Serum Elabela Level as a Reliable Biomarker for Predicting of Liver Fibrosis in Iraqi Patients with Chronic Hepatitis C

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Abstract

Background: Elabela is a newly discovered peptide hormone that has been implicated in liver disease. **Objective:** The main objective of the current work is to assess whether variations in blood Elabela levels among chronic hepatitis C (CHC) patients from Iraq might be used as a biomarker for liver fibrosis. **Materials and Methods:** A case-control study was conducted in Baghdad, Iraq. The overall sample size (n = 80) that met the inclusion criteria was divided into two groups as follows: 40 patients who were diagnosed with CHC and 40 healthy matched individuals. The aspartate aminotransferase-to-platelet ratio index (APRI) was used to identify the group of patients at risk for liver fibrosis. The routine complete blood count, liver function, and serum Elabela tests were performed. Serum Elabela level was evaluated by using the enzyme-linked immunosorbent assay technique. **Results:** Serum Elabela was significantly higher in the CHC group (33.89 ± 8.51 ng/mL) than in the control group (18.11 ± 5.27 ng/mL). In addition, the percentage of CHC patients at a high risk of developing fibrosis was 42.5%. Also, the high-risk fibrosis group showed a significantly higher concentration of Elabela and APRI than the other groups (low-risk and control) at $P < 0.0001$. Alanine aminotransaminase and aspartate aminotransaminase showed a high increase while a low decrease in both Hb and platelet count against the healthy group ($P < 0.0001$). **Conclusion:** High serum Elabela level in CHC patients compared to the control group was associated with liver fibrosis and could be used clinically as a reliable biomarker to determine the high-risk patient in need of invasive liver biopsy and hazardous therapeutics.

Keywords: APRI, chronic hepatitis C, Elabela, liver fibrosis

Introduction

One serious public health issue affecting millions of individuals worldwide is viral liver infections. Five major distinct types of viral hepatitis have been described, from them are hepatitis B and C, which express chronic behavior and a high risk of liver damage or even hepatic cancers.[1] Hepatitis C viral (HCV) infection is caused by a single-stranded RNA virus belonging to the Flaviviridae family and the mode of transmission of this infection is mainly blood-borne route.[2] The natural history of an infected person with HCV includes the incubation period ranging from 14 to 180 days, acute viral illness only affects 15% of infected individuals, more than 80% of patients develop chronic hepatitis C (CHC) and about one-third of them end up with liver fibrosis and/or cirrhosis.[3] A study conducted in Thi-Qar Province, Iraq showed that the main route of infection was blood transfusion and the high-risk group for getting CHC were patients with thalassemia and renal dialysis.[4] Another national study in Karbala Governorate showed that the prevalence of CHC has decreased over the last decades and the majority of cases were from rural areas and old age.[5]

Due to the chronic behavior of CHC, a high percentage of patients exhibit progressive hepatic fibrosis, which is the leading cause of liver cirrhosis, usually complicated by

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hepatocellular carcinoma and advanced liver diseases.[6] Thus, early detection of liver fibrosis is considered as a challenge for monitoring progression and therapeutic strategy. Liver biopsy is the top choice for screening for liver fibrosis associated with chronic liver disorders, including CHC.[7] However, liver biopsy is regarded as an invasive technique accompanying high complications such as bleeding and underestimation of the severity of liver damage due to the small sample size.[8] Transient elastography using ultrasound technique is also used as a helpful tool for staging liver fibrosis.[9] Both the above techniques were expensive and not available in common practice.

