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HCV Relapse in Hemodialysis Egyptian Patients after Treatment with Direct Acting Antiviral Drugs

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Abbreviations:
HCV: Hepatitis C Virus;
HD: Hemodialysis;
CKD: Chronic Kidney Disease;
DAAs: Direct-Acting Antivirals;
SVR: Sustained Virologic Response;
RNA: Ribonucleic Acid;
PCR: Polymerase Chain Reaction;
ALT: Alanine Aminotransferase;
AST: Aspartate Aminotransferase;
AFP: Alpha-Fetoprotein;
ESRD: End-Stage Renal Disease;
HBV: Hepatitis B Virus;
HCC: Hepatocellular Carcinoma;
INR: International Normalized Ratio;
CBC: Complete Blood Count;
IU: International Units;
EIA: Enzyme Immunoassay;
AUC: Area Under the Curve;
OR: Odds Ratio;
CI: Confidence Interval;
GIT: Gastrointestinal Tract;
HTN: Hypertension;
DM: Diabetes Mellitus;
WBCs: White Blood Cells;
MPV: Mean Platelet Volume;
N/L ratio: Neutrophil to Lymphocyte Ratio;
PPV: Positive Predictive Value;
NPV: Negative Predictive Value;
SE: Standard Error; Z: Z-score.

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ABSTRACT

Background/Aims: HCV infection is a major health problem in Egypt, and unfortunately, its prevalence is higher in hemodialysis patients than in the general population. The advent of DAA led to an increased rate of recovery and lower rates of side effects compared to standard interferon therapy. Still, relapse of HCV is not uncommon among these patients. The aim of the current study was to assess the incidence of relapse among hemodialysis patients with HCV after treatment with different regimens of direct-acting antivirals (DAAs) and to identify the risk factors that might be associated with this relapse.
Materials and Methods: This case-control study was conducted at a Teaching Hospital, between June 2018 and June 2023. The study included 250 hemodialysis patients with chronic HCV and previously treated with DAAs and achieved SVR. Patients were reassessed after 6 months of completion of treatment course. They were classified according to DAA treatment response into patients with HCV relapse (186 patients) and a non-relapse group (64 patients). Both groups were assessed regarding predictors and risk factors for HCV relapse.
Results: Hypertension was significantly more prevalent in the relapse group (p=0.0001). The Sofosbuvir + Daclatasvir + Ribavirin regimen was most commonly used in the relapse group (53.2%), while Ritonavir/Ombitasvir/Paritaprevir + Ribavirin was more frequent in the non-relapse group, both showing statistical significance (p=0.0001).
Conclusion: Pre-treatment HCV viral load, liver cirrhosis, and elevated alfa-fetoprotein were significant predictors of relapse. Liver cirrhosis and Sofosbuvir-based regimens were associated with higher relapse rates among these patients.
Keywords: HCV treatment, hemodialysis, direct acting antivirals, relapse

INTRODUCTION

Hepatitis C virus (HCV) is a blood-borne RNA virus that primarily infects the liver, leading to mild to severe chronic inflammation. It remains a major global health concern due to its association with cirrhosis and hepatocellular carcinoma (HCC), affecting an estimated 58 million people worldwide, with 1.5 million new cases annually (1). The prevalence of HCV among hemodialysis

(HD) patients varies widely, ranging from 1% to 90% globally, with lower rates in northern Europe and higher rates in regions such as North Africa, Asia, and South America (2).

Egypt bears the highest burden of HCV worldwide, with a reported prevalence of 14.7% among individuals aged 15 to 59 years (3). However, through a nationwide treatment campaign, Egypt has successfully treated over four million patients, reducing the prevalence of viremic HCV infection from 7% in 2015 to 0.4% in 2021, making it the first country validated by the WHO for its efforts toward HCV elimination (4).

The introduction of direct-acting antivirals (DAAs) has revolutionized HCV treatment, particularly for patients with chronic kidney disease (CKD) and those on HD. DAAs achieve sustained virologic response (SVR) rates of 90-95%, providing effective and well-tolerated treatment options. While sofosbuvir, an NS5B polymerase inhibitor, undergoes substantial renal clearance, most DAAs do not require dose adjustments in severe CKD or HD patients (5). Despite their high efficacy, some patients, particularly those with cirrhosis, still experience HCV relapse, though predictive indicators remain poorly understood (6).

