Elbrolosy et al. Egyptian Liver Journal (2021) 11:19
https://doi.org/10.1186/s43066-021-00092-w

Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE Open Access

Hepatitis C core antigen: a simple predictive marker for treatment response to the new direct-acting antiviral drugs in chronic HCV Egyptian patients

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Abstract

Background: Successful eradication of hepatitis C virus (HCV) has great impact on the prognosis of HCV-related complications and the associated mortality. The development of the new direct-acting antiviral drugs (DAAs) has revolutionized the treatment of HCV infection. HCV core antigen (HCVcAg) is a recently developed marker that displayed a good correlation with HCV RNA assays. Our main objectives were to correlate between serum levels of HCVcAg and HCV RNA loads in chronic HCV patients as well as to explore the potential value of HCVcAg assay in predicting treatment response to the new DAAs. The study enrolled a total of 280 chronic HCV-infected patients scheduled to start the new regimen for treatment of chronic HCV by all-oral, interferon-free DAAs. According to the viral load, the studied individuals were arranged into three groups corresponding to mild, moderate, and sever viremia. Serum level of HCVcAg was determined by ELISA technique and HCV RNA viral loads were quantified using the real-time PCR system. The assays were performed three times for all participants: prior to initiation of treatment, at the end of treatment (week 12), and 3 months post-treatment cessation (week 24).

Results: A statistically significant difference between HCV RNA and HCVcAg baseline levels among different viremia groups was detected ($P < 0.001$). There was a significant positive correlation between HCV RNA and HCVcAg baseline values among all the studied cases ($P < 0.05$) with a correlation coefficient of 0.752, 0.976, and 1.00 respectively for mild, moderate, and severe viremia groups. 92.9% (260/280) of the studied patients achieved sustained virologic response, 3.6% (10/280) were non-responders, and 3.6% (10/280) had recurrent viremia/relapse as regards RT-PCR results.

Conclusion: HCVcAg is a promising alternative to HCV RNA assay. The ELISAs for HCVcAg proved excellent correlations with HCV RNA levels. Moreover, HCVcAg can be introduced as a simple and highly specific tool for monitoring the new DAA regimens particularly in low-resource settings.

Keywords: HCV core antigen, HCV RNA assay, New direct-acting antiviral drugs

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Background

The prevalence of HCV infection varies significantly all over the world. Treatment and monitoring of HCV infection are of great concern, especially in developing countries [1]. The highest prevalence of HCV in the world occurs in Egypt with estimates higher than 10% among the general population. There are approximately 3.7 million persons in Egypt that have chronic HCV infection in 2015 [2].

In clinical practice, serological detection of anti-HCV antibodies is usually used for diagnosis of HCV infection. However, most assays are not able to distinguish patients with an ongoing active infection from those who have spontaneously cleared the virus [3]. Sometimes, there is a long seronegative interval throughout the course of HCV infection during which anti-HCV antibodies are undetectable. Immunosuppression may result in an insufficient antibody response as well. Therefore, anti-HCV assays still need additional confirmation [4].

Nucleic acid-based techniques for HCV RNA are currently used to confirm the diagnosis of HCV infection and to monitor the antiviral therapy because of their high specificity and sensitivity. However, the complexity and cost of such molecular diagnostics can constrain their use in low-resourced settings [5]. Likewise, cheaper and simple diagnostic tools and follow-up algorithms are in urgent need to enhance the global efforts for HCV eradication by the year 2030 particularly in low- and middle-income countries [6].

The HCV core antigen (HCVcAg) is a 21-kDa structural phosphoprotein of the HCV capsid and comprising the first 191 amino acids of the viral polyprotein. Hepatitis C virus core antigen is highly conserved across HCV genotypes. It exists in both complete virions and RNA-free core protein structures [5]. During viral assembly, HCVcAg is released into the plasma/serum and can be detected earlier than antibodies during the course of HCV infection. Recently, less-expensive and time-consuming immunoassay techniques for detecting HCVcAg have become available [7].

Viral kinetics of HCV no longer predict treatment duration or outcome; consequently, there is no longer value for repeated measurement of HCV RNA load. There is however great evidence that the amount of HCVcAg in the blood correlates well with the HCV RNA level. Thus, HCVcAg can identify patients with active HCV infection and is a surrogate marker for viral replication. Furthermore, HCVcAg assay may be superior to the current two-step diagnostic approach in terms of time and cost-saving benefits. The novel approach has also established its clinical utility in the screening of active HCV infections for anti-HCV antibody-positive individuals [8].

