Original Article

Outcome of Direct-Acting Antiviral Drugs on Treatment of Naïve Cirrhotic and Non-cirrhotic HCV Patients in Assir Region, Saudi Arabia: A Retrospective Cohort Study

Mohammed Attieh Alzahrani, Ibrahim Mohammed Almanjahi[1], Yahia Assiri, Omer Assiri[2], Hassan Organ, Aasem Alshehri[3], Mohammed Abdullah AlFahadi[4], Abdullah Mohammed Alshehri[1], Mushabbab Saeed Hammad[1], Khalid Nebrawi[1], Abdulaziz Saad Alshahrani[5], Abdullah Mohammed Algarni[3], Ibrahim Ali Alghamdi[3], Mohammed Safar Alshahrani[6], Mohammed Elbagir K Ahmed[7]

Department of Medicine, College of Medicine, King Khalid University, Abha, [1]Department of Gastroenterology, Assir Central Hospital, Abha, [2]Department of Medicine, King Khalid University Medical City, Abha, [3]Department of Medicine, Assir Central Hospital, Abha, [4]Department of Medicine, New Najran General Hospital, Najran, [5]Department of Internal Medicine, Najran, University, Najran, [6]Department of Medicine, King Faisal Medical City, Abha, Saudi Arabia, [7]Department of Medicine Faculty of Medicine, University of Khartoum, Sudan

Abstract

Context: Direct-acting antiviral drugs (DAAs) have revolutionized HCV treatment, but their long-term impact on liver disease severity, fibrosis progression, and hepatocellular carcinoma (HCC) incidence among treatment-naïve cirrhotic and non-cirrhotic patients in Saudi Arabia remains underexplored. This study evaluated the sustained virological response (SVR), liver disease severity, fibrosis progression, and HCC incidence among treatment-naïve cirrhotic and non-cirrhotic HCV patients treated with DAAs in Saudi Arabia. **Methods and Materials:** A retrospective cohort study was conducted at Assir Central Hospital, Saudi Arabia, from March 2019 to December 2022. The study enrolled 52 adults (>18 years) comprising both cirrhotic and non-cirrhotic HCV patients who had received DAA treatment at least 6 months (24 weeks) prior. Demographic data, laboratory results, HCV genotype, and viral load were collected. Liver fibrosis was assessed using Fibroscan, while liver disease severity was evaluated using Model for End-stage Liver Disease (MELD) and Child-Pugh scores. HCC screening was performed using alpha-fetoprotein (AFP), ultrasound, and triphasic CT abdomen. **Results:** Findings included no significant changes in laboratory values (INR, bilirubin, albumin, liver enzymes) before and after treatment. However, cirrhosis cases increased post-treatment ($P = 0.033$), while HCC incidence remained stable. The most prevalent HCV genotype was 4 (64%), with Sofosbuvir/Daclatasvir being the most prescribed medication (44%). **Conclusion:** DAA treatment in treatment-naïve cirrhotic and non-cirrhotic HCV patients in Saudi Arabia demonstrated efficacy in achieving SVR and maintaining liver function. However, continued monitoring is crucial post-treatment, particularly for detecting fibrosis progression and cirrhosis development.

Keywords: Cirrhosis, direct-acting antiviral drugs, fibrosis, HCV, hepatocellular carcinoma, Saudi Arabia

Background

Hepatitis C virus (HCV) infection is a significant global health challenge, with an estimated 71 million people living with chronic HCV infection worldwide.[1,2] The prevalence of HCV varies geographically, with certain regions experiencing a higher disease burden, including the Middle East and North Africa (MENA) region, including Saudi Arabia.[2,3] HCV infection is a leading cause of chronic liver disease, cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality, making it a priority area for public health interventions and research efforts.[4,5]

Access this article online

Quick Response Code:

Website: www.njbcs.net

DOI: 10.4103/njbcs.njbcs_93_24

In Saudi Arabia, the prevalence of HCV infection has been a cause for concern, with studies indicating varying prevalence rates across different population groups.[6,7] Studies estimated

Address for correspondence: Dr. Mohammed Attieh Alzahrani, College of Medicine, King Khalid University, Abha, P. O. Box 61421, Saudi Arabia.
E-mail: dr_mohdaz@hotmail.com

Submitted: 30-Aug-2024 **Revised:** 04-Oct-2024
Accepted: 04-Oct-2024 **Published:** 21-Nov-2024

