ORIGINAL ARTICLE

AG-2021-183
doi.org/10.1590/S0004-2803.202202000-33

Assessing predictors of directly acting antivirals' failure as a further step towards more efficient HCV elimination programs: IL28B (IFNL4) gene polymorphism has no role while higher estimated creatinine clearance is a forgotten factor

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Received: 22 September 2021
Accepted: 17 January 2022

ABSTRACT – Background – Sustained virologic response (SVR) rates after directly acting antivirals (DAAs) for hepatitis C virus (HCV) exceed 95%. This encouraged policymakers to put plans to achieve HCV elimination by 2030. The remaining percentage of non-SVR12 can affect HCV eradication strategies in the real-world especially the compliance of large numbers of treated persons to follow up for assessment of virologic response cannot be guaranteed. **Objective –** We aimed to assess predictors of failure to achieve SVR after receiving sofosbuvir plus NS5A inhibitor as an important step towards achieving better HCV eradication strategies. **Methods –** During the period from 1st November 2018 to 1st November 2019, 1581 treatment-naive patients received sofosbuvir plus daclatasvir ± ribavirin at our unit and 10 patients were referred to us with HCV relapse after the same regimens. A total of 163 out of the 1581 patients were lost for follow-up before assessment of virologic response and excluded from the analysis. 20 out of the remaining patients failed to achieve SVR12. Data from the 30 patients with non-SVR12 were included in the case-control analysis. **Results –** Every unit increase in estimated creatinine clearance using modification of diet in renal disease study (MDRD) score, total bilirubin, and INR was associated with 1.03, 13.92, and 80.08 times greater odds of non-SVR12 (P<0.001, P=0.0016, P=0.02) respectively. The presence of liver cirrhosis on ultrasonography increases the odds by 10.03. (P=0.009). **Conclusion –** Higher MDRD score, INR, total bilirubin, and presence of sonographic features of liver cirrhosis are predictors of failure to achieve SVR12 using sofosbuvir plus NS5A inhibitor.

Keywords – Hepatitis C; viral hepatitis; liver; clinical pharmacology; cirrhosis.

INTRODUCTION

Chronic hepatitis C virus (HCV) is one of the principal causes of liver cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality[1]. About 60–80% of HCV-infected patients develop chronic hepatitis and 10–20% of those patients develop cirrhosis within 20–30 years of infection. About 1–5% of patients with liver cirrhosis develop liver cancer and 3–6% progress to liver decompensation. The risk of death after a decompensation episode is between 15–20% within the following year[2,3].

Interferon (IFN) had long been used as an anti-HCV therapy but it had a lot of side effects and low sustained virologic response rates (SVR). New directly acting antivirals (DAAs) for HCV treatment are profoundly successful in providing levels of SVR that exceed 95%. Such regimens are often very secure and convenient, requiring oral drug administration once or twice every day for few weeks[3]. These characteristics encouraged policymakers to put plans to achieve HCV elimination by 2030. Egypt where the highest prevalence of HCV is present is one of few countries in the world which is actively and effectively going to this goal through mass treatment of HCV-infected persons[4].

Although DAAs achieve high SVR, the remaining percentages of non-response and viral relapse can affect HCV eradication strategies in the real-world when these strategies are implemented on large scales[3]. This issue is very important, especially the compliance of large numbers of treated persons to follow up for assessment of virologic response cannot be guaranteed. This issue should be put into consideration in planning for cost-effective HCV eradication strategies.

We aimed to assess predictors of DAAs failure among HCV Egyptian patients who were going to receive sofosbuvir plus NS5A inhibitor as an important step towards achieving better HCV eradication strategies.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
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METHODS

Materials

This prospective study was conducted from 1st November 2018 to 1st November 2019 and then followed by a nested case-control study. A total of 2041 patients with positive HCV antibodies sought HCV antiviral therapy at Alexandria University Viral Hepatitis Treatment Unit. Out of them, 1747 (85.6%) patients had viremia on performing PCR for HCV RNA. 31 (1.8%) patients were treatment-experienced (10 of them after sofosbuvir plus daclatasvir). 107 patients have been excluded from treatment due to the presence of medical contraindications: the presence of unmanageable HCC or other tumors, advanced liver disease (Child-Pugh class C) patients, pregnancy, or lactation. 28 patients with stage four or five chronic kidney disease have received non-sofosbuvir-containing regimens. The remaining 1581 treatment-naive patients received sofosbuvir plus daclatasvir ± ribavirin. A total of 163 (10.3%) patients were excluded from the analysis due to loss for follow-up before assessment of virologic response. Data from the 10 patients with HCV relapse after sofosbuvir plus daclatasvir who were referred to our unit for treatment were included in the case-control analysis. Age and sex matched 120 controls were selected randomly from the respondent population. The flow chart of the study is shown in FIGURE 1.

