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B-type natriuretic peptide (BNP) in HCV-positive Egyptian patients: the impact of HCV eradication on plasma BNP levels

Ali Nada[1], Aliaa Sabry[1], Naglaa S. Elabd[2*], Azza M. Abdu Allah[3], Nada Elnaidany[4] and Mohamed Abbasy[1]

Abstract

Background: Chronic hepatitis C virus (HCV) infection represents a major health-related burden in Egypt. HCV is considered as a major cardiovascular risk factor. BNP (B-type natriuretic peptide) has been determined as a credible diagnostic and prognostic cardiac biomarker. We aimed to assess plasma BNP in HCV-positive Egyptian patients prior and after HCV eradication by direct-acting antiviral agents (DAAs) therapy. Eighty-nine chronic HCV-positive patients were enrolled in our prospective research. They were provided with DAAs therapy in the form of sofosbuvir and daclatasvir without or with ribavirin for 12 weeks. History, clinical evaluation, and laboratory assessment: CBC, liver and kidney function tests, viral markers (HCVAb, HBVsAg, and HIVAb) by ELISA, HCV RNA by real-time PCR, and BNP by ELISA were assessed. FIB-4 and aspartate aminotransferase-to-platelet ratio index (APRI) scores were ranked.

Results: Plasma BNP displayed a non-significant ($p = 0.124$) increase of its serum mean values in post eradication of HCV than its baseline values. Baseline BNP exhibited a significant positive correlation with FIB4 ($r = 0.411$, $P < 0.001$) and APRI score ($r = 0.418$, $p < 0.001$) with a considerably negative correlation with platelets ($r = -0.274$, $p = 0.009$), in addition to higher pretreatment BNP values in cirrhotic than in non-cirrhotic patients ($p < 0.001$), while non-significant relations were found regarding sex, BMI, and drug regimen (with or without ribavirin) ($p = 0.950$, 0.845, and 0.738, respectively). Additionally, plasma BNP values considerably decreased post-treatment in patients presented with higher baseline BNP values and more advanced liver disease (higher FIB4, APRI, and the presence of liver cirrhosis).

Conclusion: Our findings propose on the one side, the necessity of cardiac monitoring during chronic HCV infection and, on the other, the valuable impacts of HCV eradication on HCV-associated cardiac morbidities.

Keywords: BNP, HCV Patients, DAAs therapy

Background

About 185 million subjects are hepatitis C virus (HCV) infected, with an assessed 2.8% rise over the last decade globally. HCV has been evaluated to be the driving cause of worldwide cases of cirrhosis and hepatocellular carcinoma (HCC). HCV prevalence estimations differ greatly worldwide- and region-specific [1, 2]; however, the most noteworthy predominance has been recorded in China, Nigeria, Pakistan, Egypt, India, and Russia those together deemed for more than half of the overall infections [3].

In Egypt, chronic HCV infection is considered as a major health burden that influences about 14.7% of the Egyptian population [4]. Egypt's prevalence of active HCV infection is diverse regarding the region, with 8% being the highest in Menoufia. As stated by the reports of 2015 survey, other governorates with a rate of about ≥ 5% involved Menya, Dakhalia, Gharbia, Behera, Sharkia, Damietta, Beni Suef, and Fayoum [5]. However, a groundbreaking reduction of the HCV epidemic in Egypt has occurred with genotype 4-effective DAAs recently introduced to the treatment protocol; combinations of DAAs

* Correspondence: naglaa_elabd@yahoo.com
[2]Tropical Medicine Department, Faculty of Medicine- Menoufia University, Menoufia, Egypt
Full list of author information is available at the end of the article

have been documented to show high rates of sustained virological response (SVR) as well as a pan-genotypic clinical efficacy in HCV genotypes [6].

The availability of high effectiveness, clear applicability, and acceptable side effect profile of all-oral, direct-acting antiviral drugs encouraged HCV treatment in clinical practice [7]. Sofosbuvir (SOF), the first high-resistance barrier nucleotide NS5B polymerase inhibitor, was affirmed for interferon-free eradication of HCV infection in Europe and the USA at the beginning of 2014 [8].

In addition to the well-known deleterious impacts on the structure and function of the liver, chronic HCV infection is linked to other severe extra-hepatic manifestations. Moreover, chronic HCV infection has been related to enhanced incidence of (CAD) coronary artery disease [9], increased hazard of carotid artery plaques as well as carotid intima-media thickening [10] and cerebrovascular events, like stroke [11]. This indicates that chronic HCV infection could be likelihood deemed to be a cardiovascular hazard factor.

N-terminal proBNP (NT-proBNP) and brain natriuretic peptides or B-type natriuretic peptide (BNP) are predominantly natriuretic hormones produced by the heart ventricles. In general population, both biomarkers were identified as accurate diagnostic and prognostic cardiac markers that correlate with congestive heart failure (CHF) symptoms and the intensity of systolic and diastolic dysfunction [12].

The clinical cardiovascular diseases' presentations are gone before by an asymptomatic phase that can be lengthy and insidious, but cardiac biomarkers can be vital in detecting pathological developments during this period that can lead to clinical cardiac events. Biomarkers are valuable tools for risk stratification of patients for disease progression and for tracking the outcome of diseases in response to therapies. So in this study, we pursued to assess plasma BNP in HCV-positive Egyptian patients before and after sofosbuvir and daclatasvir with or without ribavirin therapy and to clear out the impact of HCV eradication on its levels.

