
Serum amyloid A level as a marker of hepatocellular carcinoma in HCV-induced liver cirrhosis

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ABSTRACT

Aim: HCV-induced cirrhosis is recognized as a leading cause of Hepatocellular Carcinoma (HCC) with a high annual incidence in Egypt. The role of serum amyloid A (SAA) has been highlighted in many inflammatory and neoplastic diseases. Accordingly, this study aimed to evaluate the potential of SAA as a biomarker for HCC in patients with HCV-induced cirrhosis and its capacity to predict HCC.

Patients and Methods: A comparative cross-sectional study was conducted on 90 HCV-induced cirrhotic patients. The patients were categorized into established HCC patients on top of HCV-induced cirrhosis (45 patients) and HCV-induced cirrhotic patients without HCC (45 patients). Besides taking history and conducting clinical, laboratory, and radiological examinations, SAA levels were recorded in all patients.

Results: Compared to non-HCC patients, most of the laboratory results were significantly deteriorated in cirrhotic HCC patients. HCC is developed substantially in patients with class C Child Paugh scores ($p < 0.001$). The mean SAA is elevated considerably in cirrhotic HCC patients than in cirrhotic non-HCC patients (70.38 ± 57.12 vs. 6.84 ± 1.91 ng/mL, respectively). At a cut-off value of >12 ng/mL, the sensitivity and specificity of SAA were 93.33% and 100%, respectively SAA, to diagnose patients with HCC in HCV-induced cirrhosis.

Conclusion: SAA is a highly sensitive and specific marker in diagnosing and predicting HCC development in HCV-cirrhotic patients.

Keywords: HCV, HCC, Cirrhosis, Amyloid A.

INTRODUCTION

liver cirrhosis is a degenerative process triggered by many causes, including the chronic inflammatory conditions of the liver causing diffuse hepatic fibrosis, in which regenerative nodules replace the normal architecture of the liver [1]. Several factors are widely reported as contributors to liver cirrhosis, including hepatitis C and B viruses (HCV and HBV), nonalcoholic fatty liver disease, autoimmune hepatitis, and other less common causes [2].

Liver cirrhosis is known to cause carcinogenic modifications in hepatocytes and alters the activity of hepatic inflammatory cells.[3] Indeed, liver cirrhosis can progress to liver cancer, especially hepatocellular carcinoma (HCC), a primary persistent hepatic malignant tumor (nearly 90% of all liver cancer) [4]. Among cirrhotic patients, the 5-year cumulative risk of developing HCC varies from 5% to 30% [5].

Per se, HCV-induced cirrhosis is recognized as a significant cause of HCC [4]. HCV-induced cirrhosis increases the risk of HCC development nearly by 20 folds with an incidence reaching 10% per year [6, 7].

The liver is the principal site for producing an acute-phase protein known as serum amyloid A (SAA) [8]. In addition to being a result of inflammation or tissue damage brought on by inflammatory mediators and cytokines in many diseases, a rise in SAA levels also promotes the progression of disease processes on its own [9].

The fact that SAA, induced by proinflammatory cytokines, contributes to many inflammatory diseases is reported, including inflammatory bowel diseases [10], rheumatoid arthritis [11], and HCV hepatitis [12]. Additionally, an elevation of SAA was reported in many cancers, such as gastric [13], lung [14], and renal cancers [15]. Even though its levels are positively correlated to the tumor stages [16], can predict the overall survival rate [17] and monitor the recurrence [18] in several malignancies.

Concerning HCC, few studies evaluated the use of SAA in HCC patients, showing the possibility of its use as a marker in HCC patients [19, 20]. Owing to the significant prevalence of HCV-induced cirrhosis that develops HCC in Egypt [7] Hence, the current work aimed to evaluate the diagnostic potential of SAA as a biomarker for HCC in patients with HCV-induced cirrhosis and its capacity for predicting HCC.

PATIENTS AND METHODS

A comparative cross-sectional study was conducted among HCV-induced cirrhotic patients admitted to the inpatient ward and outpatient clinics of the Faculty of Medicine and Medical Research Institute, Alexandria University. The duration of the study was 6 months. Patients were categorized into two groups: HCC HCV-induced cirrhosis patients and

non-HCC HCV-induced cirrhosis patients. Patients with liver cirrhosis for causes other than HCV, patients with comorbidities causing elevation of serum amyloid A such as active infections, autoimmune diseases such as chronic colitis, and joint diseases were excluded from the study. Also, patients with high AFP and no hepatic nodules were detected on ultrasound, and patients with diabetes were on insulin therapy. The sample size was calculated using G power software 3.1.9.7, based on the difference of serum amyloid A level between HCC cirrhotic patients and cirrhotic patients without HCC providing an effect size of 0.7 (20), giving a sample of 34 patients in each group at the alpha error of 0.05 and a power of 80%. We raised the sample to 90 patients (45 patients in each group).

