has proven to be the best predictor of disease progression. In older individuals, increased rates of fibrosis progression may be related to oxidative stress, decreased hepatic blood flow, reduced immune activity, or mitochondrial toxicity [5].

The most significant features associated with fibrosis and liver regeneration are hepatocellular apoptosis and cytokine-induced inflammation. It has recently been suggested that the susceptibility to liver fibrosis induced by HCV is related to genes that regulate apoptosis. The most representative study

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involved a French and Swiss cohort of more than 1000 patients, which investigated the genetic susceptibility of patients with chronic hepatitis C (HCC) to liver fibrosis. This study concluded that the progression of liver fibrosis is closely linked to genomic variants that are associated with the apoptosis of hepatocytes [6]. With regard to the processes of inflammation and liver fibrosis, hepatic stellate cells (HSCs) are responsible for the recruitment of inflammatory cells into the liver parenchyma, along with intercellular and vascular adhesion molecules. HSCs are also responsible for the recruitment of inflammatory cytokines and are essential in the initialisation step of fibrosis. The adhesion molecules, which belong to the immunoglobulin family, precede the recruitment of inflammatory cells to extravascular sites of inflammation and are essential for the initiation of this process [7]. Our study aimed to elucidate the possible interaction between apoptosis, inflammation, and fibrosis in patients with chronic HCV. We measured the serum levels of markers of apoptosis and inflammation in selected patients with chronic HCV infection who were either treatment-experienced or treatment-naïve, and we correlated these markers with hepatic fibrosis.

## METHODS

This was a cross-sectional study of patients from the Department of Gastroenterology/Viral Hepatitis of the Hospital de Clinicas de Porto Alegre (HCPA, Porto Alegre, Brazil). Patients with HCV, as determined by the presence of anti-HCV antibodies (ELISA) and confirmed by the presence of HCV RNA (> 50 IU/ml) by polymerase chain reaction (PCR), were evaluated for inclusion in this study. Patients with HCV monoinfections who were aged from 18 to 60 years underwent both clinical and pathological examinations. Patients with chronic renal failure, malignancies, alcohol abuse, or pregnancy and/or those who were taking immunosuppressant agents were excluded. Body mass index, the levels of glucose and insulin, HOMA-IR, lipid profile, and the extent of fibrosis (METAVIR) were determined, as were the serum levels of CK-18 (M30-Apoptosense, ELISA - Lausen, Switzerland), Fas, Fas-L, I-CAM, V-CAM, MIF, and PAI (HSEP-63k, Milliplex, Millipore, Copenhagen, Denmark). The patients were divided into three groups: treatment-naïve, those with a sustained virologic response (SVR), and non-responders (NR). The measurements were performed in duplicate according to the manufacturers' guidelines. The study was approved by the Ethical Committee of the HCPA and conformed to the ethical guidelines of the Declaration of Helsinki. Informed consent was obtained from all included patients.

### *Histological Analysis*

Liver biopsies were evaluated irrespective of the presence of other markers. Histological features were analysed with the METAVIR group scoring system. Fibrosis was staged on a scale of F0 to F4 as follows: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = few septa, F3 = numerous septa without cirrhosis, and F4 = cirrhosis. Scores of F0, F1, or F2 indicated initial fibrosis, while scores of F3 or F4 indicated advanced fibrosis.

### *Statistical Analysis*

The data were entered into Excel and then exported to SPSS version 18.0 for statistical analysis. The frequencies and percentages of the categorical variables were obtained. Quantitative variables with normal distributions were described by the mean and standard deviation, and variables with asymmetric distributions were described by the median and interquartile range (25th and 75th percentiles). Categorical variables were compared by Fisher's exact test or the chi-square test. Quantitative variables with normal distributions were compared by Student's t test for independent samples or by analysis of variance (ANOVA) followed by a post hoc Tukey test. Quantitative variables with skewed distributions were compared by the Mann-Whitney U test or the Kruskal-Wallis test. A significance level of 5% was considered for established comparisons.

## RESULTS

### *Patient Characteristics*

Fifty-five patients with a mean age of 47.3 years were included. These patients were predominantly female (65.5%), and most were infected with HCV genotype 1 (75.6%) and presented with grade 2 fibrosis according to the METAVIR index (41.8%). The percentage of steatosis according to the liver biopsies was less than 5% in all samples. Table 1 shows the demographic and clinical characteristics of the patients who were included in this study. Most of the patients were female and were infected with HCV genotype 1. The age of the patients was similar in the 3 groups. With regard to the METAVIR index, the majority of patients presented with early fibrosis (F0 to F2) (p = 0.055).

