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Effects of comorbid conditions and prescribed chronic medications on the treatment plan for chronic hepatitis C infection: A cross-sectional retrospective study

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Abstract

Background: Chronic hepatitis C (CHC) infection is a potentially life-threatening condition characterized by various complications, including end-stage liver disease and cirrhosis. The mortality rate associated with CHC has been increasing due to the presence of comorbidities and the use of chronic medications. Therefore, the objective of this study was to investigate the impact of these comorbidities and chronic medications on the treatment plan for CHC.

Methods: To achieve this objective, a cross-sectional retrospective study was conducted at a tertiary hospital in Jeddah, Saudi Arabia. The study population included patients aged 12 years and above who were diagnosed with CHC between 2016 and 2021. Patients below the age of 12 were excluded from the study. A total of 170 patients with CHC were included in the analysis. The study aimed to evaluate the relationship between CHC complications and the treatment approach.

Results: The mean age of the study participants was 66.78 years, with a higher proportion of female patients. The findings revealed a significant association between hypertension ($p = 0.042$) and cirrhosis ($p = 0.007$) with changes in the treatment plan for CHC. Moreover, the presence of diabetes mellitus ($p = 0.045$), renal diseases ($p < 0.001$), and hypothyroidism ($p = 0.004$) were significantly associated with HCV clearance after the initiation of therapy. Additionally, the use of proton pump inhibitors ($p = 0.033$) and levothyroxine ($p = 0.025$) was found to be associated with a higher rate of CHC clearance.

Conclusion: In conclusion, this study highlights the prevalence of comorbid conditions and the use of chronic medications among patients with CHC. The findings emphasize the importance of considering the effects of comorbidities and chronic medications when developing treatment plans for CHC infections. By taking these factors into account, healthcare professionals can optimize the management of CHC and improve patient outcomes.

KEYWORDS
chronic hepatitis C, clearance, comorbidities, cross-sectional, Saudi Arabia

1 | INTRODUCTION

Hepatitis C virus (HCV) infection is the primary cause of hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC), and is also an indicator for liver transplantation. It remains a significant global health issue. About one third of individuals infected with HCV experience an acute infection, which is often asymptomatic and self-limiting. However, the majority of patients develop CHC, which is the main cause of advanced liver damage and has systemic clinical consequences affecting multiple organs.[1,2] CHC has a global prevalence rate of approximately 58 million, with 1.5 million new cases detected every year.[3] While a country-level study predicts that the prevalence and burden of CHC will remain the same in the coming years,[4] the Ministry of Health has recently launched the "National Program for HCV Detection and Treatment" in its second phase. The program aims to alleviate the burden of the virus.[5] The side effects and low treatment success rate of the Pegylated Interferon (IFN)-γ regimen, which has been the primary treatment for CHC since the 1990s,[6] created an urgent need to develop more potent and tolerable regimens. As a result, the subsequent development of faster-acting and more effective direct-acting antiviral agents (DAAs) has made them the current primary treatment regimen in Saudi Arabia. According to the Saudi Association for the Study of Liver Diseases and Transplantation, these DAAs have a treatment success rate of up to 97%.[7]

A DAA-based regimen has shown significant improvements in both hepatic and extra-hepatic manifestations of CHC, including type 2 diabetes mellitus, hypertension,[8] depression, hepatic encephalopathy,[9] and a reduced progression of chronic kidney disease.[10] However, certain conditions and the concurrent use of specific medications may present unpredictable challenges in terms of patient-specific management and prognosis, which can lead to a diminished quality of life.

The wide range of systemic complications associated with CHC includes various extrahepatic manifestations. These complications are attributed to HCV's ability to replicate using cellular mechanisms in different organs, along with several hypothesized pathophysiological mechanisms.[11] It is believed that HCV facilitates the pathogenicity of neuropsychiatric disorders through neuro-invasion and the induction of inflammatory processes.[12]

Furthermore, HCV disrupts metabolic pathways, leading to the development of multiple cardiovascular events such as ischemic stroke, acute coronary syndrome, heart failure, and peripheral arterial disease.[13] Vitamin D deficiency and malnutrition are also linked to the severity of CHC, particularly in patients with cirrhosis.[14]

It is important to consider the possibility of drug–drug interactions (DDIs), both direct and indirect, with various agents and chronic medications. DDIs can impede the effectiveness of the CHC treatment regimen, potentially increasing disease severity and progression. On the other hand, certain interactions may enhance treatment outcomes, resulting in a more significant response to liver and systemic complications. The chronic use of proton pump inhibitors (PPIs) has been associated with an increased incidence of HCC in patients with chronic liver disease.[15] Conversely, the use of tricyclic antidepressants has been found to reduce the risk of hepatic cirrhosis.[16] In the United Kingdom, the most common psychological condition among individuals with CHC was depression (26.1%), followed by obesity (11.3%) and non-hepatic tumors (5%).[1]

Additionally, potential DDIs have been observed in the treatment of CHC with various agents, including antidepressants (38.6%), anti-diabetics (9.3%), immunosuppressants (6.1%), statins (4.9%), and antiretrovirals (4.9%).[1] A nationwide, population-based study conducted in South Korea revealed that approximately 84.8% of individuals with CHC had comorbid conditions, including hypertension, esophagitis, dyslipidemia, diabetes mellitus, peptic ulcer, and hepatitis B virus co-infection. Within this group, an average of 8.1 prescribed medications per year was observed, and 97% of CHC patients were using other medications with potential DDIs, such as dexamethasone (25.9%), clarithromycin (8.7%), fluconazole (6.2%), and alfuzosin (1.7%).[17] The concomitant use of these medications can impact the pharmacokinetics and pharmacodynamics of different DAAs, highlighting the importance of close monitoring and individualized management plans to prevent avoidable complications.[7]

Given that the new country-level program aims to improve the health-related quality of life for individuals with CHC,[3] it is crucial to gain more knowledge regarding various contributing factors to achieve this goal. Therefore, this study aims to determine the impact of different comorbid conditions and prescribed chronic medications on the management plan for CHC.