During the last decade, great interest has been focused on the development of direct-acting antiviral drugs (DAAs). These agents have the ability to block essential enzymes regulating HCV replication. Several new oral, interferon-free antiviral drugs were approved, representing an additional bonus of extension into pan-genotypic activity [9].

The proximate target of anti-HCV therapy is to achieve sustained virologic response (SVR)/virologic cure meaning that HCV RNA is undetectable for at least 12 weeks after cessation of therapy. In the year 2011, the FDA accepted SVR-12 as endpoint for future trials because HCV relapse usually occurs within the first 12 weeks after the end of treatment [10].

In the era of DAAs, many studies reported that HCVcAg could be employed as a simple marker to establish active infection, to initiate the requirement for treatment and then to evaluate viremia after completion of DAAs therapy as well [11]. The main objectives were to verify the utility HCVcAg assay in predicting treatment response to the new oral, interferon-free DAA regimen by comparing it with the established methods for quantification of HCV RNA.

Methods

This prospective study was carried out at the Department of Medical Microbiology and Immunology, in collaboration with Tropical Medicine Department, Faculty of Medicine, Menoufia University, and Department of Hepatology and Gastroenterology, National Liver Institute, Menoufia University, during the period from December 2018 to April 2020. The study involved 280 patients (100 females and 180 males). All patients were over 18 years of age, had compensated liver disease, and were diagnosed to have chronic HCV infection by enzyme-linked immunosorbent serum anti-HCV assay and confirmed by real-time PCR. All the recruited cases were scheduled to receive the new DAAs therapy for treatment of HCV infection as recommended by the Egyptian National Committee for Control of Viral Hepatitis (NCCVH).

The included patients were prescribed sofosbuvir (SOF)/daclatasvir (DCV) (easy to treat) or SOF/DCV/ribavirin (RVN) (difficult to treat) according to the NCCV H as follows:

- *Easy to treat group*: Comprises treatment-naïve patients, total bilirubin < 1.2 mg/dl, serum albumin > 3.5 g/dl, INR < 1.2, and platelet count > 150,000/mm^3
- *Difficult to treat group*: Comprises IFN-experienced patients, total bilirubin ≥ 1.2 mg/dl, serum albumin (2.8–3.5 g/dl), INR (1.2–1.7), and platelet count of 50,000–150,000/mm^3

Table 1 Baseline routine and specific laboratory investigations of the studied groups

Lab investigations	Total cases (No. = 280)			Test of significance	*P* value
	Group I (No. = 140)	Group II (No. = 80)	Group III (No. = 60)		
	Mean ± SD	Mean ± SD	Mean ± SD		
ALT (IU/ml)	58.6 ± 7.8	75.0 ± 20.6	122.0 ± 66.4	**Kruskal-Wallis test** = 17.6	< 0.001**
AST(IU/ml)	44.1 ± 13.3	65.0 ± 23.3	114.2 ± 67.6	**Kruskal-Wallis test** = 17.14	< 0.001**
ALP (IU/ml)	29.8 ± 14.8	75.1 ± 24.4	134.8 ± 68.8	**Kruskal-Wallis test** = 21.24	< 0.001**
GGT (IU/ml)	12.7 ± 7.5	30.1 ± 10.8	63.3 ± 12.1	**Kruskal-Wallis test** = 20.14	< 0.001**
Total bilirubin (mg/dl)	1.1 ± 0.27	1.2 ± 0.84	1.8 ± 1.2	**Kruskal-Wallis test** = 0.73	0.69
Albumin (g/dl)	3.8 ± 0.54	3.7 ± 0.39	3.4 ± 0.37	**ANOVA test** = 0.85	0.44
PT (s)	14.5 ± 2.1	14.5 ± 1.6	14.9 ± 2.2	**ANOVA test** = 0.08	0.92
PT concentration (%)	86.3 ± 19.5	86.8 ± 9.5	84.9 ± 13.9	**ANOVA test** = 0.05	0.95
INR	1.2 ± 0.17	1.2 ± 0.15	1.2 ± 0.18	**ANOVA test** = 0.09	0.91
Hb (gm/dl)	13.6 ± 1.7	13.6 ± 1.3	12.8 ± 2.8	**ANOVA test** = 0.41	0.67
PLT ($X10^3$/mm)	186.2 ± 48.3	189.9 ± 57.4	157.0 ± 62.6	**Kruskal-Wallis test** = 1.60	0.45
Glucose (mg/dl)	92.9 ± 30.5	90.1 ± 25.6	98.2 ± 36.9	**Kruskal-Wallis test** = 0.16	0.92
Creatinine(mg/dl)	0.81 ± 0.12	0.81 ± 0.09	0.83 ± 0.13	**ANOVA test** = 0.88	0.92
Urea (mg/dl)	35.0 ± 10.9	44.5 ± 9.1	39.5 ± 11.3	**ANOVA test** = 2.08	0.15