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Alzahrani MA, Almanjahi IM, Assiri Y, Assiri O, Organ H, Alshehri A, *et al.* Outcome of direct-acting antiviral drugs on treatment of naïve cirrhotic and non-cirrhotic HCV patients in Assir Region, Saudi Arabia: A retrospective cohort study. Niger J Basic Clin Sci 2024;21:190-5.

the overall prevalence of HCV antibodies among the general population at 1.65%. However, prevalence rates were higher among specific subpopulations, such as hemodialysis patients, where prevalence rates ranged from 8% to 57.7%.[8,9]

The transmission routes of HCV are diverse and include blood transfusions, healthcare-related exposures, injection drug use, and unsafe injection practices.[6,8] Implementing stringent blood safety measures, including screening of blood donors for HCV antibodies and nucleic acid testing, has significantly reduced the risk of transfusion-related HCV transmission. However, challenges persist in other transmission routes, highlighting the importance of targeted prevention and control strategies.[5,8,9]

Historically, the treatment landscape for HCV relied heavily on interferon-based regimens, which were associated with significant side effects, low efficacy rates, and long treatment durations. The advent of direct-acting antiviral drugs (DAAs) marked a paradigm shift in HCV therapy, offering highly effective, well-tolerated, and shorter-duration treatment options.[10,11]

DAAs target specific viral enzymes and proteins in the HCV replication cycle, disrupting viral replication and leading to sustained virological response (SVR) rates exceeding 95%. The introduction of DAAs has transformed HCV treatment, enabling cure rates previously considered unattainable and reducing the burden of chronic liver disease and its associated complications.[10,12,13]

Several studies have demonstrated the real-world effectiveness of DAAs in achieving SVR and improving clinical outcomes among HCV-infected individuals. Studies assessed the efficacy and safety of DAAs across various patient populations and genotypes, reporting overall SVR rates exceeding 95%. These findings underscore DAA therapy's high cure rates and clinical benefits.[10,14,15]

Furthermore, DAAs have shown efficacy in diverse patient populations, including treatment-naïve and treatment-experienced individuals, as well as those with advanced liver disease, such as cirrhosis and compensated or decompensated liver function. The improved tolerability and shorter treatment durations of DAAs have also contributed to higher treatment adherence and patient satisfaction compared to interferon-based regimens.[16,17]

Despite the remarkable success of DAAs in HCV treatment, challenges remain, particularly in addressing access barriers, optimizing treatment strategies for specific patient populations, and addressing emerging issues such as drug resistance and reinfection.[10-13] Additionally, the long-term impact of DAAs on liver disease progression, fibrosis regression, and HCC incidence requires further investigation through longitudinal studies with extended follow-up periods.[12,13,15]

Study Aim

To evaluate the long-term outcomes of DAAs on treatment-naïve cirrhotic and non-cirrhotic HCV patients in Saudi Arabia, focusing on fibrosis severity, liver disease severity, and the incidence of HCC. The long-term outcomes are (1) the SVR rates at least 24 weeks after DAA treatment, (2) the severity of liver disease post-HCV eradication using Model for End-stage Liver Disease (MELD) and Child-Pugh scores, (3) the degree of liver stiffness measurement post-HCV eradication using Fibroscan, and (4) the incidence of HCC post-HCV eradication.

Table 1: Characters of the included participants and HCV genotype and management (n=52)

Parameter		Frequency (%)
Age, y	24 to 35	15 (28.8%)
	36 to 50	17 (32.7%)
	51 or more	20 (38.5%)
Sex	Male	27 (51.9%)
	Female	25 (48.1%)
Nationality	Saudi	47 (90.4%)
	Non-Saudi	5 (9.6%)
BMI Categories	Underweight	1 (2%)
	Normal	17 (34.7%)
	Overweight	19 (38.8%)
	Obese	12 (24.5%)
Medical history	CKD	6 (46.2%)
	DM	6 (46.2%)
	HTN	5 (38.5%)
Duration	8 weeks	2 (5.7%)
	12 weeks	24 (68.6%)
	24 weeks	9 (25.7%)
HCV genotype	G1	3 (6%)
	G1A	6 (12%)
	G1A, G4	1 (2%)
	G1b	2 (4%)
	G2	3 (6%)
	G3	1 (2%)
	G4	32 (64%)
	G1, G4	1 (2%)
	G3, G4	1 (2%)
HCV medication	Sofosbuvir/Daclatasvir	22 (44%)
	Zepatier	6 (12%)
	Harvoni	13 (26%)
	Viekirax/other	9 (18%)

Methodology

Study design

The aim of this retrospective cohort study was to evaluate the outcomes of DAAs in treatment-naïve cirrhotic and non-cirrhotic HCV patients. The study design facilitated data collection at a single point in time, providing a snapshot of treatment outcomes and associated factors in the study population.