Methods

The present work is a prospective research that was carried out on 89 chronic HCV participants. Patients were treatment-naive chronic HCV patients attended for HCV treatment clinic at the National Liver Institute (NLI) or outpatient clinic of Tropical Medicine Department, Faculty of Medicine, Menoufia University from August 2019 and December 2020. Patients were diagnosed by finding out HCV antibodies then assured by real-time PCR. They consisted of 26 males and 63females.

Patients included in this study were chosen as specified by the following criteria: age more than 18 years, positive HCV antibodies by ELISA that were assured by PCR for HCV RNA, treatment-naïve, and, additionally, patients with Child–Pugh score ≤ 8. All patients with HBV (hepatitis B virus) or HIV (human immunodeficiency virus) co-infection, renal impairment, hepatocellular carcinoma or any extra-hepatic malignancy, patients with DM or uncontrolled hypertension, cardiac patients, renal diseases, hyperthyroidism, and obese patients (BMI > or = 30) as well as pregnant females were precluded from the study.

For all patients, history was assessed together with detailed clinical evaluation including estimating BMI. Imaging valuation was performed for all participants by abdominal ultrasound. Laboratory evaluations, including complete blood count, liver function tests (prothrombin time and international normalized ratio (INR), alanine transaminase (ALT), aspartate transaminase (AST), serum total and direct bilirubin, and serum albumin), were investigated. Serum creatinine, fasting blood sugar, lipid profile, and α-fetoprotein were estimated. HCV antibodies, HBVsAg, and HIV antibodies were done by ELISA. HCV RNA level was quantitatively estimated by real-time PCR with a threshold for detection level 15 IU/mL. Plasma B-type natriuretic peptide (BNP) was assessed by ELISA. Upper GIT endoscopy was done when indicated.

For all participants, we calculated aspartate aminotransferase-to-platelet ratio index (APRI) as well as FIB-4 scores. APRI was estimated utilizing the subsequent formula: (AST/upper limit of normal)/platelet count (platelets $\times 10^9$ /L) × 100 [13], and FIB-4 score was estimated utilizing: age (y) × AST (IU/L)/platelet count ($\times 10^9$/L) $\times\sqrt{}$ALT (IU/L) formula [14].

Ethical approval

For all participants, an explanation about the study was provided together with informed consents obtained from each one before being enlisted in the study. The study was carried out after approval from the National Liver Institute Ethical Committee and according to the Helsinki Declaration.

HCV patients received DAAs therapy in the form of sofosbuvir 400 mg/day and daclatasvir 60 mg/day with or without ribavirin for 12 weeks according to the approved treatment recommendation (EASL) [15] and the national guidelines. During DAAs therapy, patients' follow-up was performed via clinical examination with lab re-evaluation including CBC and liver and kidney function tests at 4, 8, and 12 weeks of starting receiving DAAs therapy. RT-PCR was performed at the fourth week and at the end of treatment (EOT) and additionally, to determine SVR12, repeated 12 weeks after stopping treatment.

Sampling

Under entirely aseptic conditions and by means of venipuncture, 8 ml of venous blood was withdrawn from everyone included in the study following 8 h of fasting. In a sterile tube, 4 ml was left to clot and subsequently centrifuged at 3000 rpm for 15 min obtaining serum that is utilized to measure serum biochemical tests including ALT, AST, albumin, total bilirubin, fasting blood glucose (FBG), creatinine, AFP, and BNP. For the residual 4 ml of blood, 2 ml was obtained in citrated tubes for assessment of INR, and 2 ml was placed in EDTA tubes for estimation of platelets count, leukocytes, and hemoglobin, in addition to PCR for quantitative assessment of HCV.

Laboratory methods

Viral marker including HCVAb, HBVsAg, and HIVAb were performed utilizing "ECLIA" by Cobas 411 analyzers (Roche Diagnostics, Germany); furthermore, QIAGEN viral RNA Mini Extraction Kit was utilized in nucleic acid extraction for HCV real-time PCR. On Synchron CX9 autoanalyzer, biochemical tests for estimation of ALT, AST, albumin, total bilirubin, fasting blood glucose, and creatinine were performed by making use of kit provided by Beckman (Beckman Instrument Inc., Fullerton, CA, USA).

BNP assessment

Measurement of plasma BNP was carried out by the ELISA method, utilizing the kit provided by Sunred, China, Catalogue No. 201-12-1288 kit using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA).

Ultrasound of the abdomen

Liver assessment was performed in axial and longitudinal views while the patient was supine and in left lateral decubitus with estimation of the size and patency size of the portal vein (PV). Additionally, we examined patients in the supine as well as the right lateral decubitus for assessment of spleen size in bipolar diameter.

Statistical data analysis

Data of this study were supplied to the computer and analyzed utilizing IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov was used to verify the normality of variables distribution. Comparisons between groups for categorical variables were assessed using Marginal Homogeneity. Test used to analyze the significance between the different stages: Paired t test was assessed for comparison between two periods for normally distributed quantitative variables, while Wilcoxon signed ranks test was assessed for comparison between two periods for abnormally distributed quantitative variables. Kruskal Wallis test was used to compare different groups. For not normally distributed quantitative variables, the Mann Whitney test to compare between two groups was performed. For correlation between quantitative variables, Spearman coefficient was utilized. At the 5% level, significance of the gained results was judged.