Patients and methods

A thorough history was taken for every patient, a clinical examination was conducted, and a blood sample was obtained. At the central laboratory of our hospital, after centrifugation of the blood samples at -80°C , patients' sera were stored until further use. Routine laboratory investigations for cirrhotic patients were performed, including complete blood count (CBC), liver enzymes (AST; Aspartate transaminase, and ALT; Alanine transaminase), liver function tests (serum bilirubin, serum albumin, PT; prothrombin time, INR; International normalized ratio), Alkaline phosphatase (ALP), renal functions tests (blood urea and creatinine), and serum Alpha-fetoprotein (AFP) level.

Enzyme-linked immunosorbent assay (ELISA) was applied to measure the total SAA using human SAA ELISA kits (ab100635, Abcam, Cambridge, MA, USA). (20) To assess the severity of cirrhosis, all patients were categorized according to Child Pugh's score into classes A, B, and C, representing good, moderately impaired, and poor liver functions, respectively.

An ultrasound examination of the abdomen was performed to confirm the presence of cirrhosis and its degree and to rule out focal hepatic lesions. Also, triphasic computed tomography (CT) of the liver is used to rule out or prove HCC (in the case of hepatic nodules detected by ultrasound). Staging was done using BCLC.

Ethical consideration

This study was approved by the Ethics Committee of the Faculty of Medicine, Alexandria University, Egypt (IRB No.: 0306180). The study was performed according to the international ethical guidelines of the Declaration of Helsinki [21] All participants were informed of the purpose and nature of the study, the privacy and confidentiality of data, and that participation was voluntary. After explaining the study protocol and assuring anonymity that all subjects would be represented by codes rather than their names', informed consent was obtained from all participants.

Statistical data analysis

The collected data was wrangled, coded, and analyzed using the SPSS software (Armonk, NY: IBM Corp version 25.0). The quantitative variables were expressed using mean \pm SD, whereas categorical data were presented in number and percentage. A chi-square test was used to estimate the difference between the categorical variables. An independent sample was used to determine whether there were any statistically significant differences between the means of the studied groups. Correlation was conducted using Pearson correlation. ROC analysis was performed to evaluate the diagnostic prediction of serum amyloid A in differentiating the presence of HCC among HCV-induced cirrhosis. Areas under the ROC curves (AUC) were compared, and cutoff values were determined according to the Youden index. Statistical significance was considered when $p < 0.05$.

Results

The mean age of cirrhotic HCC patients was 52.62 ± 6.73 years, and of the cirrhotic non-HCC patients was 53.49 ± 6.54 years. Males were more than females in both groups (57.8 vs. 42.2%). Easy fatigue, jaundice, and encephalopathy were reported in both groups. However, easy fatigue was reported more significantly in cirrhotic HCC patients than in cirrhotic non-HCC patients ($p= 0.030$). History of bleeding, lower limb edema, hepatomegaly, and ascites were related considerably to cirrhotic HCC ($p= 0.006, 0.006, 0.003, \text{ and } 0.006$, respectively). (Tab 1).

Tab 1. Sociodemographic characteristics of the studied patients.

	Cirrhotic HCC patients (n= 45)	Cirrhotic non-HCC patients (n= 45)	p ^a
Age (years)			
Min. – Max.	40.0 – 64.0	41.0 – 69.0	0.537
Mean \pm SD	52.62 ± 6.73	53.49 ± 6.54	
Sex			
Male	26 (57.8)	26 (57.8)	1.000
Female	19 (42.2)	19 (42.2)	
Clinical symptoms			
Easy fatigue	33 (73.3)	23 (51.1)	0.030*
Jaundice	29 (64.4)	20 (44.4)	0.057
Encephalopathy	26 (57.8)	18 (40.0)	0.092
History			
Bleeding	31 (68.9)	18 (40.0)	0.006*
Lower limb edema	28 (62.2)	15 (33.3)	0.006*
Hepatomegaly	14 (31.1)	3 (6.7)	0.003*
Splenomegaly	36 (80.0)	32 (71.1)	0.327
Ascites	29 (64.4)	16 (35.6)	0.006*

^a; chi-square test was used to assess categorical variables, while the independent t-test was used to evaluate continuous variables *; Significant ($p \leq 0.05$)

Many cirrhotic HCC patients were classified as class C following the Child Paugh score (23 patients; 71.1%), with a significant difference between cirrhotic HCC patients and cirrhotic non-HCC patients in terms of the Child Paugh score ($p < 0.001$). (Tab 2).