Achieving SVR, defined as undetectable HCV RNA for 12 or 24 weeks post-treatment, is the ultimate goal of therapy (7). However, recurrence of HCV RNA after achieving SVR can occur, categorized as either reinfection or relapse. Reinfection is diagnosed when HCV reappears more than 12 to 24 weeks post-SVR, whereas relapse typically occurs within the first few months or even years after DAA therapy (8,9). Manns (2013) suggested that the low sensitivity of laboratory tests could explain some late relapses (10), while Pawlotsky (2016) linked relapse to drug-resistant viral mutations that cause the virus to re-emerge after a period of undetectability (11). Factors such as high baseline viral load, younger age, genotype 1b infection, and resistance-associated variants in the NS3 and NS5 regions have been associated with relapse (12).

In Egypt, HCV genotype 4 predominates, accounting for over 85% of infections, with subtype 4a being the most common (80.6%), followed by other subtypes such as 4g, 4l, and 4n (13). Given this genetic distribution, studies on HCV relapse in Egypt primarily focus on genotype 4.

HCV infection in HD patients is linked to higher rates of liver-related, cardiovascular, and all-cause mortality, emphasizing the need for treatment in this population. Despite the efficacy of DAAs, data on HCV recurrence after treatment in HD patients remain scarce. Understanding the risk factors associated with relapse is crucial for minimizing recurrence and optimizing treatment outcomes.

The current study was to assess the incidence of relapse among hemodialysis patients with HCV after treatment with different regimens of DAAs after achieving SVR and to identify the risk factors that might be associated with this relapse to avoid which is avoidable in the future.

MATERIALS AND METHODS

Our study is a case-control study where hemodialysis patients with chronic HCV infection and previously treated with DAAs at dialysis units in a Teaching Hospital, in the duration between June 2018 and June 2023 were enrolled in the present study.

Inclusion and Exclusion Criteria

Inclusion criteria: ESRD Patients on chronic hemodialysis of both sexes and those aged more than 18 who received a DAA regimen and achieved SVR were included in the study.

Exclusion criteria: Patients having co-infection with HBV, patients who received a renal allograft, and patients with autoimmune disease (autoimmune hepatitis, systemic lupus, and rheumatoid arthritis), patients with HCC were excluded from the study (diagnosed by triphasic CT and alphafetoprotein).

Patients Groups

A total of 300 HCV-positive hemodialysis patients were included in the current study. After exclusion criteria were applied, 250 patients were eligible to be included (*fig. 1*). The included patients were further divided according to incidence of relapse/ non-relapse into 2 groups: Group I included 64 patients who did not

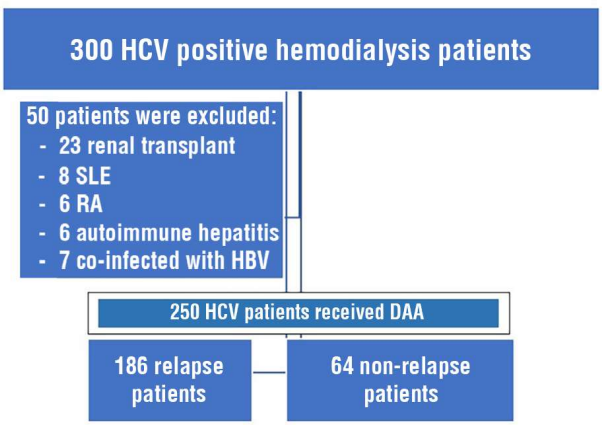

Figure 1 - Summary of study population

experience relapse and Group II included 186 patients with relapse.

Relapse was detected by reappearance of viral load using quantitative PCR technique 6 months later after primary disappearance following treatment with DAAs.

Methods

The participants in the study were subjected to:

A thorough history is taken with special consideration for the demographic data (age, gender, occupation), special habits of medical importance, associated medical disorders (DM, HTN, cardiac diseases), and original kidney disease. Abdominal examination and abdominal ultrasound for evaluation of liver size, presence of hepatic focal lesions, and splenomegaly. Lab investigations included full liver panel and INR, CBC, and serum alpha-fetoprotein.

Liver cirrhosis was diagnosed based on a combination of laboratory investigations and imaging studies. The diagnosis was supported by a platelet count of less than 150,000 per microliter, provided there was no alternative explanation, and an albumin level below 3.5 mg/dL in the absence of albuminuria or malnutrition. Additional laboratory markers included an AST level greater than ALT, an INR exceeding 1.2, and a bilirubin level above 1.5 mg/dL. Furthermore, imaging studies, specifically ultrasound findings consistent with cirrhosis, were used to corroborate the diagnosis.