Results

This study was carried out on 89 patients with chronic HCV participants, of which there were 26 (29.2%) males and 63 (70.8%) females, with age ranging between 27 and 65 with a mean age of 50.1 ± 9.9. All studied patients received treatment for 12 weeks (63 patients (70.8%) received SOF + DAC and 26 (29.2%) patients received SOF+DAC+RIB) and none of them needed dose modifications; in addition, they showed undetected HCV RNA in week 4, (EOT) end of treatment, and 12 weeks after stopping treatment (SVR12). The basic clinical, laboratory, imaging, and endoscopic data are presented in Table 1.

Comparisons of the assessed parameters prior and after treatment revealed that BMI was not significantly changed pre- and post-treatment ($p = 0.446$). Comparing laboratory investigations before and after treatment showed that ALT ($p < 0.001$) and AST ($p < 0.001$) were considerably decreased post-treatment; however, total bilirubin showed to have slightly increased and INR did not change post-treatment. CBC showed a non-significant decrease in platelet count and WBCs ($p = 0.111$ and 0.072, respectively) with significantly lower hemoglobin concentration ($p < 0.001$). In addition, FIB4 ($p = 0.003$) was considerably decreased where FIB4 < 1.45, 1.45–3.25, and >3.25 was 48.3%, 47.2%, and 4.5%, respectively, prior treatment, while, 57.3%, 42.7%, and 0%, respectively, post-treatment. Also, APRI score ($p = 0.033$) significantly differ with lower values post-treatment where APRI score < 0.5, 0.5–1.5, and >1.5 was 51.7%, 43.8%, and 4.5, respectively, prior treatment, while 58.4%, 41.6%, and 0%, respectively, as displayed in Table 2.

Estimation of the plasma BNP variations in studied patients prior and post eradication of HCV showed a non-significant ($p = 0.124$) increase of its plasma mean values in post-treatment than prior treatment 24.4 ± 25.6 and 21.4 ± 23.9, respectively (Table 2 and Fig. 1a).

Table 3 demonstrated correlation analysis, utilizing spearman coefficient, between pretreatment BNP levels and studied parameters where our results displayed significant positive correlations between BNP and FIB4 ($r = 0.411$, $p < 0.001$ and) and also with APRI score ($r = 0.418$, $p < 0.001$) together with a significant negative correlation between BNP and platelets ($r = -0.274$, $p = 0.009$) as presented in Fig. 1b. However, no association was observed with other laboratory or imaging finding

Table 1 Distribution of the studied cases according to different clinical parameters (n = 89)

	No. (%)
Sex	
Male	26 (29.2%)
Female	63 (70.8%)
Age (years)	
Mean ± SD.	50.1 ± 9.9
Median (min.–max.)	50 (27–65)
BMI (kg/m^2)	
Mean ± SD.	26.9 ± 2
Median (min.–max.)	27.1(22.9–29.9)
HCV PCR	
Mean ± SD.	918883.5 ± 1228408
Median (min.–max.)	336000 (5592–5330000)
Liver echogenicity	
Normal	61 (68.5%)
Cirrhotic	28 (31.5%)
Spleen (US)	
Normal	79 (88.8%)
Enlarged	10 (11.2%)
FIB4 score	
Mean ± SD.	1.7 ± 0.9
Median (min.–max.)	1.5 (0.6–5.2)
APRI score	
Mean ± SD.	0.6 ± 0.4
Median (min.–max.)	0.5 (0.1–1.9)
Type of drugs	
SOF + DAC	63(70.8%)
SOF + DAC + RIB	26(29.2%)

SD standard deviation, *BMI* body mass index, *APRI score* aspartate aminotransferase-to-platelet ratio index score, *SOF* sofosbuvir, *DAC* daclatasvir, *RIB* ribavirin

and with studying the correlation analysis between post-treatment BNP levels with the same parameters, and a non-significant correlation was found.

Additionally, we observed that higher pretreatment BNP values were detected in patients with liver cirrhosis (mean was 31.9 ± 38.4) than in patients with normal liver echogenicity (mean was 16.6 ± 9.9) by US (p < 0.001). Furthermore, BNP levels increased with increasing FIB4 where its mean values were 13.7 ± 4.4, 22.7 ± 11.3, and 91.2 ± 85.8, respectively, with FIB4 < 1.45, 1.45–3.25, and > 3.25, respectively, and also with increasing APRI score where its mean values were 14.5 ± 5.1, 19.9 ± 6.3, and 115.1 ± 58.2, respectively, with APRI score < 0.5, 0.5–1.5, and > 1.5 respectively (Fig. 1c, d). No significant relations were found regarding sex, grade of BMI, and drug regimen (with or without ribavirin) (p = 0.950, 0.845, and 0.738, respectively. Also, we perceived that post-treatment BNP levels were not significantly related to the sex, BMI, the drug regimen, liver echogenicity, and FIB4 or APRI scores as presented in Table 4.

