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Outcome of direct-acting antiviral treatment in patients with hepatitis C virus/hepatitis B virus coinfection

El-Araby Mohamed Ibrahim Shalaby[1*], Eman Abdelsameea[2], Mary Naguib[3], Asmaa Gomaa[2] and Imam Waked[2]

Abstract

Background Oral direct-acting antiviral (DAA) regimens for chronic hepatitis C virus (HCV) infection have greatly improved treatment efficacy, with sustained virological response (SVR) rates of > 95% for HCV monoinfected patients. However, hepatitis B virus (HBV)/HCV coinfection is more complex than monoinfection with HBV or HCV alone. We evaluated the SVR rate at 12 weeks post-treatment with DAAs in patients with HCV/HBV and evaluated the rate of HBV reactivation during and 6 months after treatment.

Results Among the included patients, 191 (95.5%) achieved SVR. Older age, low platelet count, high serum creatinine, and higher liver stiffness value measured by fibroscan were predictors of failure to achieve SVR. The 16 patients (8%) with HBV reactivation patients had significantly higher ALT and serum creatinine and a high HCV RNA viral load at baseline compared with that of those without HBV reactivation.

Conclusion Patients who received DAAs to treat HCV/HBV coinfection showed a high SVR. However, it is important to be aware of the potential risk for HBV reactivation during and after treatment with DAAs.

Keywords HCV, Treatment, Direct-acting antivirals (DAAs), HCV-HBV coinfection

Background

Hepatitis B and C viral infections are among the leading causes of chronic liver disease worldwide. According to the World Health Organization, over 250 million people are currently infected with hepatitis B virus (HBV) and more than 70 million are infected with hepatitis C virus (HCV) [1].

While HBV and HCV share a preference for replication in hepatocytes, their life cycles are completely different. HBV, is a DNA virus that replicates in the nucleus, while HCV is an RNA virus that replicates exclusively in the cytoplasm of hepatocytes. However, both viruses have RNA replicative intermediates and can theoretically interact in coinfected cells, leading to varying viral expression and serologic patterns [2].

Coinfection is defined as the presence of two or more replicating organisms within the same host. HBV and HCV coinfection can occur in two ways. Because HBV and HCV have some common modes of transmission, namely intravenous drug use, blood transfusion, and vertical transmission, viruses can be cotransmitted simultaneously [3].

However, HCV/HBV coinfection may also occur by superinfection, meaning one virus is acquired in a patient with a preexisting chronic infection of the other virus. Superinfection is the most common mechanism of developing coinfection, and HCV superinfection is seen more commonly than HBV superinfection [4].

*Correspondence:
El-Araby Mohamed Ibrahim Shalaby
alarabyshalby2277@yahoo.com
[1] Department of Hepatology and Gastroenterology, Port Said Fever Hospital, Port Said 42511, Egypt
[2] Department of Hepatology and Gastroenterology, National Liver Institute, Menoufia University, Shebin El-Kom, Egypt
[3] Department of Clinical Pathology, National Liver Institute, Menoufia University, Shebin El-Kom, Egypt

Recent advances in all-oral direct-acting antiviral (DAA) regimens for HCV have greatly improved treatment efficacy, with sustained virological response (SVR) rates of >95% for HCV monoinfected patients. Unfortunately, HBV reactivation and HBV-related clinical reactivation during or after DAA therapy are not infrequent and can lead to mortality. However, the longer-term clinical course of HBV after DAAs among HBV/HCV-coinfected patients remains unclear [5, 6].

This study aimed to determine the rates of SVR at 12 weeks after treatment with DAAs in patients with HCV/HBV coinfection and to evaluate the risk of HBV reactivation during and 6 months after treatment.