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Primary Diagnosis of HCV infection was established by detection of Anti-HCV antibody in serum or plasma by enzyme immunoassay (EIA) or by use of COBAS AmpliPrep / COBAS TaqMan (Roche Diagnostics Ltd – Germany) with a lower limit of detection ≤ 15 international units (IU).

HCV RNA PCR testing was carried out to all positive anti- HCV antibody patients at baseline (before DAA treatment), at the end of treatment (to detect response to treatment), and also 12 weeks after the end of treatment for detection SVR and after 6 months to detect relapse.

Patients received DAAs according to Egyptian protocol for the treatment of HCV (fig. 2)

Naïve cirrhotic patients were treated with one of the following regimens for 12 weeks: Sofosbuvir/ Daclatasvir, Sofosbuvir/Simprevir, Sofosbuvir/ Ledipasvir, or Paritaprevir/Ombitasvir/Ritonavir. Treatment-experienced or cirrhotic patients received one of the following regimens for 12 weeks: Sofosbuvir/Daclatasvir/Ribavirin, Sofosbuvir/ Simeprevir/ Ribavirin, Sofosbuvir/ Ledipasvir /Ribavirin, or Paritaprevir/Ombitasvir/Ritonavir/ Ribavirin. The medication dosages were as follows: Sofosbuvir, one 400 mg tablet taken orally once daily with or without food; Daclatasvir, 60 mg taken orally once daily with or without food; and Ribavirin with a dose of 200 mg, every other day given on dialysis day, 4 hours before dialysis. The combination of Ombitasvir, Paritaprevir, and Ritonavir (Qurevo) was administered as two capsules, containing 25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir.

Monthly follow-up examinations were conducted for all patients at virology unit. During these sessions and in between monthly visits, side effects were identified by telephone or further visits, if necessary. During each visit, we check the patient's compliance with treatment.

Sample Size

The sample size was calculated using the G-power program according to the prevalence of relapse after treatment of HCV-infected hemodialysis patients with DAAs in a previous study by Liu et al., (14). Having an alpha error of 0.05 and a power of 80%; 190 cases were included.