Interestingly, after calculating delta BNP that represent the change of BNP after HCV eradication (BNP after – BNP before treatment), we observed that delta BNP was not significantly correlated to age (r = 0.128 and p = 0.234), as well as being not related to sex, BMI, or drug regimen (p = 0.620, 0.150, and 0.698, respectively) (Fig. 2b). However, it was considerably related to liver echogenicity (p = 0.001) where delta BNP was – 12.8 ± 39.1 in patients with cirrhotic liver and 10.2 ± 34.7 in patients with normal liver echogenicity (Fig. 2a). Similarly, it was significantly related to FIB4 score (p <0.001), delta BNP in patients with FIB4 > 3.25 was – 67.6 ± 91.8 while that in < 1.45 FIB4 patients was 16.1 ± 38.5. Furthermore, delta BNP was considerably related to APRI score (p < 0.001) as delta BNP values in patients with APRI score > 1.5 and < 0.5, respectively, were – 96.3 ± 58.7 and 12.6 ± 37.5, respectively (Table 5 and Fig. 2c, d)

Discussion

Around 399,000 individuals die every year from HCV or from complications linked to its chronic infection including liver cirrhosis, liver failure, or hepatocellular carcinoma (HCC). Six major HCV genotypes have been identified in the Middle East and Africa including Egypt, HCV genotype 4 is the most prevalent [15].

Besides the widely known harmful effects of HCV on the liver structure and function, its chronic infection is connected with different extra-hepatic manifestations, such as glomerulonephritis, non-Hodgkin B cell lymphoma, mixed cryoglobulinemia, pulmonary fibrosis, autoimmune diseases, and ocular and dermatological diseases, whose mechanisms blamed in its pathogenesis are persistent immune system stimulation in addition to the tropism of the HCV virus for other tissues [16].

Moreover, chronic HCV has been also associated with higher risk of cardiovascular diseases. In reality, some authors have been hypothesized that chronic HCV infection could take part in the atheromatous process basically by means of increased oxidative stress, chronic inflammation, and insulin resistance (IR) as well as replication of HCV virus on the pre-existing plaques. Furthermore, few studies have investigated the potential hazardous effects of HCV infection on both right and left heart; nevertheless, the findings are conflicting. Hypertrophic and dilated cardiomyopathies have been depicted as extra-hepatic morbidity linked to chronic HCV; however, their true frequency is quiet unknown [17].

Compared to interferon-based therapy (IBT), DAAs have demonstrated outstanding efficacy safety and

Table 2 Comparison between pre and post-treatment according to different clinical and laboratory parameters

	Pre (n = 89)	Post (n = 89)	Test of sig.	P
BMI (kg/m^2)				
18.5–24.9	22(24.7%)	18(20.2%)	MH = 2.828	0.157
25.0–29.9	67(75.3%)	71(79.8%)		
Mean ± SD.	26.9 ± 2	26.8 ± 2.1	Z = 0.763	0.446
Median (min.–max.)	27.1(22.9–29.9)	27.1(20.7–29.4)		
Total bilirubin				
Mean ± SD.	0.9 ± 0.2	1.2 ± 0.2	Z = 6.922*	< 0.001*
Median (nin.–max.)	0.8 (0.6–1.6)	1.2 (0.7–1.6)		
INR				
Mean ± SD.	1.1 ± 0.1	1.1 ± 0.1	Z = 1.068	0.286
Median (min.–max.)	1 (1–1.4)	1 (1–1.3)		
ALT				
Mean ± SD.	49.3 ± 28.6	36.4 ± 7.6	Z = 7.237*	< 0.001*
Median (min.–max.)	45 (14–199)	36 (16–50)		
AST				
Mean ± SD.	44.7 ± 18	34.3 ± 7.3	Z = 7.003*	< 0.001*
Median (min.–max.)	43 (15–100)	34 (17–60)		
Creatinine				
Mean ± SD.	0.9 ± 0.2	1.0 ± 0.2	Z = 1.866	0.062
Median (min.–max.)	0.9 (0.6–1.4)	0.9 (0.6–1.6)		
FIB4				
< 1.45	43 (48.3%)	51 (57.3%)	MH = 28.0*	0.003*
1.45–3.25	42 (47.2%)	38 (42.7%)		
> 3.25	4 (4.5%)	0 (0%)		
Mean ± SD.	1.7 ± 0.9	1.6 ± 0.6	Z = 2.199*	0.028*
Median (min.–max.)	1.5 (0.6–5.2)	1.4 (0.7–3.0)		
APRI				
< 0.5	46 (51.7%)	52 (58.4%)	MH = 37.0*	0.033*
0.5 –1.5	39 (43.8%)	37 (41.6%)		
> 1.5	4 (4.5%)	0 (0%)		
Mean ± SD.	0.6 ± 0.4	0.5 ± 0.2	Z = 4.464*	< 0.001*
Median (min.–max.)	0.5 (0.1–1.9)	0.4 (0.1–0.9)		
HB				
Mean ± SD.	13.5 ± 1.4	12.6 ± 1.2	t = 7.009*	< 0.001*
Median (min.–max.)	13.7 (9–16)	12.6 (10–15.0)		
Platelet count				
Mean ± SD.	209 ± 65.3	199.3 ± 61.9	Z = 1.592	0.111
Median (min.–max.)	202 (83–478)	198 (101–417)		
WBCs				
Mean ± SD.	6.7 ± 1.8	6.1 ± 1.4	Z = 1.802	0.072
Median (min.–max.)	6.3 (3.6–10.3)	5.9(4.5–9.3)		
BNP level TTT				
Mean ± SD.	21.4 ± 23.9	24.4 ± 25.6	Z=1.536	0.124
Median (min.–max.)	16 (0.7–165.5)	18.4 (8.7–180.7)		
Delta BNP level	3 ± 37.5			