2 | METHODS

2.1 | Study design, sitting, and eligibility criteria

This retrospective cross-sectional study was conducted at King Abdulaziz Medical City, a 750-bed tertiary healthcare center located in Jeddah, a metropolitan city in Saudi Arabia with a population of 4.86 million people. The study focused on patients with CHC who were admitted to the medical center. The inclusion criteria consisted of male and female patients aged 12 years and above who had been diagnosed with CHC of any genotype between January 2016 and January 2021. Patients under the age of 12 were excluded as they were not eligible for the treatment regimen involving pan-genotypic DAAs. A non-probability purposive sampling technique was employed, and all patients who met the eligibility criteria were included in the final analysis.

2.2 | Outcomes and definitions

The study was approved by the Institution Review Board of the King Abdullah International Medical Research Center under study number SP21J/108/03 on March 30, 2021. Due to the retrospective nature of the study, the ethics committee waived the requirement for patient consent. The data collection process involved accessing and extracting information from patient records in the institution's electronic database. Confirmation of CHC was based on the detection of HCV antibodies in the blood, indicating past or current infection. Active infection was further confirmed by detecting HCV RNA using polymerase chain reaction (PCR). Patient data were recorded in an Excel sheet without any identifiable information.

Various variables related to CHC were collected, including demographic data, common comorbidities, chronic medications, risk factors, and complications associated with CHC. The DAA regimens were classified based on their mechanism of action, and the frequency of their prescription was calculated. For example, Harvoni, which consists of Ledipasvir and Sofosbuvir, active substances with different mechanisms of action targeting NS5A and NS5B polymerases, was included in the analysis. Changes in treatment regimens, which involve modifying or adjusting the therapeutic approach for patients with CHC infection, including altering medications, adjusting dosages, or introducing new therapeutic interventions, were documented along with complications of CHC, such as liver cirrhosis, HCC, and portal vein hypertension. Receiving treatment refers to the administration of therapeutic interventions in the management plan of patients with CHC, such as any of the DAA ± Ribavirin (RBV) and ± Interferon (INF). The frequency of common comorbidities, such as diabetes, hypertension, asthma, hepatitis B virus, thyroid diseases, psychological diseases, anemia, infections, cardiovascular diseases, renal diseases, and the use of chronic medications like insulin and beta blockers, as well as risk factors such as smoking, alcohol consumption, and hemodialysis, were recorded as well.

2.3 | Data management and statistical analysis

Data analysis was conducted using SPSS statistical software, version 20, obtained through an institutional license provided by King Saud bin Abdulaziz University for Health Sciences. In this study, the dependent variable is the treatment plan for chronic hepatitis C (CHC) infection. We aimed to determine the impact of comorbid conditions and chronic medications on the treatment plan for CHC. The independent variables in the study include various comorbid conditions and chronic medications. The comorbid conditions were coded as binary variables (present or absent), and the chronic medications were coded as binary variables (used or not used). Qualitative variables, such as comorbidities, were presented as percentages. Quantitative variables were described using a parametric approach, reporting the mean and standard deviation. The chi-squared test and Fisher's exact test were used to compare qualitative variables, and statistical significance was set at a p value < 0.05. Logistic regression analysis was performed to identify predictors of CHC clearance, including comorbidities, chronic medications, and complications. Patient privacy and confidentiality were ensured, with data coding and restricted access limited to the research team members. Hard and soft copies of the data were securely stored within the healthcare institution premises and accessible only to the primary investigator.

3 | RESULTS

The study included a total of 170 patients diagnosed with CHC, out of which 90 (52.9%) were female and 80 (47.1%) were male. The mean age of the patients was 66.78 years with a standard deviation of 12.29. Among the participants, 87 (51%) received anti-HCV treatment, while 83 (48.8%) did not receive any treatment. The majority of patients (57.6%) did not receive any DAA treatment. Among those who did receive treatment, the most commonly used regimen was a combination of NS5A and NS5B inhibitors, which was prescribed to 52 patients (30.6%). RBV and Interferon INF were added to the DAA treatment regimen in 34 (20%) and 9 (5.3%) patients, respectively.

A subset of CHC patients (12.4%) experienced a change in their treatment. Specifically, the proportion of patients receiving DAA + RBV decreased from 20% to 13.5%, while the proportion of patients receiving DAA + INF decreased from 5.3% to 3.5% of the patients. Regarding HCV genotypes, the most common genotypes observed were genotype 1 (18.2%) and genotype 4 (19.4%). However, the genotype had not been determined for the majority of patients (61.2%) (Table 1).

Out of the 170 patients with CHC, 165 patients (97.05%) were reported to have comorbidities. The most frequent comorbidities observed were hypertension, diabetes mellitus, renal diseases, and cardiovascular diseases, which appeared in approximately half of the patients (Supporting Information: Figure S1A). Similarly, the majority of patients (95.88%) with CHC were using chronic medications. The most commonly prescribed medications were PPIs, antihypertensive drugs, and beta-blockers (Supporting Information: Figure S1B). Approximately a quarter of the patients with CHC had additional risk factors. These risk factors included dialysis, smoking, and a history of blood transfusion (Supporting Information: Figure S1C). Cirrhosis was present in over 60% of the patients, indicating an advanced stage of liver disease. Furthermore, around one third of the patients experienced HCC (Supporting Information: Figure S1D).