Exclusion criteria were determined as per the Supreme Council and National treatment programme of Hepatitis C updated Treatment Protocol December 2019 [12]. These included Child's C cirrhotic patients, platelet count less than 50,000/mm^3, serum albumin < 2.8 g/dl, total serum bilirubin > 3 mg/dl, INR > 1.7, patients co-infected with HIV, hepatocellular carcinoma (HCC) except 6 months after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI), extra-hepatic malignancy except after 2 years of disease-free interval, pregnancy or inability to use effective contraception, and inadequately controlled diabetes mellitus.

All patients had given informed consent about the study and ethical approval was provided by the Ethics Committee of Menoufia University which came in accordance with the ethical guidelines of the 2013 "Helsinki Declaration".

According to the HCV viral load, the studied patients were arranged into three groups: group I involved 140 patients with mild viremia (< 200,000 IU/ml), group II involved 80 patients with moderate viremia (200,000:2,000,000 IU/ml), and group III involved 60 patients with severe viremia (> 2,000,000 IU/ml) [13].

All patients were subjected to proper history taking and clinical examination. Laboratory investigations regarding complete blood picture, liver profile (including ALT, AST, ALP, GGT, serum albumin, total bilirubin, direct bilirubin, and INR), kidney function tests, and viral hepatitis markers for HbsAg and HCV antibodies were collected from each patient's file.

Blood samples were collected from all participants and then sera were stored at − 20 °C until assayed for quantitative estimation of HCV RNA and HCVcAg levels.

Quantitative estimation of HCV RNA level by real-time reverse transcription-polymerase chain reaction (RT-PCR)

The assay was done 3 times for each patient as follows: PCR-1, prior to initiation of treatment to ensure the diagnosis of HCV infection and to determine the

Table 2 Mean values of baseline levels for both HCV RNA (IU/ml) and HCVcAg (Peiu/ml) assays among the studied groups

Studied groups	Baseline levels					
	HCV RNA serum level (IU/ml) Mean ± SD	Kruskal-Wallis test *P* value	Post hoc test	HCVcAg serum level (Peiu/ml) Mean ± SD	ANOVA test and *P* value	Post hoc test
Group I (*n* = 140)	95648.1 ± 50814.0	Test = 22.76 *P* < 0.001**	P1 < 0.001** P2 = 0.001** P3 = 0.002*	1.4 ± 0.35	Test = 69.69 *P* < 0.001**	P1 = 0.002* P2 < 0.001** P3 < 0.001**
Group II (*n* = 80)	1082313.0 ± 558186.7			2.6 ± 0.68		
Group III (*n* = 60)	4812067.8 ± 1837006.9			5.9 ± 1.5		

*Significant
**Highly significant

baseline viral load; PCR-2, at the end of treatment (week 12) to assess end of treatment response (ETR) [14]; and PCR-3, 3 months post-treatment cessation (week 24) as a follow-up step to assess sustained virologic response (SVR-12) [14].

Procedure

The procedure involved three main steps: HCV RNA extraction, conversion of HCV RNA to complementary DNA (Cdna), and amplification and detection of the amplified products. HCV RNA extraction was performed by using artus® HCV RG RT-PCR kit (Qiagen GmbH, Germany, Cat No. 4518263) according to the manufacturer's instructions. HCV levels were determined using the Rotor-Gene Q MDx (Rotor-Gene Q MDx, Qiagen, Germany) Light Cycler Real-Time PCR System using Rotor-Gene-3000 software version 6.0.23. An internal quality control serum was included during RT-PCR [15].