Methods

This retrospective study included 200 patients with HCV/HBV coinfection who received DAAs for 12 weeks. Patients were recruited from the virology clinics at the National Liver Institute Hospital, Menoufia University, Ismailia Fever Hospital, and Port Said Fever Hospital from October 2014 to October 2018. Patients with HCV/HBV coinfection, aged 18 years or older, with positive HBsAg with detectable HBV-DNA levels (<2000 IU/mL) and positive anti-HCV-Ab with detectable HCV RNA who were eligible for HCV treatment by interferon-free DAAs were included in the study. Patients with HCV monoinfection, chronic HBV monoinfection, organ transplant, or child-C cirrhosis were excluded from the study. The study was reviewed and approved by the ethical committee of the National Liver Institute with Institutional review board number (NLI IRB) 00003413.

Patients' medical files were reviewed, and data was collected including medical history and physical findings with results of the following laboratory investigations: liver tests included alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct), and albumin (Alb) measured using Cobas Integra 800 Auto analyzer (Roche Diagnostics Ltd.–Germany. Catalog number M, 87432). The prothrombin test was performed using the BFT II Analyzer (Dade Behring Marburg GmbH, D-35041 Marburg, Germany). Renal tests included blood urea (mg/dL) and serum creatinine (mg/dL). Alfa feto protein (AFT) was also measured for all studied patients (ng/mL). The complete blood count included the hemoglobin level (Hb), hematocrit (HCT), white blood cell count (WBCs), red blood cell count, and platelet count (PLT) and was performed via the Sysmex Automated Hematology Analyzer KX-21N (Sysmex Corporation, Kobe 651-0073, Japan). A quantitative polymerase chain reaction (PCR) was performed to detect the HBV-DNA level, measured via COBAS AmpliPrep/COBAS TaqMan (Roche Diagnostics Ltd.–Germany) with a detection limit of 10 IU/mL. HBV-DNA levels were expressed in IU/mL. A quantitative PCR was also used to detect the HCV RNA level, measured via the VERSANT HCV RNA 3.0 Assay Byer Analyser System. Liver stiffness values were expressed in kilopascals (kPa) and were assessed by fibroscan, in compliance with technical recommendations. Treatment regimens of DAAs included sofosbuvir and daclatasvir with or without ribavirin for 12 weeks.

HBV infection follow-up

All patients were systematically followed up for 24 weeks after end of treatment. HBV reactivation was defined by a ≥2 log increase in HBV replication from baseline levels or a new appearance of HBV DNA (to a level of ≥100 IU/mL) in a person with previously stable or undetectable levels and by Reversion to HBsAg positivity or the appearance of HBV DNA in the absence of HBsAg [4]. Treatment regimens for HBV reactivation included entecavir or tenofovir according to Egyptian guidelines.

Statistical analysis

Data was coded, entered, and analyzed using SPSS version 22. Descriptive statistics were performed as appropriate for all collected variables. The quantitative variables were compared using paired *t* test or one-way analysis of variance. The comparison of qualitative variables was performed using chi-square test or Fisher's exact test. Linear regression was used to model the relationship between a scalar response and one or more explanatory variables (also known as dependent and independent variables).

Results

Among the 200 patients with HCV/HBV coinfection who received DAAs for 12 weeks, 191 (95.5%) achieved SVR following treatment. The mean age was significantly lower in patients who achieved SVR than in patients who did not (45.14±7.32 vs. 55.4±4.53 years, $p<0.001$). In addition, there was a significant difference in gender between groups ($p=0.01$), as shown in Table 1.

Patients who did and did not achieve SVR showed statistically significant differences in fasting blood sugar ($p<0.001$), PLT ($p=0.001$), serum albumin ($p=0.001$), and serum creatinine ($p=0.006$). Moreover, the baseline liver stiffness was significantly higher in patients who did not achieve SVR than in those who did (12.65±4.43 vs. 7.77±2.54 kPa, $p<0.001$) (Table 1). Further, 31.9% of patients who achieved SVR had splenomegaly, compared to a rate of 88.9% in patients who did not achieve SVR ($p<0.001$), while there was no significant difference between groups in the levels of Hb, WBC, ALT, AST, international normalized ratio (INR), prothrombin concentration (PC), total or direct bilirubin, or AFP.