No significant associations were found between the studied comorbidities and the need to change CHC treatment, except for a slight association observed in patients with normal blood pressure (odds ratio [OR] = 0.390, p value = 0.042). However, it is important to note that this association may not have clinical significance (Supporting Information: Table S1). Similarly, there was no observed association between chronic medications and the need to change CHC treatment (Supporting Information: Table S2). While the presence of several risk factors did not affect the treatment of

TABLE 1 Demographic characteristics and treatment regimen of CHC patients.

N	Mean	SD
Age		
170	66.78	12.297
	n = 170	%
Gender		
Male	80	47.1
Female	90	52.9
Genotype		
Not available	104	61.2
1	31	18.2
2	0	0.0
3	2	1.2
4	33	19.4
Receive treatment?		
No	83	48.8
Yes	87	51.2
Original Treatment		
No direct-acting antiviral	98	57.6
NS5A + NS3/4A inhibitors	13	7.6
NS5A + NS5B inhibitors	52	30.6
NS5A + NS3/4A + NS5B inhibitors	5	2.9
NS3/4A inhibitor	1	0.6
NS5B + NS3/4A protease inhibitors	1	0.6
Original + ribavirin (RBV)		
No	136	80.0
Yes	34	20.0
Original + Interferon (IFN)		
No	161	94.7
Yes	9	5.3
Change of treatment?		
No	149	87.6
Yes	21	12.4
Replacing + ribavirin (RBV)		
No	147	86.5
Yes	23	13.5
Replacing + Interferon (IFN)		
No	164	96.5
Yes	6	3.5

Abbreviations: CHC, chronic hepatitis C; N, number of patients; SD, standard deviation.

TABLE 2 Association of change of CHC treatment with CHC complications.

	Change of treatment?						
	No		Yes				
	N = 149	%	*N* = 21	%	OR	95% CI	*p*
Portal hypertension							
No	125	(88.0)	17	(12.0)	1.23	0.38–3.96	0.754[a]
Yes	24	(85.7)	4	(14.3)			
Cirrhosis							
No	59	(96.7)	2	(3.3)	6.23	1.40–27.73	0.007[b]
Yes	90	(82.6)	19	(17.4)			
Hepatocellular carcinoma							
No	100	(86.2)	16	(13.8)	0.64	0.22–1.84	0.403[b]
Yes	49	(90.7)	5	(9.3)			
Hepatic encephalopathy							
No	137	(87.8)	19	(12.2)	1.20	0.25–5.79	0.685[b]
Yes	12	(85.7)	2	(14.3)			

Abbreviations: CHC, chronic hepatitis C; CI, confidence interval; OR, odds ratio.

[a]Fisher's exact test.

[b]Chi-squared test.

CHC (Supporting Information: Table S3), it is important to note that cirrhotic patients had to change from the ideal anti-HCV regimen due to the complication of cirrhosis (OR = 6.23, *p* value = 0.007, Table 2).

Out of the patients who initiated anti-HCV therapy, HCV clearance was achieved in 85 patients, representing a clearance rate of 50%. However, it was found that patients with diabetes mellitus and renal diseases had a significantly lower likelihood of HCV clearance with treatment. The OR for diabetes mellitus was 0.537 with a *p* value of 0.045, while the OR for renal diseases was 0.275 with a *p* value of <0.001. These findings suggest that patients with diabetes mellitus and renal diseases may have a reduced response to anti-HCV therapy in terms of achieving HCV clearance. On the contrary, patients with hypothyroidism had a significantly higher likelihood of clearing HCV infection after starting anti-HCV therapy compared to individuals with normal thyroid function. The OR for hypothyroidism was 3.609 with a *p* value of 0.004. These findings suggest that patients with hypothyroidism may have a more favorable response to anti-HCV therapy in terms of achieving HCV clearance (Table 3).

HCV clearance after initiating anti-HCV therapy was found to be significantly associated with the use of PPIs and levothyroxine. Patients who were using PPIs had an OR of 2.172 with a *p* value of 0.033, indicating a higher likelihood of achieving HCV clearance. Similarly, patients using levothyroxine had an OR of 2.598 with a *p* value of 0.025, suggesting an increased likelihood of HCV

TABLE 3 Association of HCV clearance with comorbidities.

	Clearance?						
	No		Yes				
	n = 85	%	*n* = 85	%	OR	95% CI	*p*
Hypertension							
No	29	(46.0)	34	(54.0)	0.777	0.416–1.450	0.427[a]
Yes	56	(52.3)	51	(47.7)			
Diabetes miletus							
No	32	(41.6)	45	(58.4)	0.537	0.291–0.989	0.045[a]
Yes	53	(57.0)	40	(43.0)			
Cardiovascular diseases							
No	47	(47.0)	53	(53.0)	0.747	0.405–1.378	0.350[a]
Yes	38	(54.3)	32	(45.7)			
Stroke							
No	77	(48.7)	81	(51.3)	0.475	0.138–1.643	0.231[a]
Yes	8	(66.7)	4	(33.3)			
Renal disease							
No	35	(36.5)	61	(63.5)	0.275	0.145–0.522	<0.001[a]
Yes	50	(67.6)	24	(32.4)			
Hepatitis B virus							
No	73	(48.3)	78	(51.7)	0.546	0.204–1.462	0.224[a]
Yes	12	(63.2)	7	(36.8)			
Human immunodeficiency virus							
No	84	(50.0)	84	(50.0)	1.000	0.062–16.253	>0.99[b]
Yes	1	(50.0)	1	(50.0)			
Dyslipidaemia							
No	75	(51.4)	71	(48.6)	1.479	0.617–3.544	0.378[a]
Yes	10	(41.7)	14	(58.3)			
Pneumonia							
No	73	(50.0)	73	(50.0)	1.000	0.422–2.371	>0.99[a]
Yes	12	(50.0)	12	(50.0)			
Chronic obstructive pulmonary disease							
No	79	(49.7)	80	(50.3)	0.823	0.241–2.807	0.755[a]
Yes	6	(54.5)	5	(45.5)			
Hypothyroidism							
No	77	(54.6)	64	(45.4)	3.609	1.442–9.033	0.004[a]
Yes	7	(25.0)	21	(75.0)			
Anxiety							
No	83	(50.0)	83	(50.0)	1.000	0.138–7.268	>0.99[b]
Yes	2	(50.0)	2	(50.0)			
Depression							
No	82	(49.4)	84	(50.6)	0.325	0.033–3.193	0.621[b]
Yes	3	(75.0)	1	(25.0)			