**Table 1** Demographic and clinical characteristics of the study population

| Characteristics | Naïve n = 23 | SVR n = 15 | NR n = 17 | p |
|---|---|---|---|---|
| Age (average/SD) | 45 (8) | 48 (9) | 51 (8) | 0.090 |
| Female (%) | 65.2 | 66.7 | 64.7 | 0.993 |
| Genotype 1 (%) | 71.4 | 66.7 | 100 | 0.154 |
| METAVIR F0 - F2 (%) | 95.5 | 66.7 | 70.6 | 0.055 |

Naïve= untreated patients, SVR = sustained virologic response, NR = non-responders, SD = standard deviation.
Variables with a symmetric distribution were described by the mean (standard deviation) and were compared by analysis of variance (ANOVA). Categorical variables were described by percentages and were compared by the chi-square test.

Table 2 shows the results of the laboratory tests that were conducted and evaluated in the study population. Higher levels of triglycerides were observed in the non-responders compared with the SVR patients (p = 0.009).

**Table 2** Laboratory tests conducted in the study population

| Variables | Naïve n = 23 | SVR n = 15 | NR n = 17 | p |
|---|---|---|---|---|
| AST | 42 (24 – 79) | 43 (20 – 200) | 38 (12 – 107) | 0.843 |
| ALT | 47 (22 – 223) | 62 (22 – 407) | 44 (18 - 77) | 0.471 |
| Total cholesterol | 161 (32) | 166 (29) | 171 (24) | 0.577 |
| HDL cholesterol | 48 (12) | 47 (16) | 48 (16) | 0.994 |
| Triglycerides | 114 (50 – 576)a, b | 88 (56 – 201)a | 122 (71 – 294)b | 0.009 |
| Glycaemia | 95 (10) | 97 (6) | 103 (17) | 0.105 |
| BMI | 29 (4)a | 25 (3)b | 25 (3)a, b | 0.020 |
| Insulin | 15 (5 – 90) | 12 (6 – 35) | 13 (6 – 22) | 0.535 |
| HOMA-IR | 3 (1 – 10) | 3 (2 – 8) | 3 (1 – 6) | 0.567 |

Naïve = untreated patients, SVR = sustained virologic response, NR = non-responders, AST = aspartate aminotransferase, ALT = alanine aminotransferase, HDL = high-density lipoprotein, BMI = body mass index, HOMA-IR = homeostatic model assessment insulin resistance.
Variables with asymmetric distributions were described by the median (minimum-maximum) and were compared by the Kruskal-Wallis test. Variables with symmetric distributions were described by the mean (standard deviation) and were compared by analysis of variance (ANOVA).
a, b: The different letters represent significantly different distributions.

Although obese individuals were excluded, BMI values were higher in the naïve group compared with the SVR group (p = 0.020). No differences were observed in the levels of aminotransferases, cholesterol, glucose, and insulin or in the HOMA-IR.

Table 3 shows the levels of inflammatory and apoptotic markers in the different groups. The levels of Fas and sVCAM-I were higher in patients with SVR compared with treatment-naïve patients (p = 0.006 and p = 0.019, respectively). No significant differences were found in the levels of CK-18, MIF, sICAM-1, sFas, or tPAI-1.

**Table 3** Inflammatory and apoptotic markers in the study population

| | Naïve n = 23 | SVR n = 15 | NR n = 17 | p |
|---|---|---|---|---|
| CK-18 (UI/L) | 214 (66 – 2435) | 141 (74 – 1146) | 204 (74 – 655) | 0.497 |
| MIF (pg/mL) | 440 (85 – 8129) | 1070 (263 – 5636) | 646 (184 – 4098) | 0.058 |
| sICAM-I (pg/mL) | 78449 (21113– 615688) | 87247 (33478 – 688432) | 92949 (23924 - 380726) | 0.326 |
| sFas-L (pg/mL) | 17 (13 – 82)[a] | 32 (16 – 121)b | 27 (13 - 93)[a]b | 0.006 |
| sFas (pg/mL) | 2475 (671 – 18928) | 3737 (1614 - 9814) | 3499 (1160 - 6541) | 0.197 |
| sVCAM-I (pg/mL) | 183606 (61422 – 525642)[a] | 356023 (94693 – 777287) [b] | 331118 (105247 - 757969)[a]b | 0.019 |
| tPAI-1 (pg/mL) | 54267 (18589 - 200570) | 53884 (18878 - 149866) | 42570 (14211 - 135330) | 0.459 |

Naïve = untreated patients, SVR = sustained virologic response, NR = non-responders, CK-18 = cytokeratin 18, MIF = migration inhibitory factor of macrophages, sICAM-I = soluble intercellular adhesion molecule type 1, sFas = soluble protein associated with apoptosis, sFas-L = binding protein soluble, sVCAM-I = soluble vascular adhesion molecule type 1, tPAI-1 = plasminogen activator inhibitor
Variables with asymmetric distributions were described by the median (minimum-maximum) and were compared by the Kruskal-Wallis test.
a, b Different letters represent different statistical distributions.