Table 1 Demographic data and laboratory investigations in the studied patients in relation to SVR to DAAs

SVR (*N* = 191)			No SVR (*N* = 9)		*P* value
Age (years)					
Mean ± SD	45.14 ± 7.32		55.44 ± 4.53		**< 0.001**
Min–Max	24–63		48–61		
Sex					
Male	106	55.5%	9	100%	**0.011**
Female	85	44.5%	0	0%	
Laboratory investigations	Mean ± SD		Min–Max		
FBS (mg/dL)	93.94 ± 24.52		125.33 ± 30.44		**< 0.001**
Hb (g/dL)	13.03 ± 1.11		13.18 ± 0.91		0.69
WBC (× 10^3)	6.52 ± 1.04		6.34 ± 0.85		0.62
PLT (× 10^3)	182.58 ± 56.84		101.89 ± 39.79		**< 0.001**
ALT (U/L)	36.11 ± 11.8		34 ± 11.17		0.59
AST (U/L)	39.71 ± 17.92		42 ± 17.5		0.74
Albumin (g/dL)	3.89 ± 0.22		3.64 ± 0.17		**0.001**
Creatinine (mg/dL)	0.74 ± 0.09		0.83 ± 0.07		**0.006**
INR	1.11 ± 0.1		1.1 ± 0.09		0.64
PC (%)	92.19 ± 7.77		92.89 ± 5.25		0.79
Total bilirubin (mg/dL)	0.55 ± 0.25		0.56 ± 0.22		0.74
Direct bilirubin (mg/dL)	0.18 ± 0.03		0.18 ± 0.02		0.75
AFP (ng/mL)	4.66 ± 1.71		4.65 ± 1.67		0.97
Liver stiffness (kPa)	7.77 ± 2.54		12.65 ± 4.43		**< 0.001**
HCV RNA level (IU/mL)	$1.05 \times 10^5 \pm 2.28 \times 10^5$		$2.43 \times 10^5 \pm 1.87 \times 10^5$		0.075

Statistical test used: sample *T* test and Fisher's exact test

SD Standard deviation, *SVR* Sustained virological response, *DAAs* Direct-acting antivirals, *N* Number, *FBS* Fasting blood sugar, *Hb* Hemoglobin, *WBCs* White blood cells, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *INR* International normalization ratio, *PC* Prothrombin concentration, *AFP* Alpha-fetoprotein, *RNA* Ribonucleic acid, *kPa* Kilopascal

P value < 0.05 is considered statistically significant (95% confidence interval)

In total, 184 patients had no HBV reactivation after HCV treatment. There was a statistically higher frequency of males in the group with HBV reactivation, compared to that in the group without HBV reactivation (81.3 vs. 55.4%, $p = 0.045$). The mean age was 44.86 ± 7.45 years in patients without HBV reactivation and 48.25 ± 4.64 years in those with HBV reactivation, which was not significantly different ($p = 0.076$) (Table 2).

Patients with and without HBV reactivation revealed a statistically significant difference in ALT ($p = 0.049$) and serum creatinine ($p = 0.042$) levels. Further, patients with HBV reactivation had higher HCV RNA levels at baseline than that in those without HBV reactivation ($p = 0.047$). However, there were no significant differences between the two groups regarding Hb, WBC, PLT, AST, serum albumin, INR, PC, bilirubin total and direct, AFP, or the presence of splenomegaly as shown in Table 2.

Three females and 13 males, with a mean age of 48 ± 4 years had HBV reactivation. Among them, 18.8% received SOF + Ledipasvir and 81.2% received SOF + DAC. Eight (50%) of the 16 patients with HBV reactivation were treated by tenofovir, and the other 50% were treated by entecavir. Patients' recovery occurred in 3 months; no cases of flare or death were observed (Table 3).