MH marginal homogeneity test, *t* paired *t* test, *Z* Wilcoxon signed ranks test, *SD* standard deviation, *p p* value for comparing between *pre* and *post*
BMI body mass index, *INR* international normalized ratio, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *HB* hemoglobin concentration, *WBCs* white blood cells, *APRI score* aspartate aminotransferase-to-platelet ratio index score, *BNP* B-type natriuretic peptide, *delta BNP* BNP after – BNP before treatment
*Statistically significant at $p < 0.05$

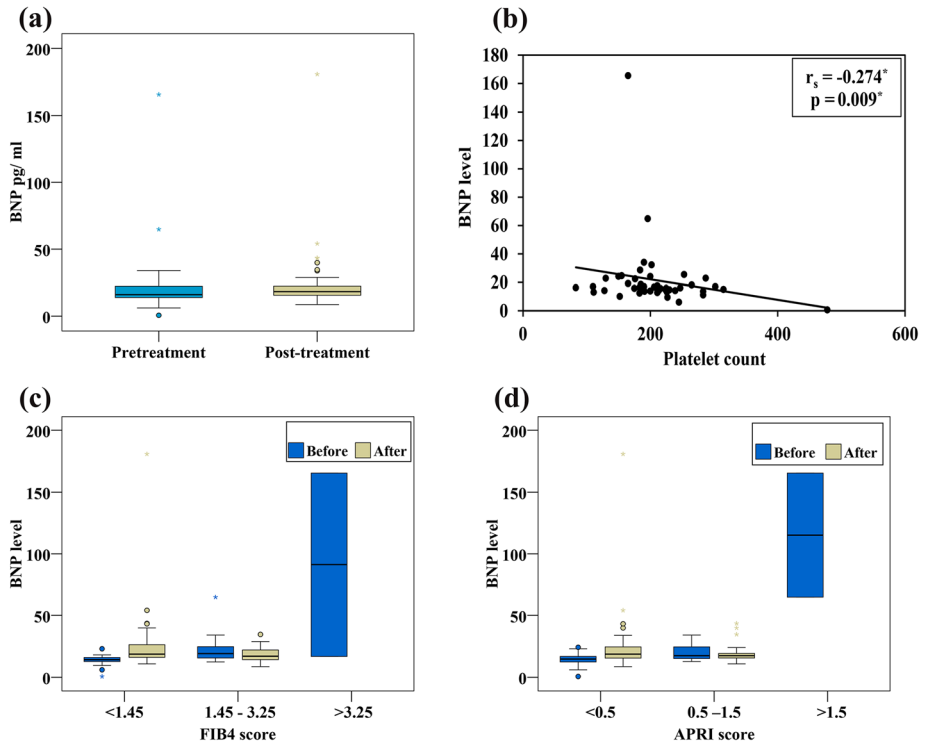

Fig. 1 **a** Comparison between plasma BNP levels pretreatment and post-treatment. **b** Correlation between plasma BNP levels and platelet count. **c** Relation between plasma BNP levels and pretreatment FIB4 score. **d** Relation between plasma BNP levels and pretreatment APRI score

Table 3 Correlation between BNP (before and after treatment) level and different laboratory parameters

	BNP level			
	Before (basal)		After	
	r_s	*p*	r_s	*p*
Age	− 0.131	0.222	0.184	0.085
Total bilirubin	0.134	0.210	0.0	1.000
Serum albumin	− 0.022	0.836	0.025	0.813
INR	0.064	0.553	0.045	0.672
ALT	0.052	0.627	− 0.142	0.185
AST	0.126	0.240	− 0.197	0.065
FIB4	0.531	<0.001*	− 0.071	0.506
APRI	0.474	<0.001*	− 0.174	0.102
HB	0.151	0.158	0.166	0.120
Platelet count	− 0.274	0.009*	− 0.098	0.361
WBC	0.023	0.831	− 0.098	0.361

r_s Spearman coefficient
INR international normalized ratio, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *APRI score* aspartate aminotransferase-to-platelet ratio index score, *HB* hemoglobin concentration, *WBCs* white blood cells, *BNP* B-type natriuretic peptide
*Statistically significant at $p < 0.05$

revolutionized paradigms for HCV towards wider approaches for cure [18]. It has been shown that HCV virologic cure invariably diminish liver inflammation, indicated by improved aminotransferase levels and decreased rates of liver fibrosis progression. SVR also contributes to regression of liver cirrhosis and improves the clinical signs of portal hypertension as well as end-stage liver disease in some patients. Additionally, it has been reported eradication of HCV was linked with general improvement in extra-hepatic comorbidities such as cryoglobulinemia, insulin sensitivity, and non-Hodgkin's lymphoma [19]. However, few studies have investigated the effects of the DAAs on cardiovascular biomarkers after HCV elimination.