(Continues)

TABLE 3 (Continued)

	Clearance?						
	No		Yes				
	n = 85	%	*n* = 85	%	OR	95% CI	*p*
Anaemia							
No	76	(50.3)	75	(49.7)	1.126	0.433–2.927	0.808[a]
Yes	9	(47.4)	10	(52.6)			
Urinary tract infection							
No	80	(50.3)	79	(49.7)	1.215	0.356–4.144	0.755[a]
Yes	5	(45.5)	6	(54.5)			

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio.

[a]Chi-squared test.

[b]Fisher's exact test.

clearance. These findings suggest that the use of PPIs and levothyroxine may have a positive impact on the effectiveness of anti-HCV therapy in terms of achieving HCV clearance (Table 4). Patients undergoing dialysis were found to be less likely to clear HCV infection after initiating anti-HCV therapy. On the other hand, patients who had undergone radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) were more likely to clear HCV infection after starting anti-HCV therapy. The OR for RFA was 9.947 with a *p* value of 0.009, while the OR for TACE was 11.200 with a *p* value of 0.005. These results suggest that patients who have undergone RFA or TACE may have a higher likelihood of achieving HCV clearance with anti-HCV therapy (Table 5). CHC complications were not found to be associated with HCV clearance after the initiation of therapy (Supporting Information: Table S4). Cirrhotic patients had to change from the ideal anti-HCV regimen (OR = 6.23, *p* value = 0.007), while clearance did not affect the outcome of cirrhosis, *p* = 0.079 (Table 6).

4 | DISCUSSION

Despite the introduction of DAAs for the treatment of CHC, there is still a need to better understand the impact of comorbid conditions and potential DDIs on the management of CHC and the clearance of HCV infections. This study aimed to assess the effects of various comorbid conditions, prescribed chronic medications, risk factors, and CHC complications on the management of CHC and the clearance of HCV infections following the initiation of anti-HCV therapy.

The study included 170 patients with CHC who were enrolled in a tertiary healthcare center located in a metropolitan city in Saudi Arabia. The majority of patients had at least one comorbidity, with hypertension, diabetes mellitus, renal disease, and cardiovascular diseases being the most common conditions observed. Additionally, a significant proportion of the study participants (95%) were using concomitant prescribed medications, which could increase the risk of potential drug interactions. The most frequently reported medication classes were PPIs, anti-hypertensive medications, and antidiabetic drugs.

Furthermore, half of the patients with CHC received a specific treatment regimen and achieved clearance of HCV infections after initiating therapy. This highlights the effectiveness of the chosen therapeutic approach in achieving successful outcomes in terms of HCV clearance. Among the patients included in the study, 21 individuals experienced both hepatic and extrahepatic manifestations and required modifications in their CHC regimen. The modification of the CHC regimen was found to be significantly associated with the incidence of hypertension and cirrhosis. These findings align with a study conducted by Chung et al., which was based on a nationwide analysis of HCV-positive veterans. In that study, medications such as antibiotics were commonly reported among the study population, suggesting possible DDIs with the DAAs used for CHC treatment. The authors of the study proposed that such DDIs might necessitate modifications in the management plan for individuals infected with HCV.[17] The antibiotics commonly prescribed in the study were primarily for the treatment of urinary tract infections (UTIs). This observation can be explained by the fact that cirrhotic patients, due to bacterial translocation and immune dysfunction, are more prone to developing bacterial infections, including UTIs.[17,18] Such infections can worsen the disease status of cirrhotic patients and contribute to increased mortality rates.[19]

A literature search has indicated that patients with compensated or decompensated liver cirrhosis have shown lower sustained virological response at 12 weeks (SVR12) rates and a higher likelihood of experiencing adverse events or requiring treatment modifications.[20,21] However, studies have demonstrated that re-treatment with pan-genotypic DAAs, particularly sofosbuvir/velpatasvir with or without ribavirin, can achieve higher SVR12 rates in populations with a lower risk of treatment failure. These findings suggest that despite the challenges posed by cirrhosis, tailored treatment approaches using specific DAAs can still yield favorable outcomes in terms of achieving sustained virological response.[22–25]

TABLE 4 Association of HCV clearance with chronic medications.