Univariate regression analysis was conducted for the prediction of SVR; age, gender, platelets count, serum creatinine, liver stiffness by fibroscan, and splenomegaly were associated with the achievement of SVR in univariate analysis. Multivariate analysis revealed that only age, platelet count, serum creatinine, and liver stiffness by fibroscan were independent predictors for achieving SVR (Table 4).

Furthermore, univariate regression analysis was conducted for the prediction of HBV reactivation; age, ALT, HCV RNA level at baseline, and the duration of HCV treatment were associated with a risk for HBV reactivation in univariate analysis. However, multivariate analysis revealed that only the HCV RNA level at baseline and the duration of HCV treatment were associated with a risk for HBV reactivation (Table 5).

Table 2 Demographic data and laboratory investigations of the studied patients according to PCR for HBV DNA after end of HCV treatment

	Patients without HBV reactivation after HCV treatment (*N* = 184)		**Patients with HBV reactivation after HCV treatment (*N* = 16)**		***P* value**
Age (years)					
Mean ± SD	44.86 ± 7.45		48.25 ± 4.64		0.076
Min–Max	24–63		41–58		
	***N* = 184**	**%**	***N* = 16**	**%**	
Sex					
Male	102	55.4%	13	81.3%	**0.045**
Female	82	44.6%	3	18.7%	
Laboratory investigations	**Mean ± SD**		**Min–Max**		
FBS (mg/dL)	95.74 ± 26		90.81 ± 20.12		0.46
Hb (g/dL)	13.01 ± 1.1		13.29 ± 1.1		0.33
WBC (x 10^3)	6.47 ± 1.04		6.98 ± 0.82		0.06
Platelets (x 10^3)	179.7 ± 59.3		170.25 ± 50.19		0.53
ALT (U/L)	35.53 ± 10.81		41.56 ± 19.27		**0.049**
AST (U/L)	39.66 ± 18.18		41.56 ± 14.14		0.73
Albumin (g/dL)	3.89 ± 0.22		3.8 ± 0.3		0.16
Creatinine (mg/dL)	0.74 ± 0.09		0.79 ± 0.1		**0.042**
INR	1.11 ± 0.1		1.08 ± 0.12		0.21
PC (%)	92.09 ± 7.62		93.74 ± 8.25		0.41
Total bilirubin (mg/dL)	0.55 ± 0.25		0.54 ± 0.29		0.98
Direct bilirubin (mg/dL)	0.18 ± 0.03		0.17 ± 0.04		0.43
AFP (ng/mL)	4.64 ± 1.63		4.92 ± 2.53		0.86
Liver stiffness (kPa)	8.87 ± 3.46		6.44 ± 1.66		0.07
HCV RNA Level (Iu/ml)	$1.15 \times 10^5 \pm 2.34 \times 10^5$		$2.92 \times 10^5 \pm 1.87 \times 10^5$		**0.047**

Statistical test used: Two sample *T* test and Fisher's exact test

SD Standard deviation, *HCV* Hepatitis C virus, *PCR* Polymerase chain reaction, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *DNA* Deoxyribonucleic acid, *N* Number, *FBS* Fasting blood sugar, *Hb* Hemoglobin, *WBCs* White blood cells, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *INR* International normalization ratio, *PC* Prothrombin concentration, *AFP* Alpha-fetoprotein

P value < 0.05 is considered statistically significant (95% confidence interval)

Discussion

In the current study, we evaluated the rate of HBV reactivation in patients with HCV/HBV coinfection following treatment for HCV; only 16 patients (8%) experienced HBV reactivation after treatment of chronic HCV infection. No cases of flare or death were observed.