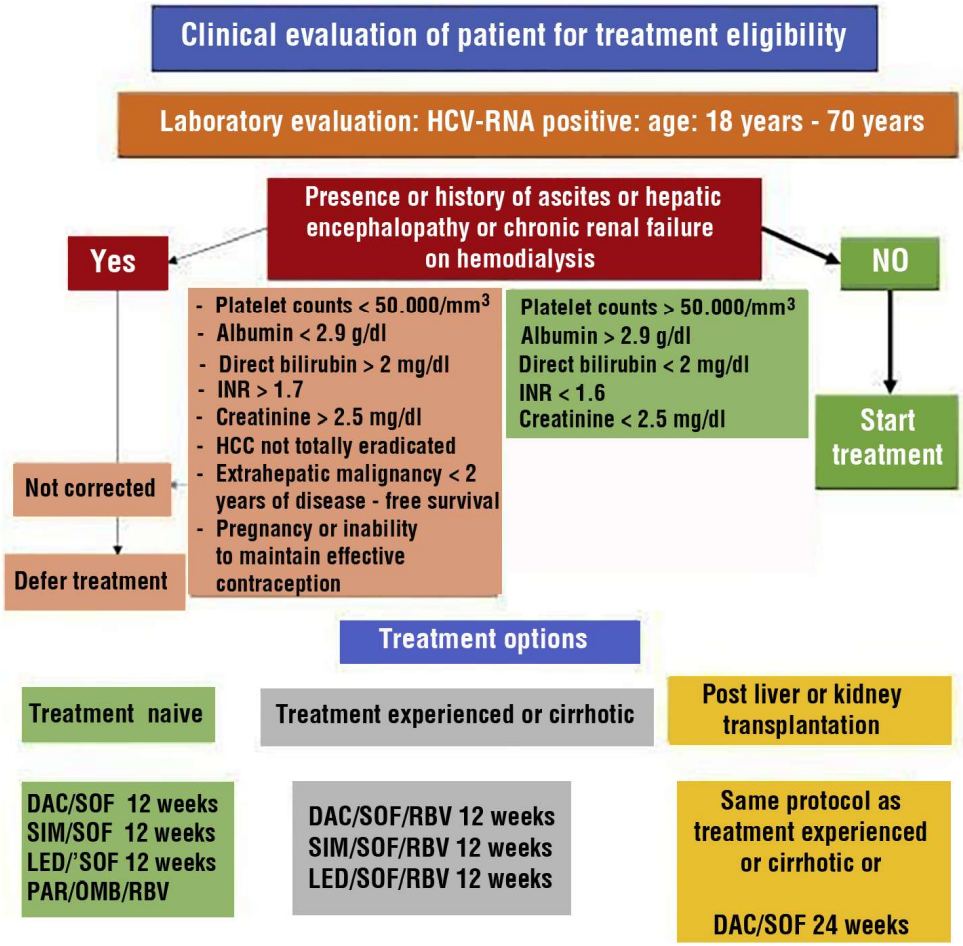
Ethical Considerations

The study adhered to strict ethical considerations. It was approved by the Ethics Committee of the Faculty of Medicine Menoufia University with IRB number (7/2020INTM). Adequate provisions were made to maintain the privacy of participants and the confidentiality of the data. Informed consent was obtained from all participants included.

Statistical Analysis

All data were tabulated in SPSS version 29. Categorical data were expressed as numbers and percentages, while continuous data were expressed as mean and standard deviations. The Chi-square test and Fisher exact test were used to compare data of categorical type. Student t-test was used to compare continuous data. Binary logistic regression was used to assess predictors for postoperative complications using

Figure 2 - Egyptian protocol for the treatment of HCV



multivariate analysis. A p-value less than 0.05 was considered of statistical significance.

RESULTS

The study included 250 HCV-infected hemodialysis patients, with 40% males and 60% females. Hypertension, diabetes, and ischemic heart disease were present in 21.6%, 18.4%, and 2.8% of patients, respectively. Liver ultrasound showed normal findings in 46.8%, while 40.4% had an enlarged liver, and 12.8% had cirrhosis. Splenomegaly was found in 49.6% of patients. The most commonly used antiviral regimen was sofosbuvir-based (152 patients), followed by ritonavir-boosted ombitasvir/paritaprevir (91 patients).

Post-treatment analysis showed a statistically significant increase in serum albumin (p=0.0001) and platelet count (p=0.002). ALT, AST, bilirubin, and HCV PCR levels significantly decreased after treatment (p=0.0001 for each). Hemoglobin levels also showed a significant reduction post-treatment (p=0.0001). However, no significant difference was observed in INR and white blood cells before and after treatment (*table 1*).

Hypertension was significantly more prevalent in the non-relapse group (p=0.0001). While, there was no statistically significant difference between the relapse and non-relapse groups regarding age, sex, diabetes, or ischemic heart disease. Also, a statistically significant difference was observed in the type of DAAs used. The sofosbuvir-based regimen was more frequently associated with relapse, particularly sofosbuvir + daclatasvir + ribavirin (p=0.0001), while the ritonavir-boosted PTV/OTV with ribavirin regimen was more commonly used in the non-relapse group (p=0.0001). Laboratory findings showed significantly lower pre-treatment albumin (p=0.008) and hemoglobin (p=0.0001) in the relapse group, along with higher ALT (p=0.006), AST (p=0.001), bilirubin (p=0.0001), and alfa-fetoprotein (p=0.0001) levels. The pre-treatment viral load was significantly higher in the relapse group (p=0.0001). There was no significant difference

Table 1 - Comparison between baseline and post- treatment laboratory investigations

	Pre- treatment mean± SD	Post- treatment mean± SD	Level of significance	p value*
Albumin (g/dL)	3.8±0.55	4±0.42	4.376	0.0001
ALT (iu/dL)	39.8±22.1	27.59±18.46	8.4	0.0001
AST (iu/dL)	46.59±27.56	27.6±11.08	11.6	0.0001
Bilirubin (g/dL)	1.03±0.5	0.83±0.26	-5.71	0.0001
INR (%)	1.15±0.18	1.13±0.14	1.32	0.186
Hemoglobin (g/dL)	12.5±1.55	11.54±1.98	10.78	0.0001
White blood cells (*10^3/mm^3)	6.5±2.3	6.6±2.9	-0.616	0.538
Platelets (*10/mm^3)	187.87±75.9	199.35±79.3	-3.1	0.002
Alfa fetoprotein median (min, max)	11.13 (0, 18.96)			
HCV. PCR (IU/L)	3654796±45632	23645±1326	-15.3	0.0001

SD: Standard Deviation, t: t-test (statistical test comparing means), ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, g/dL: Grams per Deciliter, INR: International Normalized Ratio, HCV PCR: Hepatitis C Virus Polymerase Chain Reaction, IU/mL: International Units per Milliliter, Bold values indicate significance of P values (p value $\leq$ 0.05).

between both groups regarding INR, white blood cells, and platelet count (*table 2*).