The finding of a cost-effective, noninvasive, and accurate biomarker of liver fibrosis represents a challenge. Blood biomarkers search is considered an invaluable measure for both non-invasiveness and limited expenses. Many blood markers have been observed, for example, bilirubin, albumin, and fetoprotein have been used for the evaluation of liver functions but all the mentioned biomarkers were very poor for the revelation of fibrosis of the liver and progression of the disease.[10] In 2003, the first study was done by Wai *et al*. to determine the stages of liver fibrosis in CHC patients. This marker is the aspartate aminotransferase-to-platelet ratio index (APRI).[11] Subsequently, APRI is a tool developed by many researchers as a guide that helps in monitoring the stage of liver fibrosis for different hepatological pathologies, including hepatitis C viral infection.[12] The scientific background of the use of APRI was that serum level rise of aspartate aminotransaminase (AST) is correlated with hepatocyte damage and reduced clearance due to liver fibrosis. Thrombocytopenia, decreased platelet count, in liver fibrosis are accounted to reduced thrombopoietin hepatic production, portal blood flow changes, and splenomegaly. Moreover, this dependable index is an inexpensive, straightforward, and easily accessible marker.[13] The diversity of the researcher's results represents one of the limitations of the use of APRI in the detection of fibrosis and cirrhosis. Chronic hepatitis, disease course, and the need for a secondary confirmatory test are among the reasons for the discrepancies in results.[14] However, these limitations of APRI measure represent invaluable tests that help to determine high-risk patients to conduct fibrosis and to avoid unnecessary liver biopsies in low-risk groups. In a large systematic review of 22 studies conducted in 2007 (4266 patients with CHC), a cutoff value of 0.5 APRI is recommended; values above this represent a high risk of fibrosis, and below this carries a low risk of fibrosis.[12]

In addition to inflammation and fibrosis of the liver tissues in CHC, a disorder of energy metabolism has also been recorded.[15,16] Hepatocyte polypeptides such as adropin, apelin, and Elabela are recognized to disturb hepatic energy metabolism.[17] Elabela is a polypeptide that acts as an endogenous ligand of apelin receptor shown to regulate energy metabolism in renal tissues and protect this tissue from ischemia.[18] Previous studies showed that Elabela protein is expressed in liver tissues and that its expression is positively correlated with liver fibrosis.[17] Therefore, the current study was conducted to evaluate Elabela serum levels in patients with CHC compared to healthy controls and to investigate whether the peptide Elabela can be used as a biomarker to predict liver fibrosis.

Materials and Methods

About 40 Iraqi patients participated in this case-control research (age range 21–71) diagnosed with chronic liver disease (CHC) for more than 6 months according to the basis of a positive anti-HCV antibody screen and a confirmatory nucleic acid test (NAT). All control subjects (40 participants; age range 20–59) underwent serological tests and were shown to be seronegative prior to being selected to take part in the study. Age, sex, and weight were matched between the two groups. The patients were chosen among those who visited the Gastroenterology Department of the Al-Yarmouk Teaching Hospital, Baghdad, Iraq, between May 2022 and February 2023.

Hepatic echogenicity, signs of portal HTN, or radiological signs of cirrhosis were assessed by abdominal ultrasound to rule out cancer of the liver or other pathologies. Laboratory investigations included serum alkaline phosphatase (ALP), AST, serum alanine aminotransaminase (ALT), serum albumin, and complete blood count (CBC). A full clinical examination was also performed.

The on-site HCV rapid test is a lateral flow chromatographic immunoassay for the qualitative detection of hepatitis C, and hepatitis C antibodies (HCVAb) in blood components (serum or plasma). It is designed to assist healthcare professionals in the detection of infection with the hepatitis C virus (HCV) in all parts of blood at a level ≥1 ng/mL, utilizing a lateral flow chromatographic immunoassay.

Risk group of fibrosis

To determine the risk group for liver fibrosis depending on previous observations using APRI values. The patient's group (n = 40) was subjected to determine who among them was at a high risk for fibrosis. A cutoff value of 0.5 for APRI was adopted to determine the value below it has a very low risk of having liver fibrosis and a value of above 0.5 index with a high risk of getting liver fibrosis.[11-13]

AST to Platelet Ratio Index (APRI)

The calculation of APRI equation is [(AST/ULN)/PLT (10^9/L)] × 100,[11] where AST represents the serum level of aspartate aminotransferase enzyme, ULN means the upper limit of normal value, which is adopted as 40 U/L and PLT means platelets count.

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A venous blood sample collection of about (10 mL) from each participant and subdivided into two. Two milliliters were put in an EDTA tube and used to measure routine test CBC, and the other portion of blood was allowed to clot and then centrifuged at (3500 rpm) for 10 min. After the separation of serum from the coagulants, it was stored at −20°C. until assay the biochemical parameters (ALP, ALT, AST, and Elabela). Elabela was quantitatively measured using the Human ELABELA ELISA Kit (Cat. No. MBS 3803412) according to the manufacturer's protocol.

Inclusion criteria

Adult patients of both sexes with seropositivity of HCV Ab.