Our results concurred with those of Kawagishi et al. [7], who compared the risk of HBV reactivation following treatment by DAA (85 patients) or interferon (IFN)-based therapy (72 patients) for HCV; they reported that six patients experienced HBV reactivation ($n = 2$) or HBV reappearance ($n = 4$) after IFN-free DAA therapies, while no patient developed HBV reactivation after IFN-based therapies. However, there was no significant difference in age or sex between patients with and without HBV reactivation or reappearance (median: 67 vs. 64 years, $p = 0.55$ and 0.13, respectively).

Doi et al. [8] also studied the frequency and factors associated with HBV reactivation in patients with HCV treated with all-oral DAAs; they reported that HBV reactivation occurred in 3.4% (5/147) of patients during DAA therapy. Similar to the results of our study, they found no significant difference in age ($p = 0.494$) or sex ($p = 0.368$) between those with and without HBV reactivation.

Belperio et al. [9] evaluated HBV reactivation among 62,920 veterans treated with oral hepatitis C antivirals and found that 9 of 62,290 patients treated with DAAs had evidence of HBV reactivation during DAA treatment. Eight occurred in patients HBsAg positive, and one occurred in a patient known to be isolated hepatitis B core antibody-positive. Seventeen other patients had small increases in HBV-DNA levels that did not qualify as HBV reactivation. Only 3 of the 9 patients identified with HBV reactivation in this cohort exhibited peak ALT elevations > 2 times the upper limit of normal.

Wang et al. [10] investigated 327 patients receiving pan-oral DAA agents for HCV infections in areas endemic for HBV in China. Ten patients were positive for HBsAg, and 124 patients had occult HBV infection.

Table 3 Characteristic of patients with HBV reactivation

	Cases = 16	%
Pretreatment		
Age (years)		
Mean ± SD	48 ± 4	
Range	41–55	
Sex		
Female	3	18.8%
Male	13	81.3%
Fibrosis stage by Fibroscan		
F0	7	43.8%
F1	5	31.3%
F2	4	25.0%
AST(IU/L)		
Mean ± SD	42 ± 14	
Range	27–75	
ALT(IU/L)		
Mean ± SD	40 ± 13	
Range	28–77	
DAAs		
SOF + Ledipasvir	3	18.8%
SOF + DAC	13	81.2%
HCV RNA (× 10^5)		
Mean ± SD	4.1 ± 0.95	
Range	2.4–6.3	
HCV SVR12		
Yes	16	100.0%
AT HBV reactivation		
Type of NUC		
ETV	8	50.0%
TDF	8	50.0%
ALT (IU/L)		
Mean ± SD	84 ± 8	
Range	72–103	
Total bilirubin (mg/dL)		
Mean ± SD	1.03 ± 0.3	
Range	0.6–1.6	
HBV DNA (× 10^3) (IU/mL)		
Mean ± SD	3.59 ± 1.04	
Range	2.3–5.8	
Outcome		
Flare		
No flare	16	100.0%
Recovery		
Recovery in 3 months	16	100.0%
Death		
No death	16	100.0%

AST Aspartate aminotransferase, *ALT* Alanine aminotransferase, *SVR* Sustained virologic response, *Sof + Dac* Sofosbuvir and daclatasvir, *Sof + Dac + RBV* Sofosbuvir, daclatasvir, and ribavirin, *DAAs* Direct-acting antivirals, *ETV* Entecavir, *TDF* Tenofovir, *NUC* Nucleot(s)ide analogs

HBV reactivation was determined by measuring HBV DNA levels and the HBsAg status in serial serum samples collected every 2 weeks during DAA treatment and then every 4 weeks after treatment until week 12. In the total study population, 10 patients (3.1%) had hepatitis; 3 cases were associated with HBV reactivation (1 case not in the icteric phase, 1 case in the icteric phase, and 1 case with liver failure) and 7 were from other causes.

However, in a previous study by El Kassas et al. [11] on chronic HCV patients with positive HBsAg who underwent DAAs in Egypt, the risk of reactivation in the absence of HBV treatment was 28.6% (95% confidence interval [CI] 15.6–46.4%), and the risk of hepatitis in the patients who experienced reactivation was 10.0% (95% CI 0.9–57.8%). Moreover, the pooled risk of reactivation in HBsAg-negative anti-HBc-positive patients was negligible (0.1%, 95% CI 0–0.3%), irrespective of the presence of anti-HBs.