Liver ultrasonography showed a statistically significant difference, with an enlarged liver and cirrhosis being more prevalent in the relapse group (p=0.00001). No significant difference was found in spleen ultrasonography. During treatment, anemia (p=0.009) and fatigue (p=0.004) were significantly more common in the non-relapse group. Overall, treatment complications were higher in the relapse group, but no significant differences were observed for headache, hepatic decompensation, or drug suspension (*table 3*).

At a cutoff point equal to 3.03, albumin had 20.4% sensitivity and 84.3% specificity, equal to 35, ALT had 62.57% sensitivity and 76.56% specificity, equal to 36, AST had 62.64% sensitivity and 57.14% specificity, equal

Table 2 - Comparison between relapse and non-relapse patients as regard baseline characteristics, DAAs, and basal laboratory investigations

	Relapse (n = 186)	Non-relapse (n= 64)	Level of significance	p value
Age (years) mean± SD	59.45±10.38	59.09±12.5	t = 0.29	0.2
Gender No. (%)			χ^2 = 1.2	0.3
Male	54 (29%)	18 (28.1%)		
Female	132 (71%)	46 (71.9%)		
Hypertension No. (%)	29 (15.6%)	25 (39.1%)	χ^2 = 15.49	0.0001
Diabetes No (%)	37 (19.9%)	9 (14.1%)	χ^2 = 1.078	0.29
Ischemic heart disease No. (%)	3 (1.6%)	4 (6.3%)	χ^2 = 3.76	0.06
Sofosbuvir+ Daclatasvir	51 (27.4%)	0	Fχ^2 = 19.3	0.0001
Sofosbuvir+ Daclatasvir+Ribavirin	99 (53.2%)	2 (3.1%)	Fχ^2 = 49.6	0.0001
Ritonavir/Ombitasvir/Paritaprevir+Ribavirin	29 (32.2%)	62 (96.9%)	χ^2 = 135.9	0.0001
Interferon7 (3.8%)	0	FX2= 0.744	0.38	
Albumin (g/dL)	3.9±0.4	4.1±0.38	-2.52	0.008
ALT (iu/dL)	42.17±24.29	33.4±15.22	2.57	0.006
AST (iu/dL)	49.28±25.4	38.39±18.7	2.75	0.001
Bilirubin (g/dL)	0.8±0.2	0.68±0.2	5.35	0.0001
INR (%) 1.14±0.17	1.13±0.17	0.534	0.591	
Hemoglobin (g/dL)	11.72±1.5	12.79±1.48	4.96	0.0001
White blood cells (*10^3/mm^3)	6.47±2.37	6.28±2.3	0.529	0.599
Platelets (*10/mm^3)	178±80.059	191.26±61.28	-1.21	0.171
Alfa fetoprotein	13.67±6.6	3.75±1.9	3.7	0.0001
HCVPCR (IU/mL)	980877 ± 6753	880739 ± 3451.2	-113.5	0.0001

SD: Standard Deviation, t: t-test (statistical test comparing means), χ^2: Chi-square, Fχ^2: Fisher's Exact Test, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, g/dL: Grams per Deciliter, INR: International Normalized Ratio, HCV PCR: Hepatitis C Virus Polymerase Chain Reaction, IU/mL: International Units per Milliliter, Bold values indicate significance of p values (p value $\leq$ 0.05).