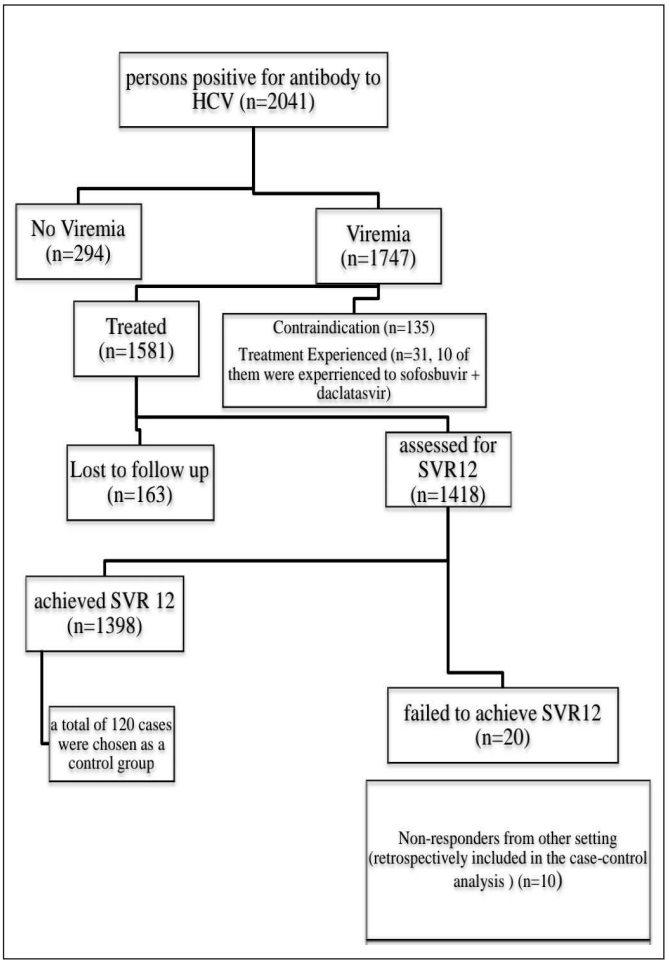

FIGURE 1. Flow chart of the study.

Informed written consent was obtained from each patient. This study had been approved by the Ethics Committee of Alexandria faculty of medicine (IRB no. 00012098) and conforms to the Declaration of Helsinki.

Methods

Patients were followed up prospectively from evaluation to start HCV treatment and till 12 weeks after the end of therapy. Data of the extra 10 patients with relapse were included retrospectively. Before DAAs initiation patients were assessed regarding their history, examination, investigations that included complete blood count (CBC), international normalized ratio (INR), alanine transaminase (ALT), aspartate transaminase (AST), total and direct bilirubin, albumin, urea, creatinine, hepatitis B surface antigen and core antibody (HBsAg, HBcAb), alfa fetoprotein (AFP). FIB-4 index was calculated for each patient[5]. Estimated creatinine clearance (CrCl) using the modification of diet in renal disease (MDRD) scoring system was calculated.

Abdominal ultrasonography was performed to assess the liver condition and to exclude the presence of any focal hepatic lesion while a tri-phasic computed tomography liver scan was performed for focal hepatic lesion characterization if present on ultrasonography and also for those with AFP ≥20 ng/mL. LI-RADS classification was used for focal hepatic lesions characterization[6].

The addition of ribavirin and the duration of sofosbuvir plus daclatasvir regimens were decided according to the guidelines of the Egyptian national program of hepatitis C treatment and to the European association for the study of the liver (EASL) 2015 guidelines[7,8].