The mechanisms of HBV reactivation are not totally understood. However, the loss of suppression of HBV replication is thought to initiate HBV reactivation. In cases where an immunosuppressive agent is administered, these drugs directly suppress the immune response to HBV replication, resulting in HBV reactivation. In HBV/HCV coinfected patients, HCV is usually the dominant virus and coexistence of HCV is believed to suppress HBV replication. Thus, HCV eradication might negate suppression of HBV replication, resulting in HBV reactivation [12].

In the present study, there was a significant difference in FBS, PLT, serum albumin, serum creatinine, and fibroscan between patients who did and did not achieve SVR, but there was no significant difference in WBC, ALT, AST, INR, PC, bilirubin total and direct, or AFP between groups. We found that patients who achieved SVR had a higher albumin level and PLT count and a lower blood glucose level, serum creatinine, and liver stiffness measurement value by fibroscan. Furthermore, 31.9% of patients who achieved SVR had splenomegaly.

Our results were similar to those reported by Shousha et al. [13]. They studied predictors of nonresponse to DAAs in patients with chronic hepatitis C and reported that at posttreatment week 4, 10,495 patients (98.5%) were responders and 160 (1.5%) were nonresponders. Approximately, 50.6% of nonresponders were males and 61.3% were cirrhotic. Nonresponders had significantly higher baseline body mass index, liver enzymes, and AFP as well as significantly lower albumin levels and PLT count by univariate analysis ($p < 0.001$).

Omar et al. [14] also reported several factors that could impact SVR12 in genotype 4 patients. These included gender, bilirubin, albumin, INR, and PLT. They found that patients who achieved SVR12 were younger;

Table 4 Univariate and multivariate regression analysis for predictors of achieving SVR

	Univariate				Multivariate			
	OR	**95% CI**		***P* value**	**OR**	**95% CI**		***P* value**
Age/year	1.977	0.910	3.050	**0.026**	1.655	1.232	2.212	**< 0.001**
Gender	1.473	0.842	2.578	**0.015**	1.121	0.978	1.878	0.122
FBS (mg/dL)	1.121	0.877	1.822	0.072				
HB (gm/dL)	1.299	0.740	2.281	0.161				
WBCs (10^3/L)	1.418	0.667	3.016	0.164				
PLT (10^3/L)	3.278	1.749	6.144	**< 0.001**	1.241	0.544	2.829	**0.008**
ALT (U/L)	1.918	1.506	2.655	0.112				
AST (U/L)	1.036	1.018	1.054	0.092				
PC (%)	1.564	1.187	1.948	0.177				
INR	1.298	0.741	2.231	0.099				
Albumin (g/L)	1.243	0.670	1.502	0.09				
Creatinine (mg/dL)	2.110	1.212	3.988	**0.004**	1.543	0.988	2.112	**0.043**
Liver stiffness (KPa)	5.992	2.432	7.670	**< 0.001**	6.551	3.761	9.882	**< 0.001**
Splenomegaly	2.321	1.198	3.211	**0.034**	1.071	0.547	1.566	0.542
HCV treatment	1.100	0.988	1.165	0.435				
HCV RNA level at baseline	1.065	0.955	1.210	0.232				

OR Odds ratio, significant, *FBS* Fasting blood sugar, *WBCs* White blood cells, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *PC* Prothrombin concentration, *INR* International normalized ratio, *kPa* Kilopascal, *SVR* Sustained virological response

Table 5 Univariate and multivariate regression analysis for predictors of HBV reactivation post-HCV treatment