HCVcAg assay

HCV core antigen serum levels were measured by enzyme-linked immunosorbant assay according to the manufacturer's instructions (Sinogeneclon Co., Ltd, China). The concentration of HCVcAg in the samples was then determined by comparing the optical density (O.D.) of the samples to the standard curve. The assay was done at the same intervals of the PCR assay.

Statistical analysis

Statistical analysis was done using SPSS version 20. Continuous/numerical data were presented as mean ± standard deviation (SD) and were compared by Kruskal-Wallis test and ANOVA test. Categorical variables were shown as numbers (percentages) and were compared by Chi-square (χ^2) test. Linear regression analysis was applied to evaluate the association between HCVcAg and HCV RNA levels. The diagnostic performance of HCVcAg and HCV RNA in the prediction of SVR-12 was expressed as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic (AUROC) curve. Statistical significance was set at P value < 0.05.

Results

Baseline routine and specific laboratory investigations of the studied groups are shown in Table 1. A highly significant statistical difference was recorded regarding serum ALT, AST, ALP, and GGT levels among the three studied viremia groups (P < 0.001). Other parameters revealed no significant difference (P > 0.05).

Baseline levels of both HCV RNA and HCVcAg assays were represented in Table 2 and Figs. 1 and 2. The recorded data denoted a statistically significant difference between the mean values of both HCV RNA and HCVcAg baseline levels among different viremia groups (P < 0.001). The level of HCVcAg was significantly higher in moderate viremia if compared with mild viremia (P < 0.002) and it was significantly higher in severe viremia if compared with moderate viremia (P < 0.001).

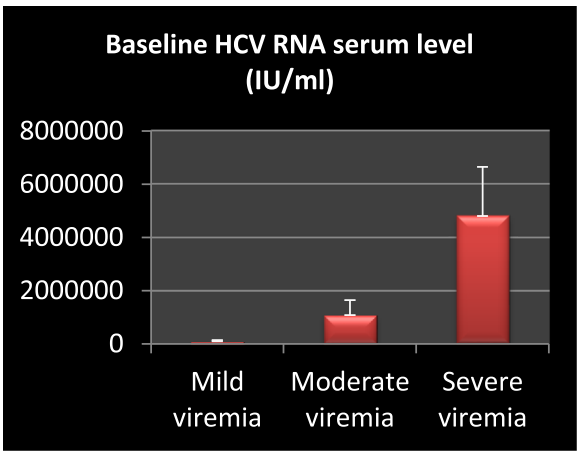

Fig. 1 Baseline HCV RNA levels (IU/mL)

Importantly, a significant positive correlation was detected between HCV RNA and HCVcAg baseline values among all the studied cases (P < 0.05) with a correlation coefficient of 0.752, 0.976, and 1.00 respectively for mild, moderate, and severe viremia groups as shown in Table 3. The correlations of HCV RNA loads (IU/ml) with HCVcAg levels (Peiu/ml) including linear regression lines were illustrated in Fig. 3a–c.

For differentiation between mild and moderate viremia, HCVcAg proved sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 87.5%, 85.7%, 77.8%, 92.3%, and 86.4% respectively when using a cutoff value

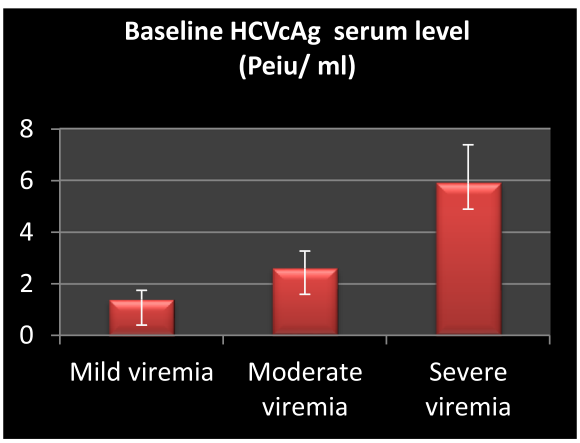

Fig. 2 Baseline HCVcAg levels (Peiu/mL)

Table 3 Correlation between baseline levels of HCVcAg (Peiu/ml) and HCV RNA (IU/ml) assays among the studied groups

Baseline HCV RNA (IU/ml)	Baseline HCVcAg (Peiu/ml)	
	r	*P* value
Group I: mild viremia group (No. = 140)	0.752	0.002*
Group II: moderate viremia group (No. = 80)	0.976	< 0.001**
Group III: severe viremia group (No. = 60)	1.00	< 0.001**

of 1.765 Peiu/ml. However, HCVcAg cutoff point of 3.42 Peiu/ml exhibited sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 100%, 87.5%, 85.7%, 100%, and 92.9% respectively for differentiation between moderate and severe viremia (Table 4).