HCV RNA levels were reassessed 12 weeks after the end of treatment using the COBAS AmpliPrep/COBAS TaqMan 48 System (limit of detection =15 IU/mL) to determine virological response. IL28B gene polymorphism SNP (rs12979860) detection by allelic discrimination using fluorogenic 5' Nuclease assay was performed for all included patients who didn't achieve sustained virologic response (SVR12) and in a matching group achieved SVR12 (1 case: four control). Genomic DNA was extracted from EDTA whole blood using the column method with the QIAamp Genomic blood DNA purification kit (QIAGEN, Germany). IL28B gene SNP (rs12979860) was detected by SNP genotyping assay (Applied biosystems-Life Technologies, Germany) using Stratagene- gene Q real-time PCR system (MX3000P, Germany)[9].

Statistical analysis of the data[10]

Data were fed to the computer and analyzed using IBM SPSS software package version 25.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of the distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the obtained results was judged at the 5% level. The chi-square test was used for categorical variables to compare between different groups. Student *t*-test was used for normally distributed quantitative variables to compare between two studied groups. Mann-Whitney test was used for non-normally distributed quantitative variables to compare between two studied groups. The odds ratio (OR) was used to calculate the ratio of the odds and 95% confidence interval of an event occurring in one risk group to the odds of it occurring in the non-risk group. Those factors demonstrated significant association in bivariate analysis and any other factors believed to be important were included in a multivariate logistic regression model.

RESULTS

Prospectively studied patients' age ranged between 18 and 84 years and 51.3% were males. The mean levels of ALT, AST, Albumin, and total bilirubin were (57.2±41.1 IU/L), (44.7±25.3 IU/L), (3.8±0.5 g/dL), and (0.55±3.0 mg/dL) respectively. Means of hemoglobin and platelets were 13.6±1.8 g/dL, and 229.6±86.8 /mm^3 respectively. The mean serum creatinine was 0.9±0.2 mg/dL. 16% of included subjects had cirrhosis on ultrasonography (TABLE 1).

TABLE 1. Characteristics of the prospectively involved subjects.

Studied variables	Total (n=1418)	Non-SVR12 (n=20)	SVR12 (n=1398)
	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	49.5±14.0	53.3±13.8	49.5±14.0
Sex (male)	728(51.3)	11 (55.0)	717 (51.3)
AST (IU/L)	44.7±25.3	50.2±29.3	44.6±25.2
Albumin (g/dL)	3.8±0.5	3.7±0.6	3.8±0.5
Total bilirubin (mg/dL)	0.55±3.0	0.7±0.4	0.5±0.3
INR	1.26±0.92	1.84±0.776	1.0±0.0
Creatinine (mg/dL)	0.9±0.2	0.8±0.1	0.9±0.2
Hemoglobin (g/dL)	13.6±1.8	13.2±1.8	13.6±1.8
WBCs (cell/mm^3)	7.3±2.4	6.9±2.1	7.3±2.4
Platelets (cell/mm^3)	229.6±86.8	205.9±110.3	230.0±86.5
Absence of cirrhosis on ultrasonography	1185 (83.6%)	7 (35.0%)	1178 (84.3%)

AST: aspartate transaminase; INR: international normalized ratio; WBCs: white blood cells.

20 patients failed to achieve SVR12 after sofosbuvir plus daclatasvir regimens (1.42%). Another 10 patients who had failed to achieve SVR12 after sofosbuvir plus daclatasvir and were referred to our center to receive another regimen were also included in comparing the treatment failure group and a matched responders group. On comparing the 30 patients who failed to achieve SVR with a control group of 120 subjects achieved SVR, there were no statistically significant differences between both groups regarding age (Z=-0.731, *P*=0.465), sex (X^2=0.007, *P*=0.935), pretreatment AST (Z=-0.451, *P*=0.652), ALT (Z=-0.047, *P*=0.963), total bilirubin (Z=-1.14, *P*=0.252), Albumin (Z=-0.076, *P*=0.940), platelets count (Z=-0.268, *P*=0.268), hemoglobin (Z=-0.353, *P*=0.724), and WBCs (t=0.205, *P*=0.789). Also, there were no significant differences between both groups regarding pretreatment FIB-4 (Z=-0.58, *P*=0.56) and pretreatment PCR HCV RNA levels (Z=-0.682, *P*=0.388). There were no statistically significant difference between both groups regarding ribavirin usage (X^2=0.31, *P*=0.580). Moreover, there was no significant difference in IL28B genotyping between both groups (X^2 =0.177, *P*=0.915).