Tab 2. Child Paugh score of the studied patients.

	Cirrhrotic HCC patients (n= 45)	Cirrhrotic non-HCC patients (n= 45)	p ^a
Child Paugh score			
A (5-6)	2 (4.4)	14 (31.1)	<0.001*
B (7-9)	11 (24.4)	25 (55.6)	
C (10-15)	32 (71.1)	6 (13.3)	

^a; chi-square test was used to assess categorical variables *; Significant (p≤0.05)

Tab 3 shows that most of the laboratory results were significantly deteriorated in cirrhotic HCC patients compared to cirrhotic non-HCC patients. RBCs, hemoglobin, WBCs, serum albumin, and PT% were substantially lower in cirrhotic HCC patients than in cirrhotic non-HCC patients (p< 0.001). Whereas ALT, AST, total and direct bilirubin, INR, AFP, urea, and creatinine were significantly higher in cirrhotic HCC patients than in cirrhotic non-HCC patients (p< 0.001).

Tab 3. CBC and laboratory findings of the studied sample.

	Cirrhrotic HCC patients (n= 45)	Cirrhrotic non-HCC patients (n= 45)	pa
RBCs			
Min. – Max.	2.9 – 4.9	3.0 – 4.4	<0.001*
Mean ± SD	3.66 ± 0.39	3.95 ± 0.3	
Hemoglobin			
Min. – Max.	9.6 – 12.1	9.9 – 13.5	<0.001*
Mean ± SD	10.87 ± 0.68	11.82 ± 0.92	
Platelets (x10³)			
Min. – Max.	97.0 – 221.0	97.0 – 233.0	0.186
Mean ± SD	140.44 ± 33.12	149.60 ± 30.1	
WBCs (x10³)			
Min. – Max.	2.0 – 5.0	2.9 – 6.0	<0.001*
Mean ± SD	3.33 ± 0.61	3.93 ± 0.83	
ALT			
Min. – Max.	21.0 – 50.0	17.0 – 38.0	<0.001*
Mean ± SD	39.24 ± 5.52	25.78 ± 5.96	
AST			
Min. – Max.	32.0 – 52.0	19.0 – 37.0	<0.001*
Mean ± SD	40.8 ± 4.71	26.82 ± 4.84	
Serum albumin			
Min. – Max.	1.5 – 3.8	2.0 – 4.2	<0.001*
Mean ± SD	2.39 ± 0.68	3.29 ± 0.73	
Total bilirubin			
Min. – Max.	1.1 – 5.5	0.2 – 4.6	<0.001*
Mean ± SD	3.34 ± 1.22	2.28 ± 1.11	
Direct bilirubin			
Min. – Max.	0.2 – 4.7	0.1 – 3.5	<0.001*
Mean ± SD	2.35 ± 1.15	1.43 ± 0.97	
PT%			
Min. – Max.	30.0 – 97.0	50.0 – 100.0	<0.001*
Mean ± SD	55.56 ± 16.9	79.36 ± 19.78	
INR			
Min. – Max.	0.9 – 2.3	0.9 – 1.9	<0.001*
Mean ± SD	1.76 ± 0.35	1.26 ± 0.38	

ALP			
Min. – Max.	56.0 – 98.0	55.0 – 99.0	0.370
Mean ± SD	73.87 ± 8.16	72.27 ± 8.67	
AFP			
Min. – Max.	230.0 – 4000.0	4.0 – 15.0	<0.001*
Mean ± SD	1524.38 ± 1154.82	8.31 ± 2.58	
Urea			
Min. – Max.	24.0 – 42.0	18.0 – 41.0	<0.001*
Mean ± SD	34.76 ± 5.0	29.73 ± 5.55	
Serum creatinine			
Min. – Max.	0.8 – 1.4	0.4 – 1.3	<0.001*
Mean ± SD	1.18 ± 0.17	0.83 ± 0.27	

a; Independent t test used to assess continuous variables *; Significant ($p \leq 0.05$).

As shown in Table 4, the mean SAA is significantly higher in Cirrhotic HCC patients compared to Cirrhotic non-HCC patients (70.38 ± 57.12 vs. 6.84 ± 1.91 ng/mL, respectively).

Tab 4. Serum amyloid A level of the studied sample.