Table 3 - Comparison of ultrasonographic data, clinical presentation, and DAAs related complications between relapse and non-relapse patients

	Relapse (n = 186)	Non-relapse (n = 64)	Level of significance	p value
Ascites	7 (3.8%)	0	Fχ^2 = 2.48	0.12
Lower limb edema	0	0		
Esophageal varices	0	0		
Hepatic encephalopathy	0	0		
Hematemesis	4 (2.2%)	0	Fχ^2 = 1.39	0.24
Melena	4 (22%)	0	Fχ^2 = 1.4	0.24
Liver ultrasonography:			Fχ^2 = 25.77	0.00001
Normal	71 (38.2%)	46 (71.9%)		
Enlarged	83 (44.6%)	18 (28.1%)		
Cirrhotic	32 (17.2%)	0		
Hepatic SOL	10 (5.4%)	0	Fχ^2 = 3.6	0.04
Spleen ultrasonography:			χ^2 =1.89	0.17
Normal	89 (47.8%)	37 (57.8%)		
Enlarged	97 (52.2%)	27 42.2%)		
Complications	120 (64.5%)	34 (53.1%)	χ^2 = 2.6	0.1
Anemia	39 (21%)	24 (37.5%)	χ^2 = 6.9	0.009
Erythropoietin stimulating agent	39 (21%)	24 (37.5%)	χ^2 = 6.9	0.009
Fatigue	7 (3.8%)	9 (14.1%)	χ^2 = 8.4	0.004
Headache	15 (8.1%)	5 (7.8%)	χ^2 = 0.004	0.95
Hepatic decompensation	7 (3.8%)	1 (1.6%)	Fχ^2 = 0.75	0.388
Drug suspension	10 (5.4%)	5 (7.8%)	χ^2 = 0.5	0.48

Fχ^2: Fisher's Exact Test, χ^2: Chi-square, SOL: Space Occupying Lesion, Bold values indicate significance of p values (p value $\leq$ 0.05).

to 0.8, bilirubin had 70.97% sensitivity and 64.06% specificity, equal to 11.7, hemoglobin had 86.02% sensitivity and 57.81% specificity, equal to 4.5, AFP had 59.68% sensitivity and 73.44% specificity ,equal to 3.03, albumin had 20.4% sensitivity and 84.3% specificity in the prediction of relapse after DAAs (*table 4*).

All significant risk factors for relapse in the previous univariate analysis were entered in 5 steps multivariate analysis using logistic regression (R: 0.599; adjusted R: 0.578), and the regression had statistical significance (p<0.001). Out of different significant risk factors in univariate analysis, cirrhotic liver by ultrasonography (p=0.0001), sofosbuvir-based regimen (p=0.0001), baseline alfa fetoprotein (p=0.01) and baseline HCV PCR (p= 0.001) were the risk factors for relapse in the multivariate analysis (*table 5*).

Sofosbuvir-based regimen had the highest Odds ratio for relapse with a statistically significant effect (OR: 162.2; p<0.001). Cirrhosis by liver ultrasound had OR 3.4 with a statistically significant effect (p=0.007) (*table 6*).

DISCUSSION

DAA therapy has significantly improved SVR rates in HCV patients (15), yet relapse remains a challenge,

Table 4 - Accuracy of difference laboratory findings in prediction of relapse

	Cutoff value	Sensitivity	Specificity	PPV	NPV	AUC
Albumin	3.03	20.4%	84.3%	79.2%	26.73%	0.370
ALT	35	62.57%	76.56%	88.19%	42.24%	0.657
AST	36	62.64%	57.14%	80.85%	34.62%	0.611
Bilirubin	0.8	70.97%	64.06%	85.16%	43.16%	0.736
Hemoglobin	11.7	86.02%	57.81%	85.56%	58.73%	0.711
Alfa fetoprotein	4.5	59.68%	73.44%	86.72%	38.52%	0.726
HCV-PCR	5181000	51.61%	79.69%	88.07%	36.17%	0.631

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, HCV PCR: Hepatitis C Virus Polymerase Chain Reaction, PPV: Positive Predictive Value, NPV: Negative Predictive Value, AUC: Area Under the Curve, Bold values indicate significance of p values (p value $\leq$ 0.05). Cutoffs with an AUC < 0.7 cannot be considered ,as values below this threshold exhibit poor discriminatory power.