Study setting

The study was conducted at Assir Central Hospital in Saudi Arabia, a tertiary care facility with advanced diagnostic and treatment modalities for liver diseases, including HCV management.

Sampling technique

The study employed a total coverage sampling technique for all eligible patients after carefully screening them through the inclusion and exclusion criteria. More than 500 patients were treated at the hospital, and after applying the selection criteria and obtaining consent to participate in the study, a final sample size of 52 was achieved.

Study population

The study included adult patients (>18 years) with a confirmed diagnosis of HCV who were treatment-naïve and had not undergone liver transplantation prior to DAA therapy. The participants were both cirrhotic and non-cirrhotic individuals who had received DAA treatment at least 6 months (24 weeks) before the study period.

Inclusion criteria

Participants included treatment-naïve chronic HCV patients who had successfully completed DAA treatment at least 6 months (24 weeks) prior to the study, who were willing and able to comply with study procedures, and provided informed consent.

Exclusion criteria

Patients with a history of liver transplantation prior to HCV therapy, co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), non-alcoholic steatohepatitis (NASH) biopsy-proven diagnosis, body mass index (BMI) > 35, active use of hepatotoxic medications, evidence of HCC or any hepatic lesion before HCV treatment, and previous treatment failure with peg-interferon plus ribavirin or first-generation DAAs were excluded from the study.

Data collection tool

Data were collected using a structured data collection form that included demographic information, medical history, laboratory results (complete blood count, coagulation profile, liver function tests, renal function tests, HCV genotype, viral load), imaging results (ultrasound, Fibroscan, triphasic CT abdomen for newly discovered hepatic lesions), and HCV medication details.

Data collection plan

Trained healthcare professionals collected data from participants during clinic visits or hospital admissions. Data collection was conducted systematically to ensure the accuracy and completeness of the information. Liver fibrosis with the Fibroscan measures the stiffness of the liver in a non-invasive way by placing a small probe on the patient's lower chest. This probe emits ultrasound waves that travel through the liver to assess its stiffness. The stiffer the liver, the more severe the fibrosis. MELD score is a scoring system for evaluating the severity of chronic liver disease using a specially calculated formula. The MELD score comprises the patient's serum bilirubin, serum Cr, and international normalization time (INR). The Child-Pugh score is a scoring system that assesses the progression of liver disease, especially liver cirrhosis. The score uses five clinical measures of liver disease (ascites, encephalopathy, serum bilirubin, albumin, prothrombin time, and albumin). Each measure is scored 1–3, with 3 indicating the most severe disorder.

Data management plan

The data was entered into a secure electronic database to which only authorized personnel had access. Participants' data were kept confidential throughout the study, with identifiers removed or anonymized during data analysis. Incomplete data were excluded from the study.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22.0. Descriptive statistics such as frequencies and percentages were used for categorical variables, while means and standard deviations were used for continuous variables. The Chi-square test (χ^2) was employed to assess associations between categorical variables, with P values < 0.05 considered statistically significant.

Ethical considerations

The study protocol was reviewed and approved by the Assir Central Hospital Ethical Committee (ACH IRB No. 20190902). Informed consent was obtained from all participants, ensuring their voluntary participation and understanding of study procedures, potential risks, and benefits. Confidentiality of participants' data was strictly maintained throughout the study period.

Results

The study included a total of 52 participants, with a breakdown of demographic and clinical characteristics as well as details regarding HCV genotype and management. The majority of participants were aged 51 or older (38.5%), followed by those aged 36 to 50 (32.7%), and 24 to 35 years (28.8%). In terms of gender distribution, slightly more than half of the participants were male (51.9%), with females comprising 48.1% of the cohort. Regarding nationality, the vast majority were Saudi nationals (90.4%), while a smaller proportion were non-Saudi (9.6%) [Table 1].

BMI categories among the participants varied, with 2% classified as underweight, 34.7% as normal weight, 38.8% as overweight, and 24.5% as obese (class 1). The medical history of the participants revealed that a notable proportion had comorbidities, with 46.2% having chronic kidney disease (CKD) and diabetes mellitus (DM) each, and 38.5% having hypertension (HTN).