Pretreatment creatinine was significantly lower among those who failed to achieve SVR. (Z=-3.47, *P*=0.001). Pretreatment estimated creatinine clearance using the MDRD score was significantly higher among those failed to achieve SVR. (Z=-4.05, *P*=0.001). In addition, INR and the presence of liver cirrhosis by ultrasonography were significantly different between responders and non-responders. (Z=-2.246, *P*=0.025), and (X^2=6.42 *P*=0.011) respectively). (TABLE 2)

TABLE 2. Comparison between patients who failed to achieve SVR12 and the control group achieved SVR12.

	Non-SVR12 n=30	SVR-12 (control group) n=120
Age (min–max)	57.0 (21.0–79.0)	55.0 (25.0–73.0)
	Z=-0.731	*P*=0.465
Sex		
Male	14 (46.67)	57 (47.50)
Female	16 (53.33)	63 (52.50)
	X^2=0.007	*P*=0.935
AST (IU/L)	34.50 (19.00–137.00)	39.50 (14.00–169.00)
	Z=-0.451	*P*=0.652
ALT (IU/L)	53.00 (14.00–137.00)	48.00 (61.00–161.00)
	Z=-0.047	*P*=0.963
Total bilirubin (mg/dL)	0.50 (0.3–1.63)	0.50 (0.20–1.20)
	Z=-0.95	*P*=0.34
Albumin (g/dL)	3.6 (2.10–4.60)	3.60 (2.50–4.60)
	Z=-0.076	*P*=0.940
INR	1.03 (0.91–1.50)	1.00 (0.55–1.80)
	Z=-2.246	*P*=0.025
Hemoglobin (g/dL)	13.20 (8.40–16.70)	13.35 (8.80–18.00)
	Z=-0.353	*P*=0.724
WBCs (cell/mm^3)	7.20±2.17	7.12±1.98
	T=0.205	*P*=0.789
Platelet (/mm^3)	199.00 (57.00–402.00)	200.00 (71.00–457.00)
	Z=-0.268	*P*=0.268
AFP (ng/mL)	4.05 (0.30–17.00)	3.40 (0.40–56.00)
	Z=-0.599	*P*=0.549
FIB4 score	1.28 (0.51–8.20)	1.62 (0.06–7.37)
APRI score	0.48 (0.14–2.57)	0.55 (0.13–3.78)
	Z=-0.761	*P*=0.447
IL28B (IFNL4) gene polymorphism		
CC	3 (10.00)	10 (8.33)
CT	23 (76.67)	91 (75.83)
TT	4 (13.33)	19 (15.83)
	X^2=0.177	*P*=0.915
Liver by ultrasonography		
No cirrhosis	18 (60.00)	98 (81.67)
Cirrhotic	12 (40.00)	22 (18.33)
	X^2=6.42	*P*=0.011
Ascites		
Present	1 (3.33)	1 (0.83)
Absent	29 (96.64)	119 (99.17)
	X^2=1.14	*P*=0.286
MDRD score	143.0 (IQR=48.25)	116.5 (IQR=40.0)
	Z=-4.05	*P*<0.001

AST: aspartate transaminase; ALT: alanine transaminase; INR: international normalized ratio; WBCs: white blood cells; AFP: alfa feto-protein; FIB-4: fibrosis-4; APRI: aspartate aminotransferase to platelet ratio index; IL28B: interleukin 28B; IFNL4: interferon lambda 4; MDRD: modification of diet in renal disease.

TABLE 3 shows the binary logistic regression model to predict response to treatment at post-treatment week 12. Every unit increase in MDRD score, total bilirubin, and INR level are associated with 1.03, 13.92, and 80.08 times greater odds of being a non-responder (P<0.001, P=0.0016, P=0.02) respectively. The presence of liver cirrhosis on ultrasonography increases the odds of being non-respondent by 10.03. (P=0.009) The ROC curve of the regression model is shown in FIGURE 2.

TABLE 3. Predictors of Non-SVR12 after sofosbuvir plus daclatasvir treatment.