Regarding treatment response to the newly prescribed regimen of DAAs, 92.9% (260/280) of the studied cases achieved sustained virologic response (SVR-12), 3.6% (10/280) were non-responders with persistent viremia throughout the course of the study, and 3.6% (10/280) had recurrent viremia/relapse after treatment cessations as proved by RT-PCR results (Table 5).

Among patients who achieved SVR (260/280), HCVcAg was 100% (260/260) undetectable at both the 12th and 24th weeks. For the patients who proved non-response to anti-HCV treatment, HCVcAg was

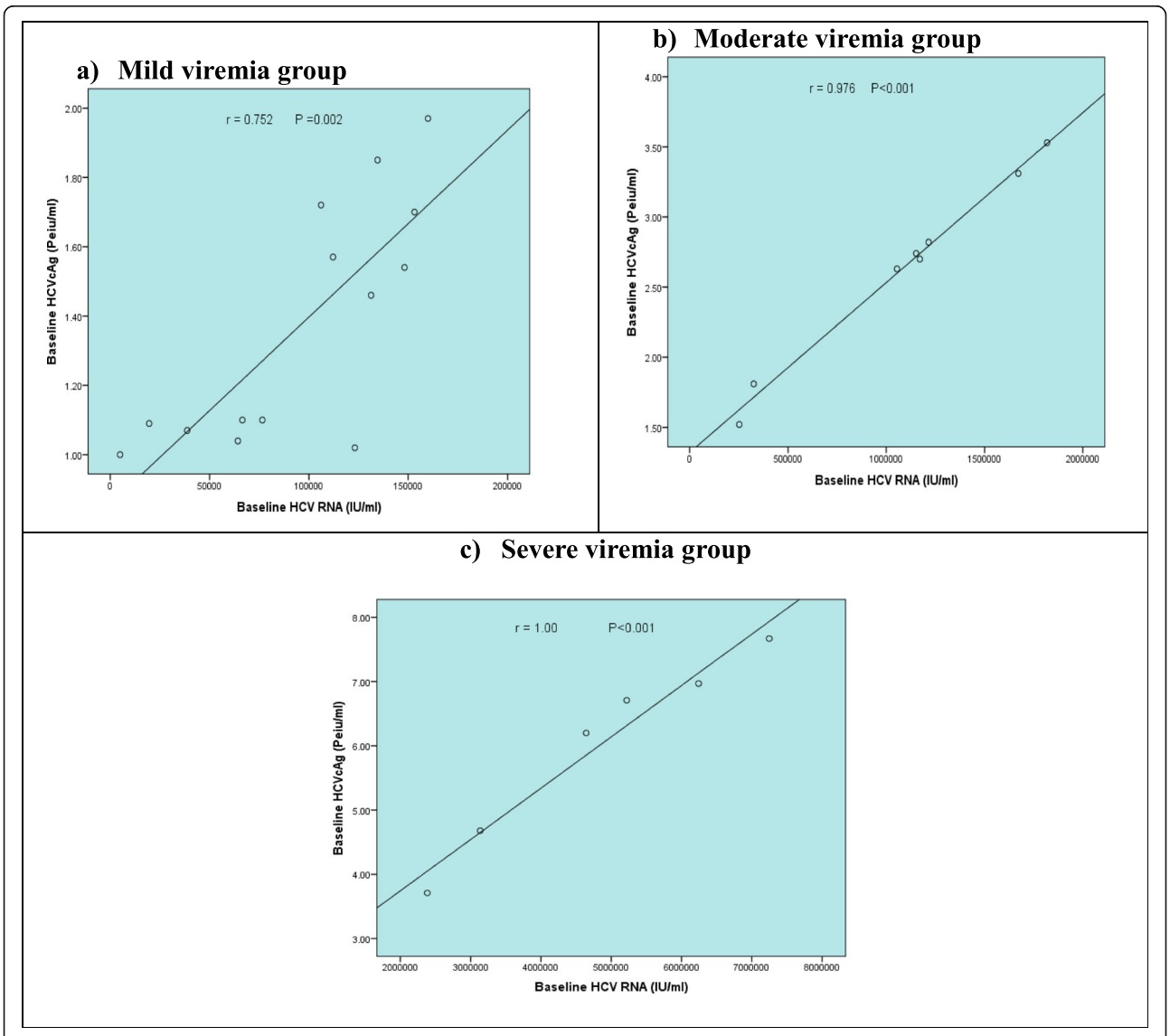

Fig. 3 a–c Correlation between baseline levels of HCVcAg (Peiu/ml) and HCV RNA (IU/ml) assays among the studied groups