Regarding the duration of HCV treatment, the majority of participants received treatment for 12 weeks (68.6%), followed by 24 weeks (25.7%), and a smaller proportion for 8 weeks (5.7%). The distribution of HCV genotypes among the participants showed that genotype 4 (G4) was the most prevalent (64%), followed by genotypes 1A (12%) and 1B (4%). Other genotypes such as G1, G2, and G3 were less common, each representing 6% or less of the cohort.

The medications used for HCV management varied, with (Sofosbuvir/Daclatasvir) being the most frequently prescribed (44%), followed by Harvoni (Sofosbuvir/Ledipasvir) (26%), Zepatier (Ombitasvir/Paritaprevir/Ritonavir) (12%), and Viekirax (elbasvir and Grazoprevir)/other regimens (18%).

Table 2 presents a pairwise comparison of laboratory values before and after treatment among the study participants. The results show that no statistically significant differences were observed in most parameters before and after treatment. Specifically, the mean INR value increased from 1.22 ± 0.84 before treatment to 5.04 ± 19.49 after treatment, although this change was not statistically significant (t = -1.383, $P = 0.173$). Similarly, there were no significant differences in bilirubin levels, sodium (Na), creatinine (Cr), albumin, hemoglobin (Hb), white blood cell count (WBC), platelet count (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), viral load, and Fibroscan score before and after treatment (all $P > 0.05$). Figure 1 is a visual presentation of the average Fibroscan scores before and after treatment using a boxplot comparing both variables. No significant changes are evident in the Fibroscan score after treatment.

Moving to Table 3, which compares Child-Pugh class and ultrasound (U/S) results before and after treatment, notable changes were observed. Before treatment, all participants were classified as Child-Pugh class A (100%), but after treatment, this proportion decreased slightly to 92%, with 6% classified as class B and 2% as class C. The differences in the Child-Pugh class before and after treatment were not statistically analyzed due to the absence of variability within Child-Pugh class A.

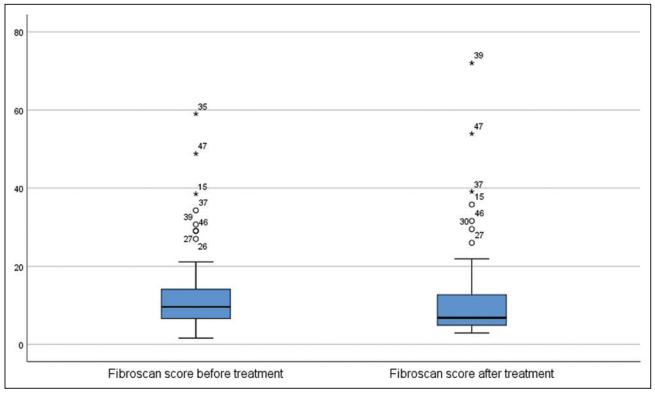

Figure 1: Boxplots of Fibroscan scores before and after treatment

Regarding U/S results, there was a significant difference observed before and after treatment ($\chi^2 = 10.509$, $P = 0.033$). Before treatment, 69.8% of participants had normal U/S results, which decreased to 45.7% after treatment. Conversely, the proportion of participants with cirrhosis on U/S increased from 14% before treatment to 37% after treatment. The percentage of participants with liver lesions remained relatively stable at 16.3% before treatment and 17.4% after treatment.

Discussion

HCV infection is a significant global health concern, particularly in Saudi Arabia, where it poses a substantial burden on healthcare systems due to its association with cirrhosis, HCC, and liver-related mortality.[1,4,5] DAAs have revolutionized the treatment landscape for HCV, offering high cure rates and improved patient outcomes.[9-12] However, the long-term impact of DAAs on liver disease severity, fibrosis progression, and HCC incidence among treatment-naïve cirrhotic and non-cirrhotic patients in Saudi Arabia remains an area of active research and clinical interest.

Our study sought to evaluate the outcomes of DAAs on various parameters among treatment-naïve cirrhotic and non-cirrhotic HCV patients.