Predictors	B	*P* value	Odd ratio	95%CI for odds	
				Lower	Upper
Constant	-8.948	0.016	0.00		
FlB4 Score	-623	0.128	.0536	0.240	1.197
Liver (absence of cirrhosis is the reference value)	2.306	0.009	10.030	1.768	56.887
Total bilirubin (mg/dL)	2.633	0.016	13.921	1.622	119.483
Albumin (g/dL)	-232	0.713	0.793	.230	2.733
INR	4.383	0.020	80.078	1.995	3213.453
APRI score	-178	0.828	0.837	.168	4.173
MDRD	.029	<0.001	1.029	1.015	1.043
IL28b (IFNL4) gene polymorphism (CC is the reference)		0.443	1		
CT	-0.994	0.250	0.370	0.068	2.009
TT	-1.263	0.224	0.283	0.037	2.169

FIB-4: fibrosis-4; INR: international normalized ratio; APRI: aspartate aminotransferase to platelet ratio index; MDRD: modification of diet in renal disease; IL28B: interleukin 28B; IFNL4: interferon lambda 4.

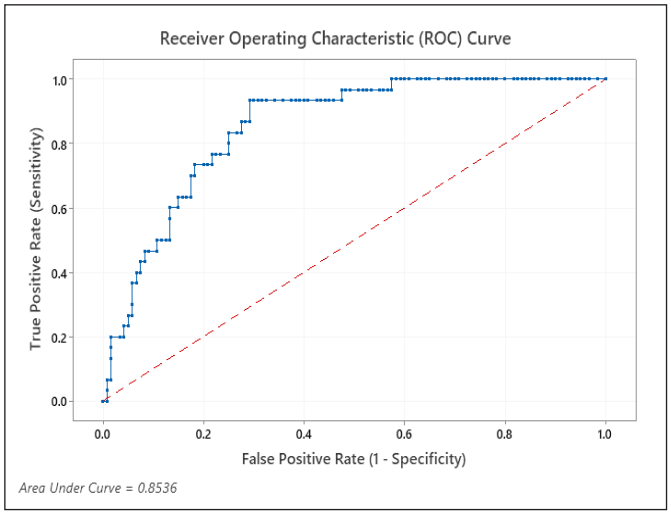

FIGURE 2. The ROC curve of the regression model.

DISCUSSION

HCV is a leading cause of liver cirrhosis and HCC. Egypt has the world's highest HCV prevalence rate[11]. HCV genotype 4 is Egypt's most common genotype accounting for approximately 90% of all patients with HCV[12]. Recently Egypt has implemented a mass screening and treatment program and considered one of few countries in the world that moves efficiently forward to the WHO's goal of HCV elimination by 2030[4].

Many challenges face HCV elimination programs[13]. One of the main challenges that face HCV elimination programs is the non-compliance of patients to assess the virological response or to receive a more potent treatment course after confirming viral non-response or relapse making them a nidus for more HCV spread. This makes it very important to identify predictors of treatment failure to establish strategies that can improve virological response rates.

Our study failed to find any significant difference between SVR12 and non-SVR12 groups regarding age, sex, ALT, AST, albumin levels, platelet counts, and FIB-4 scores. This comes in the same line with Janssen et al.[14] results but different from other studies which reported lower platelet counts and higher FIB-4 scores to be associated with lower SVR rates[15,16]. In our study, reporting of cirrhosis on ultrasonography was significantly associated with a higher risk of non-SVR. Shousha et al. also reported in their retrospective study that cirrhosis was a main predictor of non-response but unlike our results, they also reported that male gender, higher AST, lower albumin levels, low WBCs, and platelets counts were independent factors associated with non-response to DAAs[17].

In our study, creatinine was significantly lower among those who showed treatment failure (P=0.001). As serum creatinine has been universally used to estimate glomerular filtration rate, these patients were found to have high CrCl as calculated by the MDRD scoring system[18]. The median estimated CrCl in the non-SVR12 group was 143.0 (IQR=48.25) which is higher than the normal range and this may indicate glomerular hyperfiltration[19]. This glomerular hyperfiltration may lead to higher clearance of sofosbuvir[20].

A United States retrospective study found that pretreatment CrCl of >80 mL/min using Cockcroft Gault equation was significantly associated with increased rates of SVR12 failure (OR, 3.24; 95%CI, 1.25–8.39; P=0.016) among HCV patients treated with Ledipasvir/sofosbuvir. Creatinine clearance >80 mL/min was the only identified possible predictor of SVR12 failure on bivariate analysis (P=0.026)[14]. In another article, pretreatment CrCl >90 mL/min was associated with a 28% absolute risk increase for SVR12 failure compared to those with lower pretreatment CrCl[20].

In a study investigating sofosbuvir in Korean patients with HCV genotype 2 infections, lower creatinine concentration was a risk factor for failure to achieve rapid virologic response (RVR) but not for SVR[21].