The aim of our study was to investigate plasma B-type natriuretic peptide (BNP) in chronic HCV Egyptian patients prior and after sofosbuvir and daclatasvir with or without ribavirin therapy and to highlight the effect of HCV eradication on plasma BNP levels.

The present study was performed on 89 chronic HCV participants; they received DAAs therapy in the form of sofosbuvir 400 mg/day and daclatasvir 60 mg/day with or without ribavirin for 12 weeks. All patients showed undetected HCV RNA in week 4, end of treatment (EOT), and SVR12. We observed that achieving SVR12 was associated with lowering ALT and AST levels, besides lowering of FIB-4 and

Table 4 Relation between BNP (before and after treatment) level and different parameters

	N	BNP level			
		Before		After	
		Median(min.–max.)	Mean ± SD.	Median(min.–max.)	Mean ± SD.
Sex					
Male	26	14.8(6.1–34)	18.2 ± 7.5	16.5(22.3 ± 12)	22.3 ± 12
Female	63	16.2(0.7–165.5)	22.8 ± 28	18.5(8.7–180.7)	25.2 ± 29.5
U(*p*)		812.0(0.950)		742.0(0.487)	
BMI					
18.5–24.9	22	15.8(6.1–84.8)	20.3 ± 15.4	16.9(13.4–23.9	17.1 ± 3.1
25.0–29.9	67	16.2(0.7–165.5)	21.8 ± 26.2	18.6(8.7–180.7)	26.2 ± 28.4
U(*p*)		716.50(0.845)		464.50(0.075)	
Type drug					
SOF + AC	63	15.8(0.7–64.8)	18.8 ± 10.6	18.6(10.8–180.7)	26.2 ± 27.9
SOF + DAC + RIB	26	16.9(6.1–165.5)	27.7 ± 40.9	16.7(8.7–43.4)	20 ± 9.7
U(*p*)		782.0(0.738)		668.0(0.173)	
FIB4					
< 1.45	43	14.2(0.7–22.9)	13.7 ± 4.4	18.8(10.8–180.7)	28.9 ± 32.9
1.45–3.25	42	19.2(12.5–64.8)	22.7 ± 11.3	17.5(8.7–34.5)	18.4 ± 6
> 3.25	4	91.2(16.9–165.5)	91.2 ± 85.8	–	–
H(p)		27.925*(<0.001*)		760.0(0.083)	
APRI					
< 0.5	46	14.8(0.7–241)	14.5 ± 5.1	18.8(8.7–180.7)	27.5 ± 32.5
0.5–1.5	39	17.6(12.8–34)	19.9 ± 6.3	17.1(10.8–43.4)	20.1 ± 8.8
> 1.5	4	115.1(64.8–165.5)	115.1 ± 58.2	–	–
H(p)		24.899*(<0.001*)		807.0(0.197)	
Liver echogenicity					
Cirrhosis	28	23.5(6.1–165.5)	31.9 ± 38.4	17.2(8.7–34.5)	19.1 ± 6.5
Normal	61	14.8(0.7–64.8)	16.6 ± 9.9	18.6(10.8–180.7)	26.8 ± 30.4
U(*p*)		336.0(<0.001*)		746.0(0.340)	

U Mann Whitney test, *H* H for Kruskal Wallis test, *p* *p* value for association between different categories
BMI body mass index, *SOF* sofosbuvir, *DAC* daclatasvir, *RIB* ribavirin, *APRI score* aspartate aminotransferase-to-platelet ratio index score
*Statistically significant at $p \leq 0.05$

APRI scores, and this was agreed with previous reports [20].

BNP as well as other structurally linked peptides, which are C-type natriuretic peptide (CNP), atrial natriuretic peptide (ANP), and urodilatin, is a member of the natriuretic peptide family. The natriuretic peptides possess a typical biochemical structure consisting of a 17 amino acid ring together with a bridge of disulfide in-between two molecules of cysteine. It was found that the ventricular myocardium is considered to be the main source of BNP synthesis and secretion. ANP is stowed in granules, and after stimulation, it could be released immediately, while only little amounts of BNP are stowed in granules and the implied mechanism for the organization of BNP secretion is speedy gene expression accompanied by de novo synthesis of the peptide. It was reported that BNP is synthesized as a prohormone (proBNP) containing 108 amino acids. When proBNP is released in the circulation, it is cleaved to egalitarian proportions into the biologically active 32 amino acid BNP, which represents the C-terminal part and a 76 amino acid N-terminal part that is biologically inactive [21].

Myocardial wall stress was notified to be the crucial stimulus for increasing the synthesis and secretion of BNP and NT-proBNP. Additionally, other stimulating agents like cytokines, myocardial ischaemia, and endocrine (paracrine) modulation by other neurohormones are also essential [21].