One of the key findings of our study was the lack of significant changes in laboratory values such as INR, bilirubin, albumin, and liver enzymes (ALT and AST) before and after DAA treatment. This suggests that DAA therapy effectively maintains liver function and does not exacerbate liver damage, aligning with previous studies demonstrating the safety and efficacy of DAAs in improving liver disease severity.[14,18,19]

However, a notable finding was the increase in cirrhosis cases post-treatment, as evidenced by ultrasound (U/S) findings. While the reasons for this increase warrant further investigation, it may be attributed to the resolution of

Table 2: Pairwise comparison of the laboratory values before and after treatment ($n = 52$)

Parameter	Before	After	*t*	*P*
INR	1.22±0.84	5.04±19.49	-1.383	0.173
Bilirubin F	0.79±0.87	0.97±2.18	-0.97	0.337
Na	135.65±17.67	138.39±3.7	-1.1	0.277
Cr	1.64±2.95	1.51±2.05	0.695	0.49
Albumin	4.68±4.79	3.95±0.56	1.101	0.276
Hb	14.07±2.12	14.14±2.43	-0.031	0.975
WBC	6.63±5.24	6.09±2.4	0.578	0.566
PLT	254.04±95.54	252.43±103.17	0.01	0.992
ALT	43.56±32.94	31.93±54.73	1.492	0.142
AST	42.06±30.41	29.79±56.39	1.403	0.167
Viral load	933182.397±1860270.341	1309680±2268381	1.365	0.305
Fibroscan score [Figure 1]	13.69±11.75	12.72±14.03	0.857	0.396

Table 3: Comparing Child-Pugh class and U/S result before and after treatment ($n=52$)

Parameter		Before treatment	After treatment	χ^2	*P*
Child-Pugh score	Child A	49 (100%)	46 (92%)	NA	NA
	Child B	0 (0%)	3 (6%)		
	Child C	0 (0%)	1 (2%)		
U/S result	Normal	30 (69.8%)	21 (45.7%)	10.509	0.033
	Cirrhosis	6 (14%)	17 (37%)		
	Liver lesion	7 (16.3%)	8 (17.4%)		

inflammation post-DAA therapy, leading to a more accurate assessment of fibrosis and cirrhosis. Although Ultrasound is an operator depend that could explain these changes. This finding underscores the importance of regular monitoring and follow-up for HCV patients' post-treatment to detect any potential disease progression promptly.[20,21]

Another critical aspect explored in our study was the incidence of HCC following DAA treatment. While no significant increase in HCC incidence was observed in our cohort, it is essential to note that the follow-up period in our study was relatively short (24 weeks post-treatment). Long-term studies with extended follow-up periods are necessary to comprehensively assess the risk of HCC development post-DAA therapy, as HCC typically manifests over a more extended period.[15,21]

Comparing our findings with existing literature, our study aligns with previous research demonstrating the efficacy of DAAs in achieving SVR and improving liver function parameters. However, the increase in cirrhosis cases post-treatment warrants further investigation and highlights the dynamic nature of liver disease assessment post-DAA therapy.[15,19,21]

Several studies have reported conflicting findings regarding the impact of DAAs on HCC incidence, with some suggesting a potential risk while others show no significant association. The varying results may be attributed to differences in study populations, follow-up durations, and underlying risk factors for HCC development. Long-term, multicenter studies with larger cohorts are needed to elucidate the true risk of HCC post-DAA therapy comprehensively.[15,18,19,22]

The results of our study have several clinical implications. First, they emphasize the importance of regular monitoring and follow-up for HCV patients post-DAA therapy, particularly in assessing the severity of liver disease and detecting signs of fibrosis progression or the development of cirrhosis. Second, our study emphasizes the need for long-term surveillance to accurately assess the risk of HCC after DAA treatment.[18,22] It is important to point out that this study's limitation is the short follow-up duration as temporal trends require longer follow-up periods to assess the changes in the long term. In addition, the sample size in the study is limited, which may challenge the generalizability of the results without larger populations.

Future research directions should focus on conducting multicenter, prospective studies with extended follow-up periods to assess the long-term impact of DAAs on liver disease progression, fibrosis regression, and HCC incidence among diverse patient populations. Additionally, exploring the role of genetic and environmental factors in HCC development post-DAA therapy may provide valuable insights into personalized management strategies for HCV patients.