Table 5 - Multivariate analysis of risk factors for relapse

	B estimates	95% confidence interval		Exponential B	p value
		Lower	Upper		
Hypertension	0.478	-0.079	0.13	1.67	0.63
Enlarged liver	0.03	-0.106	0.203	0.01	0.538
Cirrhotic liver	0.186	0.82	0.25	0.01	0.0001
Space occupying lesion in the liver	0.266	0.28	0.89	2.96	0.0001
Sofosbuvir-based regimen	0.713	0.31	0.978	1.54	0.0001
Ritonavir/ombiasevir/paritaprevir	-0.072	-0.39	0.259	5.8	0.69
Albumin	-0.005	-0.095	0.084	1.6	0.903
ALT	0.078	-0.001	0.003	1.015	0.15
AST	-0.026	-0.002	0.002	0.9	0.64
Bilirubin	-0.058	-0.279	0.094	0.6	0.33
Hemoglobin	0.051	-0.013	0.042	1.3	0.3
Alfa fetoprotein	-0.138	-0.006	-0.001	1.004	0.01
HCV PCR	-0.14	-0.005	-0.02	1.1	0.001

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, HCV PCR: Hepatitis C Virus Polymerase Chain Reaction, Bold values indicate significance of P values (P value ≤ 0.05).

Table 6 - Odds ratio for predictors of relapse

						95% Confidence Interval	
Predictor	**Estimate**	**SE**	**Z**	**p**	**Odds ratio**	**Lower**	**Upper**
Hypertension: Yes – No	0.419	0.466	0.89787	0.369	1.520	0.609	3.791
Cirrhotic liver	1.232	0.455	2.71091	0.007	3.430	1.407	8.360
Liver space occupying lesion	4.315	2174.990	0.00198	0.008	74.834	0.000	123.45
Sof.based vs. Ritonavir- boosted	5.089	0.781	6.51583	<.001	162.2	35.097	749.612

Bold values indicate significance of P values (P value ≤ 0.05).

especially in hemodialysis patients due to the lack of a protective immune response and factors like liver cirrhosis (16). This study aimed to identify risk factors for relapse post-DAA treatment in 250 hemodialysis patients, divided into 186 relapse and 64 non-relapse cases, to help minimize preventable recurrences.

The included patients had a mean age of 52.66 ± 11.57 years, with female predominance (60%). Similarly, Elmowafy et al. (17) reported lower mean age values in their study on hemodialysis patients with male predominance (67.6%). A large meta-analysis including 27 relevant articles and 1464 hemodialysis patients found that the mean age was 48.6 ± 11 years, with male predominance (18).

About 21.6% of the included patients were hypertensive, and 18.4% were diabetic. A similar prevalence rate of hypertension and diabetes among HCV hemodialysis patients was reported by Elmowafy et al. (17). Additionally, Gohel et al. (19) reported similar findings.

Four DAA regimens were used. A sofosbuvir-based regimen was used in 152 patients, and ritonavir-boosted ombitasvir/paritaprevir was used in 91 patients. Both regimens have been evaluated in many previous studies, as the ritonavir-boosted regimen was the only validated DAAs regimen in hemodialysis patients due to its low renal clearance and had been evaluated in many studies (17,20-22). Later, the safety of the sofosbuvir-based regimen in low-clearance patients was guaranteed in different studies, which explained their results by noting that the metabolites of sofosbuvir are safe and do not cause harm to low-clearance patients (23,24).

In the current study, age and sex were not considered statistically significant predictors for relapse, as there was no significant difference between the relapse and no-relapse groups regarding these factors. Similarly, Eletreby et al. (25) did not find that age or sex were significant predictors for relapse or treatment failure. In contrast to our findings, Osinusi et al. (26) reported that the odds of relapse were significantly higher in male participants (odds ratio (OR)., 6.09; 95% CI, 1.17-31.6). Additionally, Degasperi et al. (27) identified age ≥ 65 years as a significant predictor for

relapse and treatment resistance. The differences between our study and these reports could be explained by racial differences and genetic variability, which may affect the virologic response.

Also, in our study, there were no statistically significant differences between the relapse and no-relapse groups regarding diabetes, while hypertension was more frequent among no-relapse patients. Similarly, Watanabe et al. (28) did not consider diabetes a risk factor for relapse after DAAs. Osinusi et al. (26) also did not find an association between diabetes, hypertension, and the incidence of relapse. In contrast, Eletreby et al. (25) found that diabetes is a significant risk factor for treatment failure and relapse among hemodialysis patients, and Mangia et al. (29) reported that the presence of comorbidities, such as diabetes or hypertension, increases the risk for relapse and even non-response to treatment.

Few cases with symptoms and signs of hepatic decompensation, such as ascites, hematemesis, and melena, were included in the current study. Thus, we could not confirm the absence of an association between relapse and any of these signs. However, Mangia et al. (29) proposed that the presence of ascites and esophageal varices are predictors for relapse. Additionally, in another Libyan study, the presence of clinical conditions related to hepatic decompensation was associated with a high relapse rate (30).