We displayed noteworthy outcomes, where overall plasma BNP changes in studied HCV patients prior and post eradication of HCV showed a non-significant difference of its plasma mean values in post-treatment compared to prior treatment indicating, to some extent, the

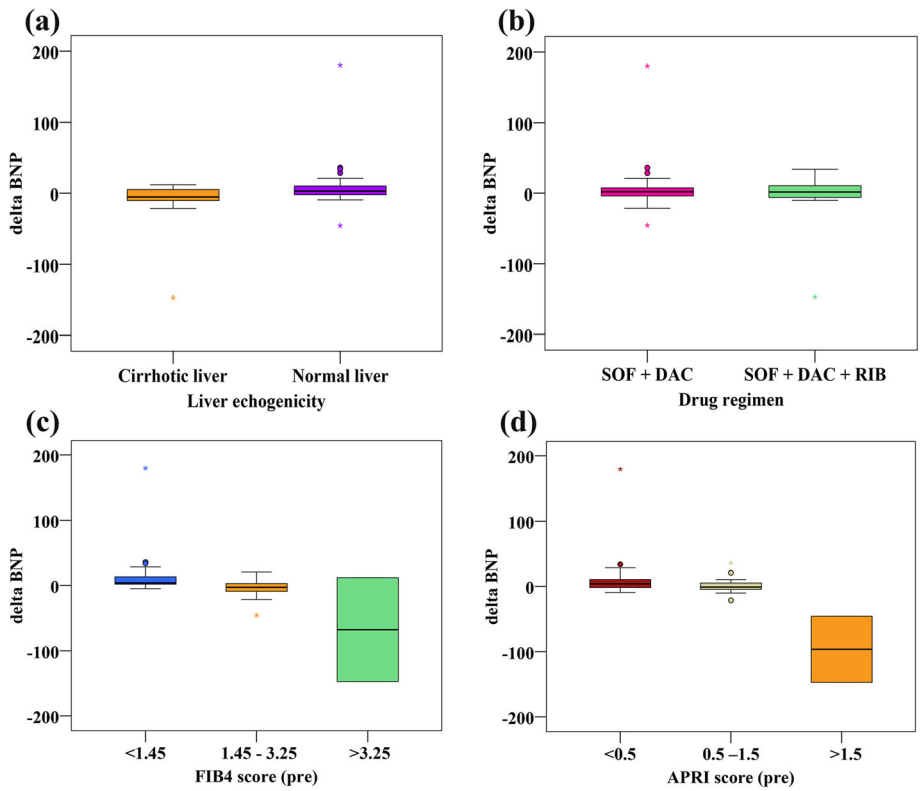

Fig. 2 **a** Relation between delta BNP and echogenicity of the liver. **b** Relation between delta BNP and drug regimen (with and without ribavirin). **c** Relation between delta BNP and pretreatment FIB4 score. **d** Relation between delta BNP and pretreatment APRI score

cardiovascular safety of used drugs. These results were in accordance with previous literature, where mean values of BNP were found to be not changed before and 3 months after HCV eradication [22].

In a former study, it was stated that plasma BNP offers prognostic details in chronic heart failure patients as well as in patients with asymptomatic or symptomatic left ventricular dysfunction [23]. Furthermore, it has been shown that plasma NT-proBNP independently foretells long-term death risk due to congestive heart failure [12]. In the general population, both biomarkers were identified as accurate diagnostic and prognostic cardiac markers that correlate with both CHF symptoms and the severity of systolic and diastolic dysfunction [24]. Moreover, these biomarkers have been shown to be associated with the extent of circulatory dysfunction in patients with liver cirrhosis [25].

In the present study we noticed a non-significant relation found between BNP levels and BMI. These results disagree with those of Wang and his colleagues who have elucidated a consistent inverse relationship between circulating BNP levels and BMI [26]. This difference can be attributed to the difference in the population samples as they classified the patients as obese defined as having a BMI of 30 or greater and non-obese with BMI less than 30. We planned in our study to exclude patients with BMI equal or more than 30 to evade the influence of obesity on BNP levels.

Our study demonstrated significant positive correlations among BNP levels and FIB4 and APRI scores together with a considerable negative correlation among BNP levels and platelets. Additionally, we observed that higher baseline BNP levels were detected in patients with liver cirrhosis than in patients with normal liver echogenicity.

A body of evidence suggests that the impact of HCV-associated inflammation on cardiovascular risk could be higher in patients with more liver damage. The profibrogenic and proinflammatory environment driving liver fibrogenesis in HCV patients may likewise be systemically activated, over and above enhancing the development of cardiovascular lesions [27]. Consistent with these data, a cohort study has found that chronic HCV patients with higher liver stiffness values had a substantial hazard for development of cardiovascular events compared to those with lower stiffness values [28]. Additionally, Maruyama and his colleagues have reported that in chronic HCV patients a considerable link was present between myocardial injury and both the severity of necroinflammatory activity and subsequent liver