	Clearance?						
	No		Yes				
	n = 85	%	*n* = 85	%	OR	95% CI	*p*
Chemotherapy							
No	68	(47.2)	76	(52.8)	0.474	0.198–1.133	0.088[a]
Yes	17	(65.4)	9	(34.6)			
Proton pump inhibitor							
No	27	(64.3)	15	(35.7)	2.172	1.057–4.466	0.033[a]
Yes	58	(45.3)	70	(54.7)			
Anti-hypertension							
No	22	(40.7)	32	(59.3)	0.578	0.301–1.113	0.099[a]
Yes	63	(54.3)	53	(45.7)			
Beta-blockers							
No	54	(52.4)	49	(47.6)	1.280	0.691–2.371	0.433[a]
Yes	31	(46.3)	36	(53.7)			
Statin							
No	64	(50.4)	63	(49.6)	1.064	0.533–2.126	0.860[a]
Yes	21	(48.8)	22	(51.2)			
Levothyroxine							
No	76	(53.9)	65	(46.1)	2.598	1.107–6.101	0.025[a]
Yes	9	(31.0)	20	(69.0)			
Antidiabetic medication							
No	51	(48.1)	55	(51.9)	0.818	0.439–1.523	0.527[a]
Yes	34	(53.1)	30	(46.9)			
Asprin							
No	68	(49.6)	69	(50.4)	0.928	0.434–1.984	0.846[a]
Yes	17	(51.5)	16	(48.5)			
Warfarin							
No	77	(49.4)	79	(50.6)	0.731	0.242–2.205	0.577[a]
Yes	8	(57.1)	6	(42.9)			
Steroid							
No	69	(50.4)	68	(49.6)	1.078	0.504–2.306	0.846[a]
Yes	16	(48.5)	17	(51.5)			
Anti-convulsant							
No	72	(49.7)	73	(50.3)	0.910	0.389–2.129	0.829[a]
Yes	13	(52.0)	12	(48.0)			
Anti-hepatitis B virus							
No	78	(48.8)	82	(51.3)	0.408	0.102–1.633	0.192[a]
Yes	7	(70.0)	3	(30.0)			
Anti-human immunodeficiency virus							
No	85	(50.3)	84	(49.7)	0.497	0.427–0.578	>0.99[b]
Yes	0	(0.0)	1	(100.0)			

(Continues)

TABLE 4 (Continued)

	Clearance?						
	No		Yes				
	n = 85	%	*n* = 85	%	OR	95% CI	*p*
Sorafenib							
No	81	(50.3)	80	(49.7)	1.266	0.328–4.885	>0.99[b]
Yes	4	(44.4)	5	(55.6)			

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio.
[a]Chi-squared test.
[b]Fisher's exact test.

TABLE 5 Association of HCV clearance with risk factors.

	Clearance?						
	No		Yes				
	n = 85	%	*n* = 85	%	OR	95% CI	*p*
Dialysis							
No	64	(45.1)	78	(54.9)	0.274	0.109–0.684	0.004[a]
Yes	21	(75.0)	7	(25.0)			
Smoker							
No	72	(50.3)	71	(49.7)	1.092	0.480–2.487	0.834[a]
Yes	13	(48.1)	14	(51.9)			
Radiofrequency ablation							
No	84	(52.5)	76	(47.5)	9.947	1.231–80.356	0.009[a]
Yes	1	(10.0)	9	(90.0)			
Transarterial chemoembolization							
No	84	(52.8)	75	(47.2)	11.200	1.401–89.567	0.005[a]
Yes	1	(9.1)	10	(90.9)			
Coronary artery bypass graft							
No	84	(49.7)	85	(50.3)	0.497	0.427–0.578	>0.99[b]
Yes	1	(100.0)	0	(0.0)			
History of surgery or blood transfusion							
No	76	(51.0)	73	(49.0)	1.388	0.552–3.490	0.484[a]
Yes	9	(42.9)	12	(57.1)			
Alcohol							
No	84	(50.0)	84	(50.0)	1.000	0.062–16.253	>0.99[b]
Yes	1	(50.0)	1	(50.0)			

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio.
[a]Chi-squared test.
[b]Fisher's exact test.

The results of a large population-based study conducted in South Korea, which included over 47,000 patients infected with CHC and had a median age of 57 years, revealed that 84.8% of the study population had one or more comorbid conditions. The most frequent comorbidities observed were hypertension, esophagitis or gastroesophageal reflux disease, dyslipidemia, diabetes mellitus, peptic ulcer, and gastrointestinal ulcer. Additionally, a majority of the patients were using one or more concomitant medications, and 97% of the population required either a dose reduction or additional monitoring to prevent potential DDIs. Pain-relieving agents were the

TABLE 6 Association of cirrhosis with HCV clearance and change of treatment.

	Cirrhosis						
	No		Yes				
	n = 61	%	*n* = 109	%	OR	95% CI	*p*
Clearance							
No	36	(42.4)	49	(57.6)	1.763	0.93–3.33	0.079
Yes	25	(29.4)	60	(70.6)			
Change of treatment							
No	59	(39.6)	90	(60.4)	6.228	1.40–27.73	0.007
Yes	2	(9.5)	19	(90.5)			

Note: Chi-squared test.

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio.

most commonly used medications, followed by gastrointestinal agents and antibiotics. The conflicting findings between the South Korean study and the present analysis regarding the profiles of comorbidities and concomitant medications could be attributed to differences in disease prevalence and the predominant HCV genotypes.[26]

In our study, we observed that 85 out of the CHC patients (50%) achieved CHC clearance after initiating therapy. We found a significant association between CHC clearance and certain medical conditions. Specifically, hypothyroidism showed a direct correlation with CHC clearance, while diabetes mellitus and renal diseases showed an inverse correlation. This means that the presence of diabetes and renal diseases reduced the likelihood of achieving CHC clearance, whereas the presence of hypothyroidism increased the likelihood. Hypothyroidism is a well-established extrahepatic complication of CHC infections, as supported by previous studies.[27–30] When thyroid hormone levels are low, it promotes the deposition of fat in the liver, impairing its ability to efficiently metabolize fat and increasing the risk of nonalcoholic fatty liver disease (NAFLD). Additionally, hypothyroidism also increases the risk of developing insulin resistance, which is another risk factor for NAFLD.