The level of sVCAM-I demonstrated a direct and statistically significant correlation with the level of sFas-L (rs = 0.778, p < 0.001) and with the level of MIF (rs = 0.621, p < 0.001). The levels of sFas-L and MIF were also directly correlated (rs = 0.526, p < 0.001).

The distribution of hepatic fibrosis was evaluated and is shown in Figure 1.

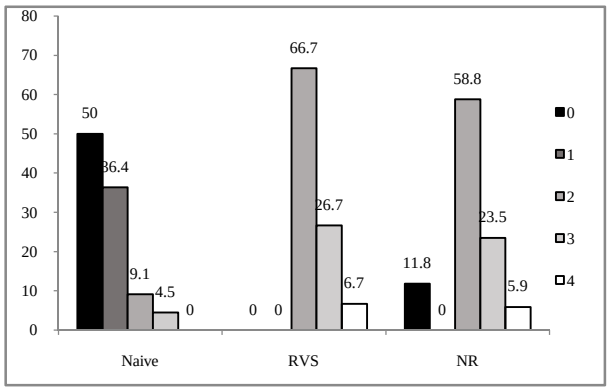


**Figure 1** Distribution of different degrees of fibrosis according to the METAVIR classification in the studied groups.

The frequency of METAVIR scores of F0 and F1 was higher in the naïve group (p = 0.001).

Table 4 shows the levels of inflammatory and apoptotic markers in the different groups. The level of the inflammatory marker sVCAM-I was higher in patients with advanced fibrosis compared with patients with early fibrosis (p = 0.009). No significant differences were found in any of the other variables (i.e., CK-18, MIF, sICAM-1, sFas-L, sFas, and tPAI-1).

**Table 4** The levels of inflammatory and apoptotic markers with respect to the degree of fibrosis observed after liver biopsy

| | Initial fibrosis (n = 44) | Advanced fibrosis (n = 11) | p |
|---|---|---|---|
| CK-18 (UI/mL) | 182.14 (139.28 – 360.57) | 214.55 (88.23 – 655.17) | 0.430 |
| MIF (pg/mL) | 618.47 (216.51 – 1393.70) | 1272.37 (645.73 – 2458.90) | 0.053 |
| sICAM-1 (pg/mL) | 79015.87 (40960.01 – 173696.93) | 117405.30 (83212.45 – 156393.60) | 0.178 |
| sFas-L (pg/mL) | 24.83 (14.72 – 36.06) | 27.11 (20.41 – 70.65) | 0.180 |
| sFas (pg/mL) | 2966.85 (1643.65 – 5081.11) | 3737.01 (3378.28 – 5116.80) | 0.132 |
| sVCAM-1 (pg/mL) | 209039.08 (133962.45 – 366003.85) | 400044.70 (246807.05 – 656279.56) | 0.009 |
| tPAI-1 (pg/mL) | 45961.60 (34618.25 – 102330.36) | 51563.88 (40697.07 – 66589.07) | 0.866 |

CK-18 = cytokeratin 18, MIF = inhibitor of macrophage migration factor, sICAM-I = soluble intercellular adhesion molecule type 1, sFASL = soluble binding protein, sFAS = soluble protein associated with apoptosis, sVCAM-I = soluble vascular cell adhesion molecule type 1, tPAI-1 = plasminogen activator inhibitor
Variables were described by the median (interquartile range: P25 to P75) and were compared with the Mann-Whitney test.

Additionally, we compared 41 patients with fibrosis (METAVIR score of F1 to F4) and 13 patients without fibrosis (METAVIR F0), and the following medians were obtained (Mann-Whitney test): CK-18 = 350.81 vs. 182.00, p = 0.716; MIF = 1148.47 vs. 536.47, p = 0.731; s-ICAM-1 = 126179.80 vs. 117042.66, p = 0.664; sFas-L = 32.99 vs. 21.49, p = 0.310; sFas = 3863.5 vs. 2925.0; p = 0.911, sVCAM-1 = 318904.04 vs. 300785.66, p = 0.407; and tPAI-1 = 59567.60 vs. 54266.96, p = 0.237.