Table 5 Relation between delta BNP and different parameters

	N	delta in BNP		Test of sig.	p
		Median (min.–max.)	Mean ± SD.		
Sex					
Male	26	1.7(− 21–35.9)	4.2 ± 14.1	*U* = 764.0	0.620
Female	63	1.9(− 147.1–180)	2.5 ± 43.7		
BMI (pre)					
18.5–24.9	22	− 1.2(− 45.4–10.4)	− 3.5 ± 14.2	*U* = 585.0	0.150
25.0–29.9	67	3.2(− 147.1–180.0)	5.1 ± 42.3		
Normal liver					
No	28	− 5.4(− 147.1–11.9)	− 12.8 ± 39.1	*U* = 492.0*	0.001*
Yes	61	2.8(− 45.4–180)	10.2 ± 34.7		
Type drug					
SOF + DAC	63	1.9(− 45.4–180)	7.4 ± 34.6	*U* = 776.0	0.698
SOF + DAC + RIB	26	1.5(− 147.1–33.9)	− 7.7 ± 42.6		
FIB4 (pre)					
< 1.45	43	3.9(− 5–180)	16.1 ± 38.5	*H* = 18.428*	< 0.001*
1.45–3.25	42	− 2.9(− 45.4–20.7)	− 3.7 ± 13.1		
> 3.25	4	− 67.6(− 147.1–11.9)	− 67.6 ± 91.8		
APRI (pre)					
< 0.5	46	3.9(− 9.5–180)	12.6 ± 37.5	*H* = 15.741*	< 0.001*
0.5–1.5	39	− 1(− 21–35.9)	1.8 ± 12.8		
> 1.5	4	− 96.3(− 147.1–− 45.4)	− 96.3 ± 58.7		

U Mann Whitney test, *H H* for Kruskal Wallis test, *p p* value for association between different categories
BMI body mass index, *SOF* sofosbuvir, *DAC* daclatasvir, *RIB* ribavirin, *APRI score* aspartate aminotransferase-to-platelet ratio index score
*Statistically significant at $p \leq 0.05$

damage [29]. Several factors were also suggested to mediate the link between HCV infection and risk of CVD development including augmented oxidative stress, modified iron homeostasis, activation of immunological, and/or inflammatory processes leading to a disrupted cytokine imbalance as well as induction of hepatic steatosis, a risk factor in insulin sensitivity and related metabolic abnormalities [30].

To the best of our knowledge, there were no considerable data available demonstrating the correlations between the change in BNP levels and the severity of liver disease. In our study, we observed that delta BNP was considerably related to liver echogenicity where BNP was significantly decreased in patients with advanced liver disease as determined by pretreatment presence of liver cirrhosis and higher FIB4 or APRI scores than its baseline values before starting treatment, as we previously reported that these patients showed baseline higher BNP levels. These results reflected the beneficial cardiac effects of HCV eradication as one of its extrahepatic manifestations.

It was formerly illustrated by Dalbeni and his colleagues that HCV is accountable for cardiac and vascular remodeling via direct cytotropic toxicity in addition to an indirect immune-mediated mechanism, most likely both are eliminated when HCV is eradicated. Moreover, they found that in participants with a detectable high cytokines concentration, they observed a significant decrease of TNF-α [17]. TNF-α has been considered to be a potent proinflammatory molecule, which is associated with cardio-toxic effect, is secreted via the activated monocytes and macrophages in response to diverse infections. It stimulates the release of acute phase proteins in the liver driving lymphocyte and endothelial activation [31]; however, Dalbeni et al. found non-significant differences in mean values of both HS-TnT and NT-proBNP as cardiac biomarkers between pretreatment and post-treatment [17]. The difference in the results of cardiac biomarkers and those we obtained may be related to the biomarker used as well as they did not calculate the delta BNP for correlating it with baseline levels or degree of liver disease

Conclusion

Our findings propose on the one side the necessity of cardiac monitoring during chronic HCV infection and, on the other, the valuable impacts of HCV eradication on HCV-associated cardiac morbidities. In spite of our

finding of a non-significant change of plasma BNP levels in post eradication of HCV compared to its baseline values, we noticed that plasma BNP values were considerably decreased post-treatment in patients presented with higher baseline BNP values and more advanced liver disease (higher FIB4, APRI, and the presence of liver cirrhosis). Given the burden of chronic hepatitis C virus infection both nationally and internationally, there is an imperative requirement to assess the worth of cardiac biomarkers that may potentially help define cardiovascular benefits of HCV eradication among HCV-infected patients more precisely and by long-term follow-up.

We acknowledge that the results were analyzed with a relatively small cohort; therefore, to implement a practical policy in real-life settings, studies with larger cohorts are a must with long-term follow-up.

Abbreviations

BNP: B-type natriuretic peptide; HCV: Hepatitis C virus; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus; HCC: Hepatocellular carcinoma; SVR: Sustained virological response; CAD: Coronary artery disease; CHF: Congestive heart failure; INR: International normalized ratio; ALT: Alanine transaminase; AST: Aspartate transaminase; APRI: Aspartate aminotransferase-to-platelet ratio index; EOT: End of treatment; ELISA: Enzyme-linked immunosorbent assay

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Authors' contributions

All authors contributed in the conception and designing of the work. NE and AN were the major contributors in writing and revision of the manuscript. AA contributed in the interpretation of the laboratory data including BNP. AN, AS, NE, and MA contributed in the collection of clinical data about HCV patients. NE corrected and edited the manuscript. The authors have read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study was carried out after approval from the National Liver Institute Ethical Committee, Menoufia University, Egypt, with ethics committee reference number NLI IRB 00003413. For all participants, an explanation about the study was provided together with informed written consent was obtained from each one before enlisted in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Hepatology, Gastroenterology Department, National Liver Institute, Menoufia University, Menoufia, Egypt. [2]Tropical Medicine Department, Faculty of Medicine- Menoufia University, Menoufia, Egypt. [3]Medical Biochemistry and Molecular Biology Department, Faculty of Medicine-Menoufia University, Menoufia, Egypt. [4]Faculty of Pharmacy, MSA University, 6th of October City, Egypt.

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