The relationship between HCV infection and diabetes is complex, involving overlapping pathophysiology and interdependent disease courses.[31,32] Seroprevalence of HCV is higher in diabetic patients,[33] although other studies have reported similar rates.[34] Furthermore, the prevalence of type 2 diabetes (T2D) is higher in individuals infected with HCV compared to uninfected individuals. The risk of HCV infection is also higher in diabetic patients compared to nondiabetics, and HCV infection itself is a risk factor for developing diabetes, particularly in individuals over 40 years of age.[35,36] This increased risk is primarily due to peripheral insulin resistance.[37] Insulin resistance has been suggested to impair SVR.[38] In fact, chronic HCV infection progresses to cirrhosis and HCC more rapidly in diabetic individuals compared to nondiabetic individuals.[33] Liver-related outcomes, including response to antiviral treatment and progression to fibrosis and cirrhosis, are more pronounced in diabetic patients.[39] However, it has been observed that glycometabolism improves after HCV eradication and achieving SVR.[40,41] It is not yet known if the presence of diabetes impacts the clearance of HCV. Achieving SVR is equally possible in both diabetic and nondiabetic patients.[42] However, T2D accelerates the progression of CHC and increases the risk of extrahepatic complications such as nephropathy and ischemic stroke.[43]

Several studies have examined the complex association between comorbid conditions and CHC clearance and progression.[16,44,45] However, our finding of a higher chance of HCV clearance among patients with hypothyroidism contradicts established evidence that links hypothyroidism to a more challenging CHC course, particularly with older treatment approaches involving IFN and ribavirin-based regimens.[46,47] This inconsistency is supported by the report by Jansen et al., where PPIs were not found to be significantly associated with CHC clearance, opposite to our finding. However, similar findings have been reported for cirrhosis.[48]

Similar to the study by Ortiz et al., the exploration of DAAs in chronic renal disease remains challenging due to the excretion of some of these drugs by the kidneys, which may increase the potential for toxicities.[49] In a related condition, poor glycemic control and diabetes have been reported as negative predictors of CHC clearance and are associated with a higher risk of DAA failure.[50]

Interestingly, we observed that patients using levothyroxine, a synthetic thyroid hormone used to treat hypothyroidism, were more likely to clear CHC, thus supporting the previously mentioned direct association with hypothyroidism. This finding is in line with the results reported by González-Colominas et al., where the use of statins and antihypertensives was significantly associated with CHC clearance.[26]

In our study, RFA and TACE of HCC were significantly associated with CHC clearance. Both RFA and TACE demonstrated better prognosis and higher local control compared to either procedure alone.[51]

Patients undergoing hemodialysis have a lower likelihood of clearing HCV infection after starting therapy. This reduced clearance may be due to changes in cytokine concentration associated with HCV persistence and severity,[52] or limitations in prescribing effective direct-acting antivirals DAAs.[53] Long-term studies have demonstrated decreased HCV-RNA levels and clearance in hemodialysis patients compared to controls.[54–56]

Apparent limitations of the current study include the limited number of cases and the lack of data on vital study variables such as genotype, the specific CHC regimen, and the criteria of CHC clearance. One major limitation is the inability to establish causality and temporality. Cross-sectional studies provide a snapshot of data at a specific point in time, making it difficult to determine the sequence of events. Without longitudinal follow-up, it is challenging to establish whether the comorbid conditions or chronic medications preceded the treatment plan for CHC infection or vice versa. Additionally, cross-sectional studies may lack the ability to adequately control for potential confounders, such as age and gender. While these factors may be measured in a cross-sectional study, they

cannot be manipulated or controlled for in the same way as in experimental or longitudinal studies. This limitation can introduce bias and make it challenging to establish a direct relationship between the exposures and outcomes of interest. However, since this is the first study in this area, further thorough investigations are needed to determine more precisely the role of patients' demographics and health conditions in the progression of complicated liver and systemic disease in CHC individuals.

5 | CONCLUSION

Most patients with CHC had comorbid conditions and were taking chronic medications. While the frequency of changes in the CHC regimen did not show an association with CHC clearance, it is important to consider the impact of comorbidities, CHC complications (such as liver cirrhosis), chronic medications, and other risk factors during the treatment of CHC infection.

AUTHOR CONTRIBUTIONS

Abdullah Awadh: Conceptualization; data curation; methodology; project administration; supervision; validation; visualization; writing—original draft; writing—review and editing. **Ziyad Badri**: Investigation; methodology; visualization; writing—original draft. **Nayef Alansari**: Investigation; methodology; visualization; writing—original draft. **Ahmed Alkhiri**: Investigation; methodology; visualization; writing—original draft. **Hussein Baharoon**: Investigation; methodology; visualization; writing—original draft. **Abdelulah Niaz**: Investigation; methodology; visualization; writing—original draft. **Alaa Al-Kathiri**: Investigation; methodology; resources; software; visualization; writing—original draft. **Enas Ghulam**: Conceptualization; formal analysis; methodology; software; validation; writing—original draft; writing—review and editing. **Mohammad Khan**: Conceptualization; formal analysis; methodology; software; validation; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in OSF at https://doi.org/10.17605/OSF.IO/MZ925.