Table 4 HCVcAg cutoff for differentiation between mild and moderate viremia

	AUC	Cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
HCVcAg (Peiu/ml)	0.929	1.765	87.5%	85.7%	77.8%	92.3%	86.4%
HCVcAg cutoff for differentiation between moderate and severe viremia							
HCVcAg (Peiu/ml)	1.00	3.42	100%	87.5%	85.7%	100%	92.9%

continuously detectable at both the 12th and 24th weeks. However, for patients who developed recurrent viremia/relapse, HCVcAg was undetectable at the 12th week and again became detectable at the 24th week post-treatment initiation (Table 6).

The degree of agreement between HCV RNA and HCVcAg results at the 12th and 24th weeks was 100% (Table 7). For evaluation of HCVcAg assay performance in prediction of treatment response at the 12th and 24th weeks, HCVcAg proved sensitivity, specificity, PPV, NPV, and accuracy of 100% (Table 8).

Discussion

HCV infection is a serious public health issue. Early detection and treatment are imperative to prevent its transmission. Limitations of anti-HCV and HCV RNA detection have restricted their applications in clinical practice [16].

HCVcAg has been proposed as an indirect marker of viral replication [16]. Recently, many assays have been developed for both qualitative and quantitative HCVcAg estimation, such as enzyme immunoassays (EIAs) or chemiluminescent immunoassays with an excellent correlation between HCVcAg concentrations and HCV RNA levels. These quantitative HCVcAg assays became promising alternatives to HCV nucleic acid-based techniques [17, 18].

In the current study, 280 patients with chronic HCV infection have been enrolled and arranged into mild, moderate, and severe viremia groups according to their HCV viral load. All studied individuals were prescribed the new regimen of anti-HCV treatment which included the new oral, interferon-free DAAs. The main targets were to correlate between baseline levels of both HCVcAg and HCV viremic load and to assess the utility of HCVcAg testing in the era of DAAs.

The recorded data denoted a highly significant statistical difference between the baseline values of both HCV RNA and HCVcAg among different viremia groups ($P < 0.001$). Furthermore, a significant positive correlation was detected between HCV RNA and HCVcAg baseline levels for all the studied cases ($P < 0.05$) (correlation coefficient; $r = 0.752$ for mild viremia, $r = 0.976$ for moderate viremia, and $r = 1.00$ for severe viremia). These finding agreed with previous reports by Soliman et al., Park et al., and Kim et al. [15, 19, 20] who confirmed excellent correlation to HCV RNA levels and that the kinetics of HCVcAg and viremia were almost similar. Thong et al. also postulated that in the overall cohort, HCVcAg levels significantly correlated with the corresponding HCV RNA levels ($r = 0.889$, $P < 0.001$). The authors recommended HCVcAg testing to be used as an alternative to HCV RNA assays in resource-limited settings [21].

Other previous studies involving other HCV genotypes demonstrated that detection of HCVcAg in serum or plasma is useful as an indirect marker of HCV replication due to the excellent correlation between HCVcAg and HCV RNA concentrations. In addition, HCVcAg assays, which are easier to perform than reverse transcription-PCR, also save time and are less expensive. HCVcAg is used currently to monitor patients undergoing antiviral therapy and to determine the clinical efficacy of such treatment [22–24].