Exclusion criteria

We excluded the patients

(1) taking antiviral treatments,
(2) suffering from toxic hepatitis due to certain medications,
(3) with autoimmune and bacterial infection,
(4) with alcoholism and fatty liver, and
(5) with other types of hepatitis

Statistical analysis

Data analysis was done by GraphPad Prism 8.0.2 (CA) software. Range, percentage, and mean ± SD were used to present the data. The difference between the two independent means was analyzed using the Student *t* test. For evaluation of the importance of correlation and analysis of linear regression, Pearson's correlation and its *t* test were used for quantitative variables. Whenever the probability value is ≤0.05, it is considered significant.

Ethical approval

The consent and signature of all participants in the study were taken on the form, in accordance with national and international rules (Declaration of Helsinki). The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee of at Al-Yarmouk Teaching Hospital, Baghdad, according to the document number 830 on April 3, 2022.

Results

The results obtained from this study recorded those 40 patients had CHC infection, with the ratio of females to males being 23/17. The control individuals were 21 female and 19 male and no considerable differences in gender between the patients and control. The average age and body weight of the CHC and control groups appear to be not different significantly. Highly increased ALT and AST levels in CHC were compared with the control category ($P < 0.0001$). CHC patients were shown to be anemic as the mean hemoglobin level was 10.38 ± 2.44 g/dL, which was significantly lower than that of the control (14.00 ± 1.75 g/dL; $P < 0.0001$). The mean value of APRI in CHC was higher (0.743 ± 0.579) and statistically significant compared with the control group (0.208 ± 0.064; $P < 0.0001$). Mean serum level of Elabela polypeptide of CHC group (33.89 ± 8.51 ng/mL) was significantly higher ($P < 0.0001$) than the results obtained from the control group 18.11 ± 5.27 ng/mL as shown in Table 1.

Table 1: Demographic and blood measures of study subjects. Represented as range and mean ± standard deviation (SD)

Parameter	CHC, $N = 40$	Controls, $N = 40$	P value
Sex (female/male)	23/17	21/19	ns
Age (years) range (mean ± SD)	(21–71) 38.53 ± 12.18	(20–59) 41.075 ± 11.12	ns
Weight (kg)	(50–117) 84.15 ± 17.77	(50–105) 79.475 ± 15.52	ns
AST (U/L)	(15–97) 52.34 ± 24.06	(16–34) 26.6 ± 4.62	<0.0001
ALT (U/L)	(20.54–137) 69.07 ± 21.52	(9–36) 21.575 ± 7.50	<0.0001
Hemoglobin (g/dL)	(6–16) 10.38 ± 2.44	(9.6–17.1) 14.00 ± 1.75	<0.0001
Platelets count × 10^9/L	(85–360) 225.5 ± 74.41	(220–498) 338.4 ± 77.63	<0.0001
APRI	(0.11–2.6) 0.743 ± 0.579	(0.1–0.36) 0.208 ± 0.064	<0.0001
Elabela (ng/mL)	(16.66–55.27) 33.89 ± 8.51	(7.9–32.5) 18.11 ± 5.27	<0.0001

In Figure 1, correlation and linear regression analysis of CHC group showed that Elabela level was markedly positive correlated with both age of patients ($r = 0.4796$, $P < 0.0017$) and APIR ($r = 0.404$, $P < 0.0097$). A strong negative correlation was recorded between platelet count and serum Elabela level. ($r = 0.559$, $P < 0.0002$). In contrast, there was no correlation seen between the Elabela level in the control group and any of the participants' age, body weight, APIR, or platelet count.

Risk of fibrosis adopted upon previous studies and meta-analysis.[11-13] Depending on the cutoff value of 0.5 of APIR revealed that 42.5% of CHC group have a high risk of fibrosis (17/40 patients). Compared with the control and low-risk group, the high-risk fibrosis group showed a high level of Elabela with high significance ($P < 0.0001$) as shown in Figure 2. The fibrosis group with a high risk showed very low concentration in contrast with the low-risk and healthy.

To evaluate the efficacy of serum Elabela as a marker of detection of the risk of liver fibrosis, in Figure 3, the receiver operation characteristic curve (ROC curve) was used and results revealed that the area under the curve was 0.8363, 95% confidence interval 0.71–0.96 and ($P < 0.0003$). The calculated cutoff value of Elabela serum value >31.44 ng/mL is considered to have risk of fibrosis with a sensitivity of 94% and specificity of 61%.