TRANSPARENCY STATEMENT

The lead author Abdullah Awadh affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Hudson B, Walker AJ, Irving WL. Comorbidities and medications of patients with chronic hepatitis C under specialist care in the UK. *J Med Virol*. 2017;89(12):2158-2164.
2. Petta S, Craxì A. Extrahepatic manifestations of chronic viral C hepatitis. *Gastroenterol Clin North Am*. 2020;49(2):347-360.
3. World Health Organization. Hepatitis C. 2023. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c2021
4. Aljumah A, Abaalkhail F, Al-Ashgar H, et al. Epidemiology, disease burden, and treatment strategies of chronic hepatitis C virus infections in Saudi Arabia in the new treatment paradigm shift. *Saudi J Gastroenterol*. 2016;22(4):269-281.
5. Ministry of Health in Saudi Arabia. National Program to Eradicate HCV and Achieve the Global Objective. 2018. https://www.moh.gov.sa/en/Ministry/MediaCenter/News/Pages/news-2018-04-09-001.aspx
6. El-Zayadi AR. Hepatitis C comorbidities affecting the course and response to therapy. *World J Gastroenterol*. 2009;15(40):4993-4999.
7. Talavera Pons S, Boyer A, Lamblin G, et al. Managing drug-drug interactions with new direct-acting antiviral agents in chronic hepatitis C. *Br J Clin Pharmacol*. 2017;83(2):269-293.
8. Drazilova S, Gazda J, Janicko M, Jarcuska P. Chronic hepatitis C association with diabetes mellitus and cardiovascular risk in the era of DAA therapy. *Can J Gastroenterol Hepatol*. 2018;2018:6150861.
9. Tagliapietra M, Monaco S. Neuroimaging findings in chronic hepatitis C virus infection: correlation with neurocognitive and neuropsychiatric manifestations. *Int J Mol Sci*. 2020;21(7):2478.
10. Khan MU, Mahmoud MI, Butt AA. Hepatitis c virus and chronic kidney disease. *Expert Rev Gastroenterol Hepatol*. 2020;14(7):579-590.
11. Mathew S, Faheem M, Ibrahim SM, et al. Hepatitis C virus and neurological damage. *World J Hepatol*. 2016;8(12):545-556.
12. Adinolfi LE, Nevola R, Rinaldi L, Romano C, Giordano M. Chronic hepatitis C virus infection and depression. *Clin Liver Dis*. 2017;21(3):517-534.
13. Nevola R, Acierno C, Pafundi PC, Adinolfi LE. Chronic hepatitis C infection induces cardiovascular disease and type 2 diabetes: mechanisms and management. *Minerva Med*. 2021;112(2):188-200.
14. Gabr SA, Alghadir AH. Handgrip strength and vitamin D as predictors of liver fibrosis and malnutrition in chronic hepatitis C patients. *Dis Markers*. 2021;2021:1-13.
15. Song HJ, Jiang X, Henry L, Nguyen MH, Park H. Proton pump inhibitors and risk of liver cancer and mortality in patients with chronic liver disease: a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2020;76(6):851-866.
16. Chen JY, Ren Y, Yan P, Belina ME, Chung RT, Butt AA. Tricyclic antidepressant use and the risk of fibrosis progression in hepatitis C-infected persons: results from ERCHIVES. *J Viral Hepatitis*. 2018;25(7):825-833.
17. Chung JW, Choi HY, Ki M, Jang ES, Jeong SH. Comorbidities and prescribed medications in Korean patients with chronic hepatitis C: a nationwide, population-based study. *Gut Liver*. 2021;15(2):295-306.
18. Corouge M, Vallet-Pichard A, Pol S. HCV and the kidney. *Liver Int*. 2016;36(Suppl 1):S28-S33.