Being closely related to HCV RNA as proved in current results, the present study involved analytical data that may support the use of HCVcAg as a prognostic marker for disease activity among HCV-infected patients and consequently to be implemented in clinical practice for the follow-up of treatment response. At a cutoff point of 1.765 Peiu/ml, HCVcAg was able to differentiate between mild and moderate viremia with sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 87.5%, 85.7%, 77.8%, 92.3%, and 86.4%, respectively. However, HCVcAg cutoff point of 3.42 Peiu/ml exhibited sensitivity, specificity, PPV, NPV, and diagnostic accuracy of

Table 5 Treatment outcomes among the studied groups according to RT-PCR results

Treatment outcomes	Total cases (No. = 280)						Total (n = 280)		χ^2 test and P value
	Group I (n = 140),		Group II (n = 80)		Group III (n = 60),				
	No.	%	No.	%	No.	%	No.	%	
Responder/SVR (No. = 260)	130	92.9	70	87.5	60	100	260	92.9	Test = 3.56 P = 0.47
Non-responder (No. = 10)	10	7.1	0	0.0	0	0.0	10	3.6	
Relapse (No. = 10)	0	0.0	10	12.5	0	0.0	10	3.6	

Table 6 HCVcAg at baseline, the 12th week, and the 24th week regarding treatment response

Response of cases (No. = 280)	HCVcAg (Peiu/ml)				
	Baseline	At the 12th week		At the 24th week	
		Detectable	Undetectable	Detectable	Undetectable
Responder/SVR (No. = 260)	2.7 ± 2.1	0 0.0%	260 100%	0 0.0%	260 100%
Non-responder (No. = 10)	1.7	10 100%	0 0.0%	10 100%	0 0.0%
Relapse (No. = 10)	3.5	0 0.0%	10 100%	10 100%	0 0.0%

100%, 87.5%, 85.7%, 100%, and 92.9% respectively for differentiation between moderate and sever viremia. In another study by Sayed et al., the Roc curve showed that the best cutoff point between mild viremia patients and moderate viremia was found > 2.3 with a sensitivity of 81.25%, specificity of 100.0%, PPV of 100.0%, and NPV of 88.9%. While Roc curve for HCVcAg between moderate and severe viremia showed that the best cutoff point was > 4.2 with sensitivity of 87.5%, specificity of 93.75%, PPV of 87.5%, and NPV of 93.7% [25].

The introduction of DAAs therapies has revolutionized the treatment response of HCV. In this context, we explored the relevance of HCVcAg testing to evaluate the potential role in monitoring virologic response to the new regimen of protease inhibitor-based therapy. In the current work, 92.9% (260/280) of the studied cases achieved sustained virologic response, 3.6% (10/280) were non-responders with persistent viremia throughout the course of the study, and 3.6% (10/280) had recurrent viremia/relapse after completing treatment as proved by RT-PCR results. These results were almost comparable to the rates reported by Nouh et al. (95.8% of patients achieved SVR-12 and 4.2% were non-responders) [26]. Rockstroh et al. also postulated that advances in the treatment of HCV infection with DAAs have demonstrated over 90% cure rates, as defined by the SVR-12. With these therapies, high SVR rates can be obtained regardless of viral genotype, degree of liver fibrosis, or previous treatment history in the majority of patient groups [27].

Regarding relapse, in this study 3.6% of the enrolled patients had a relapse/recurrent viremia as proved by RT-PCR results after 3 months from completing treatment with the DAA combination therapy. Other studies conducted by Wang et al. and Rutter et al. revealed that about 13% of cases had relapse 3 months after completing treatment regimen with DAAs. They suggested that relapsed cases are probably attributed to emergence of treatment resistance-associated variants with reduced replication fitness compared with the wild type virus. If these resistance-associated variants cannot be eliminated by the required combination regimen, strains with reduced replication fitness may persist in low concentration and may account for late relapses [16, 28].

Interestingly, HCVcAg was able to detect 100% (260/260) of patients who achieved SVR-12, 100% (10/10) of those who were non-responders, and 100% (10/10) of patients who developed recurrent viremia/relapse during

Table 7 Degree of agreement between HCV RNA and HCVcAg results at the 12th and 24th week among the studied groups

HCV RNA at the 12th week					Total
			Positive	Negative	
HCVcAg at the 12th week	Positive	No.	10	0	10
		% (within HCV RNA at the 12th week)	100.0	.0	3.6
	Negative	No.	0	270	270
		% (within HCV RNA 12th week)	.0	100.0	96.4
Total		No.	10	270	280
		% (within HCV RNA 12th week)	100.0	100.0	100.0
HCV RNA at the 24th week					Total
			Positive	Negative	
HCVcAg at the 24th week	Positive	No.	20	0	20
		% (within HCV RNA at the 24th week)	100.0	.0	7.1
	Negative	No.	0	260	260
		% (within HCV RNA at the 24th week)	.0	100.0	92.9
Total		No.	20	260	280
		% (within HCV RNA at the 24th week)	100.0	100.0	100.0