	Cirrhotic HCC patients (n= 45)	Cirrhotic non-HCC patients (n= 45)	pa
Serum amyloid A			
Min. – Max.	8.0 – 200.0	4.0 – 12.0	<0.001*
Mean ± SD	70.38 ± 57.12	6.84 ± 1.91	

a; Independent t test used to assess continuous variables *; Significant ($p \leq 0.05$).

Using ultrasound, hepatomegaly and ascites were significantly more common in cirrhotic HCC patients than in cirrhotic non-HCC patients ($p < 0.001$, $p = 0.006$, respectively). (Tab 5).

Tab 5. Ultrasound abdomen findings of the studied sample.

	Cirrhotic HCC patients (n= 45)	Cirrhotic non-HCC patients (n= 45)	pa
Ultrasound abdomen			
Splenomegaly	32 (71.1)	32 (71.1)	1.000
Hepatomegaly	18 (40.0)	3 (6.7)	<0.001*
Ascites	29 (64.4)	16 (35.6)	0.006*

a; chi-square test was used to assess categorical variables *; Significant ($p \leq 0.05$).

Tab 6 demonstrates the triphasic CT findings in HCC patients. The number of HCC lesions varies from one to more than three. Portal hypertension was detected in 10 Cirrhotic HCC patients (22.2%), and pathological lymph nodes were shown in 13 patients (28.9%).

Tab 6. Triphasic CT findings of cirrhotic HCC patients.

	Cirrhotic HCC patients (n= 45)
Portal vein invasion	
Yes	10 (22.2)
No	35 (77.8)
Number of HCC lesions	
One	10 (22.2)
Two	12 (26.7)

Three	12 (26.7)
More than three	11 (24.4)
Pathological lymph nodes	
Yes	13 (28.9)
No	32 (71.1)

To assess the diagnostic performance of SAA in diagnosing patients with HCC in HCV-induced cirrhosis, ROC curve analysis (Figure 1) showed that at a cut-off value of >12 ng/mL (AUC= 0.992), the sensitivity and specificity of SAA was 93.33% and 100%, respectively. (Tab 7)

Tab 7. Diagnostic performance of serum amyloid A in diagnosis of HCC in HCV-induced cirrhosis.

	AUC (95% CI)	Cut off point	Sensitivity% (95% CI)	Specificity% (95% CI)	P
Serum amyloid A	0.992 (0.945 – 1.000)	>12.0	93.33 (81.7 – 98.6)	100 (92.1 – 100)	<0.001*

AUC; area under the curve, CI; Confidence interval, *; Significant (p<0.05).

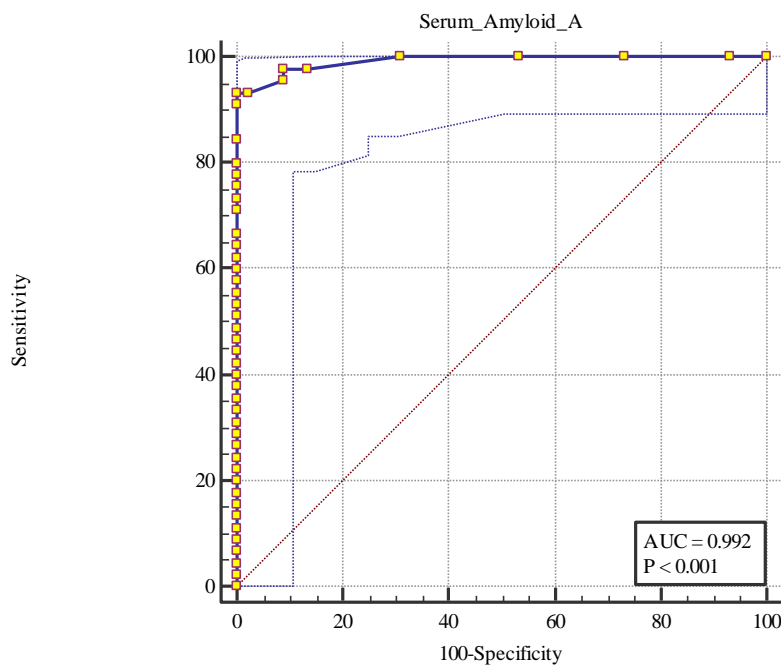


Fig 1. ROC curve analysis of serum amyloid A.

Discussion

The concept that chronic inflammation induces cancer has been published in earlier research [22, 23]. It is commonly acknowledged that several types of inflammatory cells considerably contribute to the microenvironment of tumors, acting as mediators of tumor development, progression, angiogenesis, and even metastasis [24]. SAA levels, released from hepatocytes, rise significantly during acute infections and tissue injury by the action of multiple cytokines that participate in the inflammatory process [12]. It was indicated that SAA levels rise significantly in chronic inflammation, which is crucial for the growth of tumors and a

variety of neoplastic disorders as well. Previous research has shown that patients with variable malignancies, such as gastric, colorectal, lung, and renal cancers, had elevated SAA levels, revealing an accepted role of SAA as a potential marker for these malignancies [13-15, 17].