The low serum creatinine has been proposed as a marker of high clearance of sofosbuvir which is chiefly eliminated through the kidneys, unlike ledipasvir and daclatasvir that are primarily biliary eliminated[22]. Thus, patients with high creatinine clearance might be at greater possibility for high rates of DDAs failure due to increased sofosbuvir clearance[20]. The decrease in serum sofosbuvir might result in NS5A monotherapy-like treatment which might increase the risk of emergence of NS5A resistance[14].

Another explanation is that creatinine is a surrogate for muscle mass. Low muscle mass is a common cause for low serum creatinine[23]. Sofosbuvir is a lipophilic prodrug that is converted to its active hydrophilic metabolite during the first-pass metabolism in the liver[24]. This means that a decrease in muscle mass can affect this active metabolite distribution and higher doses may be needed to achieve the required therapeutic concentrations[25]. We recommend further research to explore if this point is applied to sofosbuvir.

IL-28A, IL-28B, and IL-29 showed significant antiviral activity against hepatitis C and hepatitis B viruses[26,27]. IL28B SNPs rs12979860 (now known also as IFNL4) became essentially a prognostic biomarker for the HCV treatment using pegylated IFN-alpha plus ribavirin. The favored CC allele of rs12979860 was correlated with an SVR rate that was two to three times greater than that of the CT or TT alleles[28].

El-Awady et al. concluded that Genotype CC is correlated with viral clearance inside the Egyptian cohort during acute infection. They found a sharp decrease in the CC genotype from healthy to chronic hepatitis C subjects and the complete absence of the CC genotype in patients with end-stage liver disease (ESLD) implying that this genotype plays a vital role in preventing the progression of HCV disease[29]. In a study carried out on Italian patients to assess the effect of immunogenic IL28B polymorphism on the natural outcome of HCV infection, the results indicated that patients with chronic hepatitis C had a lower C allele frequency compared to patients who spontaneously removed HCV[30]. Other studies on African and European HCV-infected patients showed that in patients with the IL-28B CC genotype (rs12979860), the spontaneous clearance of HCV was three times higher than in persons with the CT and TT genotypes[31].

IL28B genotype was considered the strongest baseline predictor of HCV response to treatment with pegylated interferon-α (IFN-α) and ribavirin[32]. With the introduction of the first generation of DAAs, the role of IL28B gene polymorphism was investigated. A Japanese study analyzed patients with HCV genotype 1 who received telaprevir plus pegylated IFN-α and ribavirin. In this study, rs12979860 CC versus CT and TT was associated with a more than a 2-fold greater probability of achieving SVR[33].

As hepatitis C treatment moved towards new directly acting antivirals, the role of IL28B in these regimens was put under investigation. In a randomized 28-day sofosbuvir dose-ranging trial, all patients who failed to achieve rapid virologic response (RVR) and SVR were with non-CC genotype[34].

In our study, there was no difference between IL28B genotyping among those who achieved SVR12 and those who didn't achieve it. CT genotype was the predominant one among our Egyptian HCV-infected subjects. Similar to our results, Ebid et al. found no correlation between IL28B genotypes and sustained virologic response to sofosbuvir plus daclatasvir or ombitasvir/paritaprevir/ritonavir plus ribavirin among Egyptian patients with genotype 4 HCV. Again, in this cohort CT genotype was the predominant one[35]. Moreover, in another study performed on hepatic transplantation hepatitis C Egyptian patients, there was no role for recipient IL28B genotype in the response to DAAs[36].

In the current regression model, the main identified determinants of non-SVR12 after DAAs were high CrCl using the MDRD scoring system, presence of liver cirrhosis on ultrasonography, higher INR, and bilirubin levels. Having liver cirrhosis on ultrasonography increased the odds ratio of non-SVR12 10 times. For each increase in MDRD score by 10 the odds ratio of having HCV viremia at week 12 after the end of treatment increases by 10.03. An increase in the INR by 0.1 increases the odds ratio of non-SVR12 by 8 times. Although bilirubin levels were not significantly different between cases and control group, in the regression model each increase in total bilirubin level by 0.1 mg is associated with increase in the odds ratio of failure to achieve SVR12 by 1.392 times. Finally, Neither FIB4, APRI, serum albumin, nor IL28B was associated with being a non-responder.