Table 8 Evaluation of HCVcAg assay performance in prediction of treatment response at the 12th and 24th week among the studied groups

	Sensitivity	Specificity	PPV	NPV	Accuracy
HCVcAg at the 12th week (Peiu/ml)	100%	100%	100%	100%	100%
HCVcAg at the 24th week (Peiu/ml)	100%	100%	100%	100%	100%

post-treatment follow-up (sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 100% in relation to PCR results). In the same field, Pischke et al. studied a group of patients who had received DAAs and concluded that early response to treatment could be assessed by the less-expensive HCVcAg assay with equal reliability as PCR testing; therefore, both assays allowed prediction of SVR-12 with the same accuracy [29]. Aghemo et al. also reported that concordance between the two tests in identifying patients who achieved SVR-12 was almost perfect where HCVcAg identified 97% of these patients [30]. In their study about the clinical utility of HCVcAg assay in the monitoring of DAAs for chronic hepatitis C, Lin et al. declared that the HCVcAg assay identified 99% of patients with SVR-12 and that both undetectability of serum HCVcAg and HCV RNA had a high positive predictive value at week 2 (98% vs. 100%) and at week 4 (97% vs. 99%) in predicting SVR-12 [8].

Regarding sensitivity and specificity of HCVcAg for assessment of post-treatment viremia, many studies were nearly parallel to our result; Arboledas et al. [31] reported that the sensitivity of HCVcAg test was 86.5% and Daniel et al. [32] showed 85.3% sensitivity. Meanwhile, Ergunay et al. [33] revealed 75.8% sensitivity. A group of studies recorded sensitivity of more than 90%, ranging from 93.26 to 96.3% as documented by Kotb et al. and Demircili et al. [34, 35]. Miedouge et al. reported that HCVcAg sensitivity was 100% [36].

In their studies, Kesli et al. and Demircili et al. [4, 35] showed results which were almost comparable to current results as regards specificity (100%). Ergunay et al. [33] revealed 95.1% specificity, while Miedouge et al. and Medici et al. respectively found 99.2% and 97.9% specificity for HCVcAg quantitative assays versus nucleic acid-based test [36, 37].

In the year 2018, the European Association for the Study of the Liver recommended that HCVcAg in serum or plasma is a marker of HCV replication that can be used instead of HCV RNA to diagnose acute or chronic HCV infection when HCV RNA assays are not available and/or not affordable. HCVcAg is an easy test with comparable sensitivity (> 90%) and satisfactory correlation with the HCV RNA. Quantification of HCVcAg is to be suggested as an attractive alternative to these expensive and demanding measurements [14].

Conclusions

HCVcAg displayed excellent sensitivity and specificity for detection of pre-treatment and post-treatment viremia in chronic HCV patients. HCVcAg successfully identified patients who achieved SVR from those with failed response and/or relapse after receiving the newly prescribed regimen of DAAs and should be considered for inclusion in routine laboratory testing. The technical feasibility of HCVcAg in diagnosis and treatment monitoring should improve access to care in areas where HCV RNA testing is not or hardly available. HCVcAg proved strong correlation with HCV RNA levels at mild, moderate, and sever viremia. 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.

Abbreviations

HCV: Hepatitis C virus; HCVcAg: Hepatitis C virus core antigen; DAAs: Direct-acting antiviral drugs; SVR: Sustained virologic response; SOF: Sofosbuvir; DCV: Daclatasvir; RVN: Ribavirin

Acknowledgements

Not applicable.

Authors' contributions

AE contributed in the conception and design of the work and was the major contributor in writing, revision, and language polishing of the manuscript. GE contributed in performing the practical section of this work. ME, NE, and MZ contributed in the collection of samples and interpretation of the clinical and laboratory data. EE contributed in the revision of the work and corrected and edited the manuscript. All authors have read and approved the final manuscript.

Funding

Not applicable. The study was fully non-funded from any organization.

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

Approval was obtained from the Ethics Committee of Faculty of Medicine, Menoufia University (No. 2311/14-8-2018). Informed written consent was obtained from each participant before enrollment in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 3 September 2020 Accepted: 10 March 2021
Published online: 18 March 2021

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