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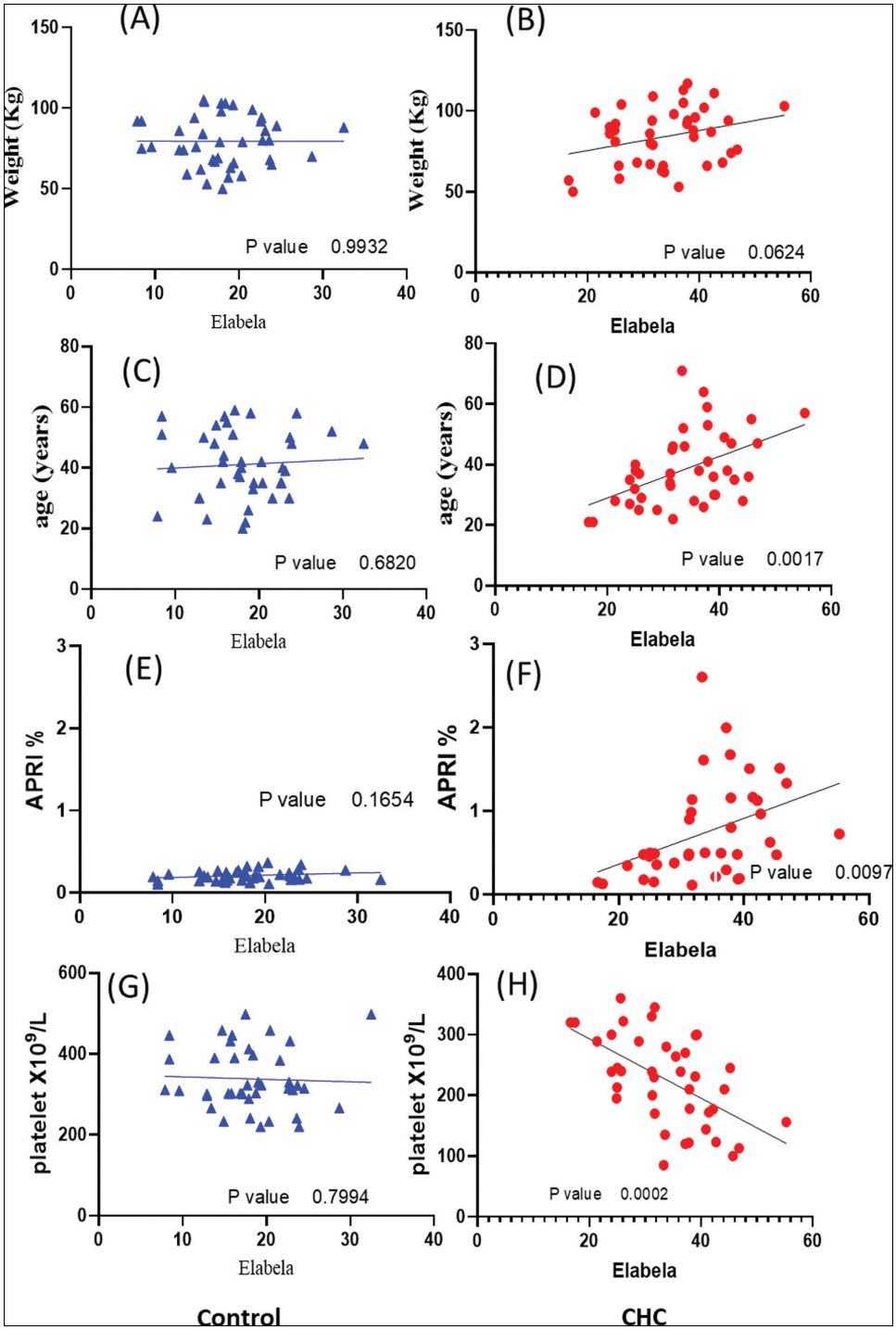

Figure 1: graphs representative of linear regression analysis of serum Elabela level with weight, age, APIR, and platelets count in the left penal in blue for the control group and in the right red for the CHC group. (A and B) a linear regression analysis of both control and CHC groups for serum Elabela and body weight in kilogram. (C and D) for Elabela and age in years. (E and F) for Elabela and APIR. (G and H) for Elabela and platelets count

Discussion

In previous studies, there is single research that addressed the Elabela in tissues of patients with CHC, however, no single study focused on investigating the level of serum Elabela and its role in CHC infection and liver fibrosis. In the current research, we reported that serum Elabela level in CHC group was significantly higher than that of the control. In addition, the level of Elabela in CHC with a high risk of fibrosis was significantly higher than that of CHC with a low risk of fibrosis.