	Univariate				Multivariate			
	OR	**95% CI**		***P* value**	**OR**	**95% CI**		***P* value**
Age/year	1.232	0.765	1.855	**0.034**	1.112	0.766	1.344	0.098
Gender	1.542	0.988	1.998	0.132				
FBS (mg/dL)	2.132	1.322	2.870	0.212				
HB (gm/dL)	0.988	0.765	1.211	0.453				
WBCs (10^3/L)	1.211	0.977	1.956	0.766				
PLT (10^3/L)	3.211	1.298	4.776	0.343				
ALT (U/L)	2.377	1.980	3.376	**0.045**	1.954	0.819	2.666	0.131
AST (U/L)	1.966	1.219	2.656	0.119				
PC (%)	0.989	0.788	1.233	0.234				
INR	1.355	1.067	1.788	0.256				
Albumin (g/L)	2.133	1.564	2.768	0.311				
Creatinine (mg/dL)	1.989	1.166	2.450	0.066				
Fibroscan (Kpa)	3.420	2.786	5.144	0.112				
Splenomegaly	2.188	1.324	2.988	0.781				
HCV RNA level at baseline	4.343	3.299	5.321	**< 0.001**	3.771	3.675	4.980	**< 0.001**
Type of HCV treatment	1.324	0.944	3.217	0.536				

OR Odds ratio, significant, *FBS* Fasting blood sugar, *WBCs* White blood cells, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *PC* Prothrombin concentration, *INR* International normalized ratio, *kPa* Kilopascal, *HBC* Hepatitis B virus, *HCV* Hepatitis C virus, *RNA* Ribonucleic acid

predominantly female; had a lower prevalence of diabetes; lower baseline levels of ALT, AST, and bilirubin; and higher levels of albumin, Hb, WBC, and PLT.

Our results agreed with those from the study by Butt et al. [15], who reported an overall SVR rate for HCV/HBV coinfected persons of 90.4%, but it ranged from 86.1% among those with advanced fibrosis/cirrhosis (FIB-4 > 3.25) to 100% among those with no or minimal fibrosis (FIB-4 < 1.45). This provides strong evidence of the association between histologic stage and virologic

outcome in these patients. This result also supports treating coinfected persons early in the course of infection before histologic stage has progressed to severe fibrosis or cirrhosis.

Soliman et al. [16] reported SVR rates of 96.29% 84.61% in noncirrhotic and cirrhotic patients, respectively, at 12 weeks after treatment ($p=0.002$). In addition, Cheng et al. [17] reported that advanced fibrosis and cirrhosis were considered negative predictive factors for achieving SVR in patients treated with an IFN-based regimen.

In the present study, there was a significant difference in ALT, serum creatinine, and HCV RNA level at baseline between patients with and without HBV reactivation. However, no significant difference was observed regarding the Hb level, WBC, PLT, AST, serum albumin, INR, PC, bilirubin total and direct, AFP, and presence of splenomegaly between the two groups. In addition, there was no significant difference between the studied groups in the fibrosis stage by fibroscan, as most patients in both groups (81.25% and 80.43%, respectively) were grade F0.

Similarly, Doi et al. [8] reported that ALT levels were significantly higher in the group with HBV reactivation than in the group with no HBV reactivation ($p=0.032$), while there was no significant difference between groups regarding WBCs ($p=0.501$), Hb ($p=0.076$), PLT ($p=0.401$), PT ($p=0.337$), total bilirubin ($p=0.656$), direct bilirubin ($p=0.256$), or AFP ($p=0.328$).

However, in the study by Kawagishi et al. [7], there was no significant difference in WBC ($p=0.69$), Hb level ($p=0.09$), PLT count ($p=0.60$), ALT level ($p=0.46$), AST level ($p=0.72$), HCV RNA level ($p=0.73$), or AFP ($p=0.30$) between patients with or without HBV reactivation or reappearance.