19. Solitano V, Plaz Torres MC, Pugliese N, Aghemo A. Management and treatment of hepatitis C: are there still unsolved problems and unique populations? *Viruses*. 2021;13(6):1048.
20. Berkan-Kawińska A, Piekarska A, Janczewska E, et al. Real-world effectiveness and safety of direct-acting antivirals in patients with cirrhosis and history of hepatic decompensation: Epi-Ter2 Study. *Liver Int*. 2021;41(8):1789-1801.
21. Cheng TS, Liang PC, Huang CF, et al. Real-world effectiveness of direct-acting antiviral agents for chronic hepatitis C patients with genotype-2 infection after completed treatment. *Kaohsiung J Med Sci*. 2021;37(4):334-345.
22. Belperio PS, Shahoumian TA, Loomis TP, Backus LI. Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir in 573 direct-acting antiviral experienced hepatitis C patients. *J Viral Hepatitis*. 2019;26(8):980-990.
23. Elhence A, Singh A, Anand A, et al. Real-world re-treatment outcomes of direct-acting antiviral therapy failure in patients with chronic hepatitis C. *J Med Virol*. 2021;93(8):4982-4991.
24. Smith DA, Bradshaw D, Mbisa JL, et al. Real world SOF/VEL/VOX retreatment outcomes and viral resistance analysis for HCV patients with prior failure to DAA therapy. *J Viral Hepatitis*. 2021;28(9):1256-1264.
25. Xie J, Xu B, Wei L, Huang C, Liu W. Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir as a hepatitis C virus infection salvage therapy in the real world: a systematic review and meta-analysis. *Infect Dis Ther*. 2022;11(4):1661-1682.
26. González-Colominas E, Batlle M, Monge-Escartín I, et al. Impact of HCV cure with drug-acting antivirals in the use of concomitant medication and lipid profile: follow-up data 2 years after the sustained virological response. *Eur J Gastroenterol Hepatol*. 2021;32(2):214-222.
27. Pavan MHP, Pavin EJ, Gonçales Jr, FL, Zantut-Wittmann DE. Virus C genotype predisposes to primary hypothyroidism during interferon-α treatment for chronic hepatitis C. *Braz J Infect Dis*. 2011;15(5):449-456.
28. Batool N, Elahi S, Saleem N, Ashraf A. Thyroid dysfunction in non-interferon treated hepatitis C patients residing in hepatitis endemic area. *BioMed Res Int*. 2017;2017:2390812.
29. Wang H, Liu Y, Zhao Y. The association of hepatitis C virus infection and thyroid disease: a systematic review and meta-analysis. *Int J Biol Markers*. 2021;36(4):3-9.
30. Antonelli A, Ferri C, Pampana A, et al. Thyroid disorders in chronic hepatitis C. *Am J Med*. 2004;117(1):10-13.
31. Vanni E, Bugianesi E, Saracco G. Treatment of type 2 diabetes mellitus by viral eradication in chronic hepatitis C: myth or reality? *Dig Liver Dis*. 2016;48(2):105-111.
32. Hum J, Jou JH. The link between hepatitis C virus and diabetes mellitus: improvement in insulin resistance after eradication of hepatitis C virus. *Clin Liver Dis*. 2018;11(3):73-76.
33. Kambale Kombi P, Batina Agasa S, Mbo Mukonkole JP, Bolukaoto Bome L, Atoba Bokele C, Kayembe Tshilumba C. Seroprevalence of hepatitis B and C virus infections among diabetic patients in Kisangani (North-eastern Democratic Republic of Congo). *Pan Afr Med J*. 2018;31:160.
34. Costa LMFC, Mussi ADH, Brianeze MR, Souto FJD. Hepatitis C as a risk factor for diabetes type 2: lack of evidence in a hospital in central-west Brazil. *Braz J Infect Dis*. 2008;12(1):24-26.
35. Mehta SH, Brancati FL, Sulkowski MS, et al. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med*. 2000;133(8):592-599.
36. Guo X, Jin M, Yang M, Liu K, Li J. Type 2 diabetes mellitus and the risk of hepatitis C virus infection: a systematic review. *Sci Rep*. 2013;3:2981.
37. Gastaldi G, Gomes D, Schneiter P, et al. Treatment with direct-acting antivirals improves peripheral insulin sensitivity in non-diabetic, lean chronic hepatitis C patients. *PLoS One*. 2019;14(6):e0217751.
38. Ashfaq UA, Khalid H. Mechanism of hepatitis C virus-induced diabetes mellitus. *Crit Rev Eukaryot Gene Expr*. 2017;27(4):363-371.
39. Desbois AC, Cacoub P. Diabetes mellitus, insulin resistance and hepatitis C virus infection: a contemporary review. *World J Gastroenterol*. 2017;23(9):1697-1711.
40. Yuan M, Zhou J, Du L, Yan L, Tang H. Hepatitis C virus clearance with glucose improvement and factors affecting the glucose control in chronic hepatitis C patients. *Sci Rep*. 2020;10(1):1976.
41. Ribaldone DG, Sacco M, Saracco GM. The effect of viral clearance achieved by direct-acting antiviral agents on hepatitis C virus positive patients with type 2 diabetes mellitus: a word of caution after the initial enthusiasm. *J Clin Med*. 2020;9(2):563.
42. Angel M, Petrosyan Y, Doyle MA, Cooper C. HCV infection characteristics, treatment uptake and outcomes in patient with diabetes mellitus. *BMC Endocr Disord*. 2022;22(1):277.
43. Gastaldi G, Goossens N, Clément S, Negro F. Current level of evidence on causal association between hepatitis C virus and type 2 diabetes: a review. *J Adv Res*. 2017;8(2):149-159.
44. Chang YK, Tseng YT, Chen KH, Chen KT. Long-term outcomes and risk factors of thyroid dysfunction during pegylated interferon and ribavirin treatment in patients with chronic hepatitis C infection in Taiwan. *BMC Endocr Disord*. 2019;19(1):36.
45. Kozielewicz D, Wietlicka-Piszcz M, Halota W. Long-term outcomes of thyroid dysfunction in patients with chronić hepatitis C treated with pegylated interferon alpha and ribavirin. *Przegl Epidemiol*. 2017;71(4):555-569.
46. Fernández J, Acevedo J, Castro M, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology*. 2012;55(5):1551-1561.
47. Fernández J, Navasa M, Gómez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology*. 2002;35(1):140-148.
48. Cruz RCR, Tanajura D, Almeida D, Cruz M, Paraná R. Urinary tract infection in non-hospitalized patients with cirrhosis and no symptoms of urinary tract infection: a case series study. *Braz J Infect Dis*. 2006;10(6):380-383.
49. Ortiz GA, Trivedi HD, Nader C. Pharmacokinetics and drug interactions of medications used to treat hepatitis C virus infection in the setting of chronic kidney disease and kidney transplantation. *Hemodial Int*. 2018;22(Suppl 1):S22-S35.
50. Pabjan P, Brzdęk M, Chrapek M, et al. Are there still difficult-to-treat patients with chronic hepatitis C in the era of direct-acting antivirals? *Viruses*. 2022;14(1):96.
51. Izumi N. Recent advances of radiofrequency ablation for early hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2011;26(Suppl 1):S115-S122.
52. Kalantar-Zadeh K, Daar ES, Eysselein VE, Miller LG. Hepatitis C inflection in dialysis patients: a link to poor clinical outcome? *Int Urol Nephrol*. 2007;39(1):247-259.
53. Fabrizi F, Messa P, Martin P. Recent advances on hepatitis C virus in dialysis population. *Kidney Blood Press Res*. 2014;39(4):260-271.
54. Furusyo N, Hayashi J, Ariyama I, et al. Maintenance hemodialysis decreases serum hepatitis C virus (HCV) RNA levels in hemodialysis patients with chronic HCV infection. *Am J Gastroenterol*. 2000;95(2):490-496.
55. Okuda K, Yokosuka O. Natural history of chronic hepatitis C in patients on hemodialysis: case control study with 4-23 years of follow-up. *World J Gastroenterol*. 2004;10(15):2209-2212.

56. Jansen JW, Linneman TW, Powderly GM, Moenster RP, Nayak L. Association between baseline creatinine clearance and treatment failure in patients with hepatitis C virus treated with ledipasvir and sofosbuvir. *Open Forum Infect Dis*. 2019;6(3):ofz087.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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