CHC infection is regarded as a common chronic infection globally and is frequently associated with severe

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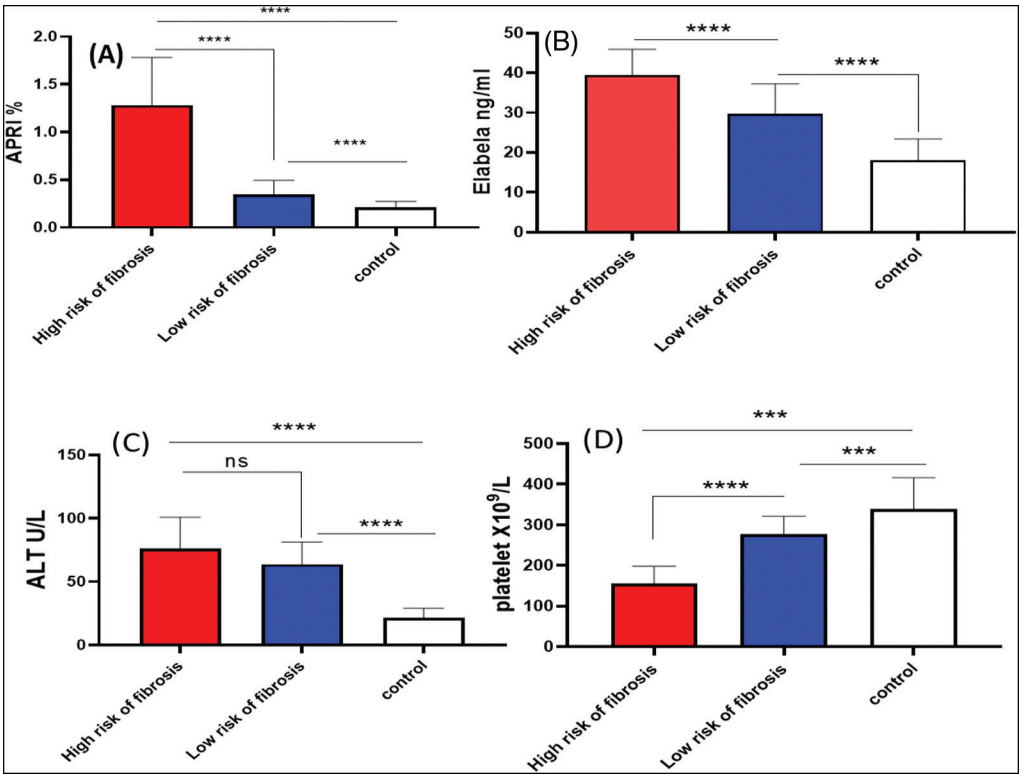

Figure 2: Graphs representative of the means measures for groups of the study (red; CHC with a high risk of fibrosis, blue; CHC with a low risk of fibrosis and white bars for healthy control group. (A) Results of APIR, (B) serum Elabela, (C) ALT enzyme, and (D) platelets count. ns means *P* value > 0.05, *** means *P* value < 0.001 and **** *P* value < 0.0001