Yeh et al. [18] studied reactivation of hepatitis B in patients of chronic hepatitis C with HBV infection treated with DAAs. They did not observe any HBV-related ALT flare abrupt rise of ALT level to >5 times the upper limit of normal during chronic (HBV) infection or hepatic decompensation, but were antagonistic in regards to ALT, where there was no ALT elevation before or at the peak of HBV-DNA levels in HBsAg-positive patients with HBV reactivation, indicating that on-treatment ALT monitoring may not be sufficiently sensitive to detect HBV reactivation. Moreover, most patients in the study by Belperio et al. [9] appeared to have "silent" or "mild" HBV reactivation characterized by normal ALT or less than a two-fold change in ALT.

In the present study, univariate regression analysis showed that age, gender, PLT count, serum creatinine, fibroscan, and the presence of splenomegaly were associated with the achievement of SVR, while multivariable analysis revealed that only age, PLT count, serum creatinine, and fibroscan were considered as predictors for SVR. Butt et al. [15] reported that factors associated with a lower likelihood of achieving SVR included cirrhosis at baseline (odds ratio [OR] 0.85, 95% CI 0.80–0.92), diabetes (OR 0.93, 95% CI 0.87–0.99), and higher pretreatment HCV RNA (OR 0.86, 95% CI 0.84–0.87).

Our results also agreed with those from the study by Jun et al. [19]. In their study, univariate analysis for baseline factors revealed that young age ($p=0.009$), genotype 2 ($p=0.001$), HCV RNA level of <800,000 IU/mL ($p<0.001$), and a baseline PLT count of $>150\times10^3/\mu L$ ($p<0.001$) were significant SVR predictors, regardless of the genotype. In multivariate analysis for treatment-related factors, SVR was associated with achievement of a rapid virological response (RVR; $p<0.001$), with a treatment adherence of ≥80/80/80 ($p<0.001$).

Yeh et al. [20] reported that the pretreatment HBsAg titer was the only factor associated with HBsAg seroclearance in univariate and multivariate analyses (hazard ratio [HR] 0.328; 95% CI 0.137–0.787; $p=0.012$). On univariate analysis, no factor was associated with HBV virological reactivation. However, after adjustment for factors with a *P* value of <0.2 in univariate analysis, they found that the pretreatment ALT level (HR 1.007; 95% CI 1.000–1.013; $p=0.035$) was positively associated with HBV reactivation, while sofosbuvir-containing regimens (HR 0.441; 95% CI 0.209–0.928; $p=0.031$) were negatively associated with HBV reactivation.

Finally, DAAs are becoming more widely available and demonstrated a high SVR when treating HCV/HBV coinfection. However, it is important to be aware of potential for HBV reactivation during and after treatment with DAAs.

Conclusion

Patients coinfected with HCV/HBV who were treated with DAAs showed a high SVR (95.5%) in our study; however, older age, low PLT count, high serum creatinine, and higher liver stiffness were considered as predictors for failure to achieve SVR. Sixteen patients (8%) developed HBV reactivation, those patients had significantly higher ALT and serum creatinine levels, but only the HCV RNA level at baseline and duration of HCV treatment were significantly associated with the risk of HBV reactivation.

Abbreviations

DAAs	Direct-acting antivirals
SVR	Sustained virological response
HCV	Hepatitis C virus
PCR	Polymerase chain reaction
HBV	Hepatitis B virus
Sof + Dac	Sofosbuvir and daclatasvir
Sof + Dac + RBV	Sofosbuvir, daclatasvir, and ribavirin
ETV	Entecavir
TDF	Tenofovir
NUC	Nucleot(s)ide analogs

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Authors' contributions
All authors co-operated in the conceptualization, design of the work, data curation, resources detection, formal analysis, interpretation of the data, the creation of new software used in the work, validation and methodology, and revision. The authors read and approved the final manuscript.

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Availability of data and materials
All data are available upon request.

Declarations

Ethics approval and consent to participate
The study was reviewed and approved by the ethical committee. Waiver of informed consent was obtained.

Competing interests
None declared.

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