The strengths of our study include that all patients were assessed and followed up prospectively starting before DAAs initiation till the virological response assessment date. The only exception was the extra 10 patients with viral relapse who were included retrospectively. The controls represented the same population, from which the cases were drawn, i.e., they were collected from the same treatment setting and so they had the same eligibility criteria. They were age and sex matched and then randomly chosen. The ratio of cases to control was 1:4 to increase the power of the study. Indeed, exceeding this ratio does not add appreciable statistical power[37].

Limitations of this study include the small number of the non-SVR12 group. Although that, we think our regression model will be efficient when applied to mass treatment campaigns. This is important because of possible failure to reach targeted patients again to assess virologic response and to retreat those with viral relapse which may affect the HCV elimination target. Another limitation was the presence of some losses for follow-up before SVR12 assessment, but they were only about 10% and excluded from the case-control analysis. This is accepted in real-life settings. Losses >20% pose serious threats to validity and so the current study's losses have little effect on its internal consistency[38,39].

Further studies are needed to investigate the effectiveness of increasing dose of sofosbuvir in those with high creatinine clearance, usage of a more potent NS5A inhibitor like velpatasvir or offering a more potent drug(s) that include a protease inhibitor in addition to the NS5A inhibitor and sofosbuvir (like sofosbuvir/velpatasvir/voxilaprevir) on SVR12 success rates in a selected group of patients especially those with high estimated creatinine clearance.

Authors' contribution

Mohsin HA, Kamal A and Ghazy RM designed the study with contribution of Matta C, Mohamed NA, Omar HH and Elhadidi AS. Matta C, Mohamed NA, Kamal A and Elhadidi AS gave administrative support. Kamal A, Tahoun M, Elhadidi AS and Mohsin HA collected and assembled data. Ghazy RM and Kamal A analyzed data. All authors interpreted data. Kamal A wrote the article. Other authors shared in the article writing. All authors revised the article critically for intellectual content. All authors approved the final version of the article.

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Kamal A, Matta C, Mohsin HA, Elhadidi AS, Ghazy RM, Omar HH, Tahoun M, Mohamed NA. Avaliação dos preditores da falha dos antivirais de ação direta como mais um passo para programas de eliminação de VHC mais eficiente: o polimorfismo genético IL28B (IFNL4) não tem destaque, enquanto maior liberação estimada do "clearence" de creatinina é um fator esquecido. Arq Gastroenterol. 2022;59(2):177-83.

RESUMO – Contexto – As taxas de resposta virológica sustentada (SVR) após ação direta de antivirais (DAAs) para o vírus da hepatite C (VHC) excedem 95%. Isso encorajou os formuladores de políticas a colocar planos para alcançar a eliminação do VHC até 2030. O percentual remanescente de não-respondedores pode afetar as estratégias de erradicação do VHC no mundo real, especialmente a conformidade de um grande número de pessoas tratadas para acompanhamento para avaliação da resposta virológica não pode ser garantida. **Objetivo –** Nosso objetivo foi avaliar os preditores de não atingir o SVR após receber o inibidor sofosbuvir mais NS5A como um passo importante para alcançar melhores estratégias de erradicação do VHC. **Métodos –** No período de 1º de novembro de 2018 a 1º de novembro de 2019, 1581 pacientes receberam sofosbuvir mais daclatasvir ± ribavirin em nossa unidade e 10 pacientes foram encaminhados por recaída do VHC após os mesmos regimes. Um total de 163 dos 1581 pacientes foram perdidos para o acompanhamento antes da avaliação da resposta virológica e excluídos da análise. 20 dos demais pacientes não conseguiram a resposta virológica sustentada (SVR12). Os dados de 30 pacientes com não SVR12 foram incluídos na análise caso-controle. **Resultados –** Cada unidade aumentada no clearence estimado de creatinina usando o escore do estudo Modificação da Dieta em Doença Renal (MDRD), bilirrubina total e INR foram associadas a 1,03, 13,92 e 80,08 vezes maiores chances de não-SVR12 (P<0,001, P=0,0016, P=0,02) respectivamente. A presença de cirrose hepática na ultrassonografia aumenta as chances em 10,03. (P=0,009). **Conclusão –** Maior escore de MDRD, INR, bilirrubina total e presença de características sonográficas de cirrose hepática são preditores de falha na realização do SVR12 utilizando o inibidor sofosbuvir mais NS5A.

Palavras-chave – Hepatite C; hepatite viral; fígado; farmacologia clínica; cirrose.

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