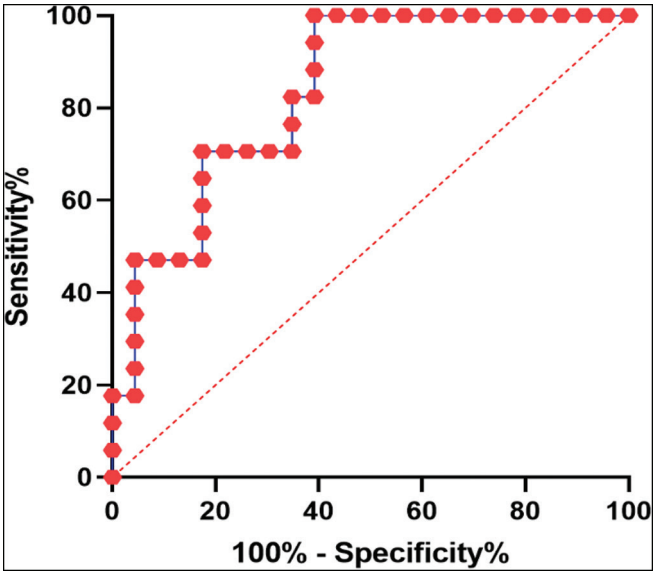

Figure 3: Graph representative of receiver operator characteristic curves of serum Elabela level of CHC groups

complications including liver fibrosis, cirrhosis, and hepatocellular carcinoma.[19] Even with the development of advanced methods of diagnosis and treatment of CHC over the last 20 years, a considerable percentage of infected patients with CHC can end up with liver fibrosis or even cirrhosis. The importance of detecting liver fibrosis complicating CHC has shown to be essential for planning of therapeutic strategy and expectation of prognosis. Chemotherapeutic and antiviral therapies commonly used in the treatment of patients with CHC associated with a rising potential of side effects and toxicity,[20] therefore an indication of treatment and even invasive methods of diagnosis such as liver biopsy are recommended for only patients with a high proportion of the expected histological lesion.[21] The finding of a noninvasive method for the detection of liver fibrosis represents a challenge for healthcare providers. In the current study, the level of Elabela in patients with CHC was highly significant compared to its level in the control group. No previous study was conducted on Elabela level in CHC infection to compare with, however, serum apelin that acts on the same receptors on hepatocytes was reported to be higher in CHC than that of the control.[22,23] Furthermore, the circulatory level of Elabela in CHC group was shown to be positively correlated with APIR used previously as an indicator of liver fibrosis with no like correlation in the control group. The increased level of Elabela and its correlation with fibrosis could be attributed to the activation of the signaling pathway of inflammation and cellular necrosis. The serum level of Elabela in CHC was shown to be positively correlated with the age and body weight of the patients. In accordance with this result, plasma apelin was positively correlated with age in liver pathology.[24] Liver

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fibrosis represents the most common complication of CHC infection. In the current study, in the high-risk fibrosis group, the serum Elabela was shown to be markedly higher when compared with the low-risk group. Another point to consider, the same group of patients was shown to have a higher APIR and liver enzyme level as well as a decrease in platelet count compared to the low-risk group. These results signify that the risk of fibrosis is associated with increased cell damage and decreased function.

To consider any biological element as a marker of diagnosis of a specific disease is very complicated and subjected to a high rate of variability. In the present findings, serum Elabela level was tested as a marker of liver fibrosis with a cutoff value > 31.44 ng/mL considered to have the risk of fibrosis with a sensitivity of 94% and specificity of 61%. However, this result represents only a small group of patients but could be used clinically to do liver biopsy or treatment with a high risk of side effect drugs for CHC patients for only a high risk of fibrosis.

Conclusions

Inflammation and necrosis represent signs of CHC. Hepatic peptides including Elabela shown to play a role in these processes. Circulating serum Elabela levels vary in different groups of the risk of fibrosis. Elabela was recorded as high level in the fibrosis group with high-risk compared to the low-risk group. However, the difficulty of depending on a new biomarker with a very small patient number as a predictor of fibrosis can be used at least to exclude the low-risk group of patients from exposure to invasive procedures and toxic therapeutics.

Study limitation

The small size of patients is one of the limitations of our study. There is a need for additional studies using more samples.

Study strengths

A study was conducted to evaluate Elabela level as a predictor in cases suffering from CHC infection and liver fibrosis. Our study is the first to be conducted on CHC disease in serum and based on the results we obtained, it is considered a good start at least to exclude the lowest-risk patients of fibrosis in this study from exposure to harmful biopsies and their consequences.

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Author contribution

EAA and AAHA-B designed research and reviewed data, wrote and revised the manuscript, and were responsible for the final revision and drafting of the manuscript; AFS collected and analyzed the data and did the literature review; and all the authors read and agreed on the final version of the manuscript.

Declaration of patient consent

All patients gave written consent prior to enrollment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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