Presence of cirrhosis on ultrasonography was identified as a statistically significant predictor for relapse in the current study. In concordance with these findings, Eletreby et al. (25) reported the presence of cirrhosis as a predictor for treatment failure and relapse after primary response, and Elmowafy et al. (17) similarly identified cirrhosis as a risk factor for relapse. In contrast, Werner et al. (31) did not find a significant association between liver imaging findings and the incidence of relapse, and Xie et al. (32) reported no statistically significant difference between relapse and no-relapse groups regarding cirrhosis on imaging.

From our results, the type of DAA regimen is a significant risk factor for relapse, with relapse occurring more frequently among patients on the sofosbuvir-based regimen and less frequently among those on the ritonavir-boosted regimen. In agreement with our findings, Sperl et al. (33) reported a 50% relapse rate among HCV hemodialysis patients treated with a sofosbuvir-based regimen, and Cheema et al. (34) also noted a high relapse rate in a similar patient population. In contrast, Tamzaourte et al. (35) proposed that a sofosbuvir-based regimen is highly effective in treating HCV hemodialysis patients, with no reported cases of relapse, and Akhil et al. (36) similarly did not observe any relapse cases with this regimen. Additionally, Xie et al. (32) reported similar relapse rates among HCV patients; however, their study included both hemodialysis patients and patients with normal renal function.

In the current study, elevated liver enzymes, low albumin, high bilirubin, and low hemoglobin were considered significant risk factors for relapse after DAAs. These findings align with those of Mangia et al., who reported that baseline AST, ALT, and albumin values are predictors of treatment outcomes. Additionally, Mangia (29) did not consider platelets or white blood cell counts as significant predictors, which is consistent with our results. Similarly, another study identified all of these biochemical markers as predictors for response and relapse after DAAs (30).

On the other hand, Watanabe et al. (28) considered platelets, white blood cells, and prothrombin time as significant predictors for relapse, in addition to ALT, AST, albumin, and bilirubin. Furthermore, Werner et al. (31) stated that baseline thrombocytopenia was associated with the incidence of relapse within three months after treatment completion. El Kassas et al., (37) in their meta-analysis, also reported an association between baseline white blood cells, platelets, albumin, and AST as predictors for relapse, although they excluded ALT.

According to our findings, a high HCV PCR at baseline is a statistically significant risk factor for recurrence after an initial response to DAAs. In agreement with our results, Elhammadi et al. (38) evaluated risk factors for non-response to DAAs using two different DAA regimens and detected a statistically significant difference in baseline HCV PCR between the groups, with the relapse group exhibiting higher mean levels. Mangia et al. (29) also reported that viral load is a significant predictor for relapse. Additionally, Watanabe et al. (28) found a significant association between baseline HCV PCR and normalization of liver enzymes after DAAs. On the other hand, Cardaba-Garcia et al. (30) did not find a significant difference between relapse and responsive groups regarding HCV PCR.

All significant risk factors identified in the univariate analysis were entered into a five-step multivariate analysis to adjust for confounders, thereby extracting the most robust predictors. Our results revealed that abnormal liver imaging by ultrasound, the presence of space-occupying lesions, and the type of DAA regimen were the most significant risk factors for relapse in the current study.

The study had several strengths, including a relatively large sample size, the inclusion of patients who received various DAA regimens, and the evaluation of a

broad range of demographic, clinical, radiological, and laboratory predictors for treatment outcomes. However, the study also had some limitations, including its single-center design, the absence of a patient registry system, and the loss of patients during the study.

CONCLUSION

In conclusion, the most significant predictors for HCV relapse after primary response to DAA in the hemodialysis population were liver cirrhosis, sofosbuvir-based regimen, and high alfa fetoprotein. Other risk factors were hypertension, degree of hypo-albuminemia, degree of liver enzymes elevation, high bilirubin and viral load by HCV PCR.

We recommend early detection and treatment before the onset of cirrhosis, as its development is a strong predictor of relapse. Caution should be exercised when using sofosbuvir-based regimens for treating HCV in hemodialysis patients, given the higher relapse rates observed with this approach. Additionally, controlling blood pressure before initiating DAA treatment is essential. Future research should aim to differentiate between relapse and reinfection, especially since hemodialysis patients are at increased risk for reinfection, to provide a clearer understanding of recurrence patterns.

Conflict of Interest

None to be declared.

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