## DISCUSSION

The progression of HCV-induced liver disease and the response to therapy are strongly influenced by viral and host genetic factors, including the genotype of the virus and genetic polymorphisms, such as those in the IL28B gene [8]. Several authors have suggested an association between apoptosis and the progression of hepatic fibrosis. Initially, patients with hepatic steatosis and steatohepatitis were studied, and apoptotic markers were used to differentiate these two groups [9–11]. These studies were able to distinguish patients with non-alcoholic steatohepatitis (NASH) from those with more advanced fibrosis, but they included heterogeneous populations, such as patients with cirrhosis, diabetes, or cancer or those who had received some type of immunosuppressive therapy. These apoptotic markers were assessed in patients with HCV and demonstrated, in addition to their usefulness in the assessment of liver fibrosis progression, utility in the monitoring of the treatment of patients with interferon and

ribavirin [12–14]. Some studies included low numbers of patients and did not exclude patients with NASH and with possible apoptotic activity from other causes. In 2012, a cohort study highlighted the genomic variants that are associated with hepatocyte apoptosis, and this study revealed a correlation between these genomic variants and the progression of liver fibrosis [6]. Our study included 55 patients with HCV. We found higher serum levels of apoptotic markers (CK-18, sFas, and sFas-L) in the population with more advanced fibrosis. This finding is consistent with results in the literature but was not significant. Repeating the study with an increased sample size may reveal statistically significant differences in populations with different stages of fibrosis.

HCV infection leads to inflammatory processes of different grades that involve the activation of adhesion molecules and cytokines that facilitate the recruitment of leukocytes to areas of inflammation [15]. Liver fibrosis follows hepatic inflammation as a result of hepatocyte injury [16]. The interactions between membrane receptors on HSCs and extracellular matrix proteins are regulated by adhesion molecules [17,18]. sVCAM-I and sICAM-I play key roles in leukocyte adhesion via the activation of HSCs and the propagation of liver fibrosis. Some authors have reported that the circulating levels of these molecules are related to hepatic inflammatory activity and fibrosis score [19,20]. Other authors have indicated that patients with HCV infection who were treated with interferon had decreased circulating levels of ICAM-I if they attained an SVR [21,22]. In contrast, a 2009 study assessed the levels of this marker in patients with HCV before and after antiviral treatment and revealed that sVCAM-I levels were higher in patients with more advanced stages of fibrosis, but the levels did not predict treatment response [15]. Subsequently, another study [23] including 134 patients with chronic liver disease concluded that the VCAM level is related to a Child-PughC. Our study shows that patients with advanced fibrosis have higher levels of sVCAM-1 compared with patients with early fibrosis; in addition, the serum levels of sVCAM-1 were higher in patients with SVR compared with treatment-naïve patients.

The role of MIF in leukocyte recruitment and in the interference of the activation of HSCs in chronic inflammatory diseases of the liver has not been well studied. The most representative study was published in 2011. The authors reported that in a murine model, MIF has an antifibrotic role and inhibits the activation of HSCs via the CD74 receptor [24]. Thus, the use of MIF as a target for therapy for chronic liver disease was suggested. Our study shows that patients with advanced fibrosis ($p = 0.053$) and those with an SVR ($p = 0.058$) are more likely to have higher levels of MIF. We also found a strong correlation between the levels of MIF and sVCAM-I ($rs = 0.621$, $p < 0.001$) and between the levels of MIF and sFas-L ($rs = 0.526$, $p < 0.001$). In our study, patients with viral clearance presented with higher levels of sVCM-1 and sFas-L, which may justify the higher MIF levels found.

Few studies on tPAI-1 and hepatic fibrosis are present in the literature. It has been shown that hyperfibrinolysis occurs in chronic liver disease along with reduced levels of plasminogen, increased levels of PAI, and an imbalance of the procoagulant system [25]. Two main hypotheses have been presented with regard to coagulation and the progression of liver fibrosis. One hypothesis involves the formation of microthrombi in the portal system, which leads to tissue ischaemia, death, and fibrosis of the liver parenchyma [26]. The other hypothesis suggests that the activation of coagulation in the vascular system may play a role in the progression of liver disease via thrombin signalling of HSCs [27]. A recent study suggested an association between elevated levels of tPAI-1 and SVR and showed an inverse correlation between tPAI-1 and liver fibrosis [28]. Our study found no significant difference in the population studied.

This study has some strength that should be emphasised. We evaluated the relationship of markers of fibrosis, apoptosis, and inflammation in a homogeneous sample. We excluded obese patients as well as those with diabetes and steatohepatitis, as these are important confounding factors in HCV-induced liver damage. Additionally, we included treated and untreated patients and aimed to understand the behaviour of these markers in the process of viral clearance. However, our study was limited by the small sample size and the inclusion of only a few patients with advanced fibrosis.

## CONCLUSION

We conclude that patients with advanced fibrosis have higher levels of inflammation as measured by the level of sVCAM-1. Additionally, patients who achieved an SVR had higher levels of serum markers of apoptosis and inflammation, as determined by the levels of sFas-L and sVCAM-1, compared with treatment-naïve patients.

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