Conclusion

In conclusion, our study contributes valuable insights into the outcomes of DAAs on treatment-naïve cirrhotic and non-cirrhotic HCV patients in Saudi Arabia. While DAAs have demonstrated efficacy in achieving SVR and improving liver function, continued vigilance and long-term surveillance are crucial in monitoring liver disease progression and HCC risk post-DAA therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Taherkhani R, Farshadpour F. Global elimination of hepatitis C virus infection: Progresses and the remaining challenges. World J Hepatol 2017;9:1239-52.
2. Thomas DL. Global control of hepatitis C: Where challenge meets opportunity. Nat Med 2013;19:850-8.
3. Lanini S, Easterbrook PJ, Zumla A, Ippolito G. Hepatitis C: Global epidemiology and strategies for control. Clin Microbiol Infect 2016;22:833-8.
4. Axley P, Ahmed Z, Ravi S, Singal AK. Hepatitis C virus and hepatocellular carcinoma: A narrative review. J Clin Transl Hepatol 2018;6:79-84.
5. Goossens N, Hoshida Y. Hepatitis C virus-induced hepatocellular carcinoma. Clin Mol Hepatol 2015;21:105-14.
6. Fallahian F, Najafi A. Epidemiology of hepatitis C in the middle east. Saudi J Kidney Dis Transpl 2011;22:1-9.
7. Mohamoud YA, Riome S, Abu-Raddad LJ. Epidemiology of hepatitis C virus in the Arabian Gulf countries: Systematic review and meta-analysis of prevalence. Int J Infect Dis 2016;46:116-25.
8. Abdo AA, Sanai FM, Al-Faleh FZ. Epidemiology of viral hepatitis in Saudi Arabia: Are we off the hook? Saudi J Gastroenterol 2012;18:349-57.
9. Alsughayyir J, Almalki Y, Alburayk I, Alalshaik M, Aljoni I, Kandel M, *et al*. Prevalence of transfusion-transmitted infections in Saudi Arabia blood donors: A nationwide, cross-sectional study. Saudi Med J 2022;43:1363-72.
10. Florian J, Mishra P, Arya V, Harrington P, Connelly S, Reynolds KS, *et al.* Direct-acting antiviral drugs for the treatment of chronic hepatitis C virus infection: Interferon free is now. Clin Pharmacol Ther 2015;98:394-402.
11. Alexopoulou A, Karayiannis P. Interferon-based combination treatment for chronic hepatitis C in the era of direct acting antivirals. Ann Gastroenterol 2015;28:55-65.
12. Gutierrez JA, Lawitz EJ, Poordad F. Interferon-free, direct-acting antiviral therapy for chronic hepatitis C. J Viral Hepat 2015;22:861-70.
13. Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: The best interferon-free combinations. Liver Int 2014;34:69-78.

14. Krassenburg LA, Maan R, Ramji A, Manns MP, Cornberg M, Wedemeyer H, *et al.* Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity. J Hepatol 2021;74:1053-63.
15. Roche B, Coilly A, Duclos-Vallee JC, Samuel D. The impact of treatment of hepatitis C with DAA s on the occurrence of HCC. Liver Int 2018;38:139-45.
16. Soliman H, Ziada D, Salama M, Hamisa M, Badawi R, Hawash N, *et al.* Predictors for fibrosis regression in chronic HCV patients after the treatment with DAAS: Results of a real-world cohort study. Endocr Metab Immune Disord Drug Targets 2020;20:104-11.
17. Wiktor SZ, Scott JD. What is the impact of treatment for hepatitis C virus infection?. Lancet 2017;390:107-9.
18. Poynard T, Mathurin P, Lai CL, Guyader D, Poupon R, Tainturier MH, *et al.* A comparison of fibrosis progression in chronic liver diseases. J Hepatol 2003;38:257-65.
19. Irvine KM, Wockner LF, Shanker M, Fagan KJ, Horsfall LU, Fletcher LM, *et al.* The Enhanced liver fibrosis score is associated with clinical outcomes and disease progression in patients with chronic liver disease. Liver Int 2016;36:370-7.
20. Verna EC, Morelli G, Terrault NA, Lok AS, Lim JK, Di Bisceglie AM, *et al.* DAA therapy and long-term hepatic function in advanced/decompensated cirrhosis: Real-world experience from HCV-TARGET cohort. J Hepatol 2020;73:540-8.
21. Pascut D, Pratama MY, Tiribelli C. HCC occurrence after DAA treatments: Molecular tools to assess the post-treatment risk and surveillance. Hepat Oncol 2020;7:HEP21.
22. Kondili LA, Gaeta GB, Brunetto MR, Di Leo A, Iannone A, Santantonio TA, *et al.* Incidence of DAA failure and the clinical impact of retreatment in real-life patients treated in the advanced stage of liver disease: Interim evaluations from the PITER network. PLoS One 2017;12:e0185728.