In this work, we tried to evaluate the potential of SAA as a biomarker for HCC in patients with HCV-induced cirrhosis. We found that SAA is significantly elevated in HCC patients caused by HCV-induced cirrhosis compared to non-HCC patients, suggesting a role of a possible role of SAA in the progression of cirrhosis and the development of HCC in cirrhotic patients on top of HCV infection. Using ROC curve analysis, we also assessed the validity of SAA as a marker for detecting HCC in patients with HCV cirrhosis. We reported that SAA is a susceptible (93.33%) and specific (100%) marker in diagnosing and predicting HCC development in HCV-cirrhotic patients.

Our findings support previous studies that assessed the role of SAA in HCC patients. For the first time in 2014, Ni et al. [19] introduced serum SAA as a novel marker for HCC identification and prognosis. They found that SAA level was significantly elevated in HCC patients than in patients with benign liver lesions. They added that SAA positively correlates to the preoperative tumor size and stage and can be used as an independent marker to predict the patient's overall survival. The authors hypothesized that the increased levels of serum SAA were primarily caused by the HCC cells rather than the normal hepatocytes. This was most likely a long-lasting impact of the local chronic inflammatory interactions between the surrounding microenvironment and the tumor cells rather than an acute phase or systemic induction.

Similarly, Wu et al. [20] studied the relationship between SAA and various stages of liver disorders, mainly about three pathogenic conditions that are closely associated with one another: hepatitis, liver cirrhosis, and HCC, as well as the usefulness of SAA for early HCC identification. They found that SAA at a higher level was found in the HCC group than in the hepatitis and the cirrhotic groups. Moreover, the SAA level was elevated in more advanced HCC, compared to early HCC, suggesting that SAA could have a role in the identification and progression of HCC.

On the other hand, Zhang et al. [25] reported a decreased expression of the SAA gene in HCC patients. Additionally, the downregulation of the SAA gene significantly correlates to the tumor grade and poor prognosis, suggesting a close association between SAA expression and anti-tumor immune pathways.

Although AFP was significantly elevated among HCC patients compared to non-HCC patients in our studies ($p < 0.001$), in the literature, the use of AFP to predict and diagnose HCC is still debated [25, 26]. Moreover, we reported that HCC was significantly found in patients with class C Child Paugh scores (advanced cirrhosis) ($p < 0.001$), proposing the more progressive the cirrhosis, the more chance of developing HCC. This was consistent with Sharaf et al. [27] who reported that all HCC patients in their study were class C according to Child Paugh scores. However, contrary to our findings, other studies [28-30], mentioned that most of the HCC patients were class A and B according to Child Paugh scores. This discrepancy may indicate the non-practicality of AFP and the Child Paugh score in predicting the development of HCC in cirrhotic patients.

Our work is limited by the relatively small population and the fact that it is a single-center study. Additionally, we did not assess the SAA levels in healthy subjects or patients with other causes of cirrhosis. We recommended further prospective multicentric case-control studies

with larger sample sizes to validate our findings not only in patients with HCV-induced cirrhosis but also in patients with other causes of cirrhosis.

CONCLUSION

Serum amyloid A is a potential marker in predicting HCC in HCV-cirrhotic patients; however, further studies are recommended to intensify its role as a sensitive and specific predictor of HCC development in HCV-cirrhotic patients.

Footnotes.

Ahmed Fathy (Assistant professor of internal medicine, gastroenterology, and hepatology unit), Mohamed Emara (Professor of gastroenterology, hepatology, and infectious diseases), and Amany Mohamed Abdalla (Assistant professor of family medicine) were the peer reviewers.

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Ethical approval: All procedures involving human participants followed the institutional and national research committee's moral standards, the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards. All authors declare that consent was obtained from the patients (or other approved parties) to publish this study.

Study protocol:

In adherence to the principles outlined in the Helsinki Declaration, the study protocol was implemented with approval from the institutional review board. Before commencing the research, written consent was obtained from the patients to utilize their clinical information.

Data and materials availability: The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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This work was done according to the **STROBE** guidelines.

Authors' contributions

M.A. conceived the concept and design of the study. A.H., M.A. tailor data acquisition—M.H. conducted statistical analysis. M.S. analyzed the data and drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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