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Original Research Article

A Cross-Sectional Study on Association between Liver Function Tests and Extra-Hepatic Manifestations in Patients with Chronic HCV Infection and HCV-HIV Co-Infection among Selected Manipuri Population

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Abstract

Introduction: Hepatitis C virus (HCV) is one of the five hepatitis virus (A-E) that primarily targets the liver. In individuals infected with HIV, HCV represents an important contributor to liver-related morbidity. Beyond hepatic involvement, hepatitis C infection is associated with several extra-hepatic manifestations (EHM) throughout its natural course. In patients with chronic HCV infection, deterioration in liver function tests has been reported to correlate strongly with the severity of extra hepatic complications.

Aim and Objectives: This study aims to document the spectrum of extra-hepatic manifestations among patients with chronic HCV infection and HCV-HIV co-infection. Additionally, the study aimed to evaluate the association between liver function test parameters and the presence of extra-hepatic manifestations.

Materials and Methods: This cross-sectional study included 60 participants, comprising 30 patients diagnosed with chronic HCV infection and 30 patients with HIV–HCV co-infection. The study was conducted in Manipur, India, between August 2022 and February 2023, and included individuals aged 18 years and above. Patients with concurrent hepatitis B virus (HBV) infection, malignancy, or established cardiovascular disease were excluded.

All participants underwent detailed clinical evaluation. Laboratory investigations included routine tests such as Random Blood Sugar (RBS), Fasting Blood Sugar (FBS), Postprandial Blood Sugar (PPBS), Liver Function Tests (LFT), Kidney Function Tests (KFT) with serum electrolytes, Complete Blood Count (CBC), Prothrombin Time/International Normalized Ratio (PT/INR), lipid profile, Thyroid Stimulating Hormone (TSH) levels, routine urine examination, Anti-Nuclear Antibody (ANA), Rheumatoid Factor (RF), chest X-ray, and ultrasonography (USG) of the abdomen.

Statistical analysis was performed using SPSS version 16. Descriptive statistics were expressed as mean, standard deviation, and percentages. Inferential analysis was carried out using the chi-square test and Fisher's exact test. A p-value was considered statistically significant if its less than 0.05

Results: Among the 30 patients with chronic HCV infection and the 30 patients with HIV–HCV co-infection, most individuals with chronic HCV belonged to the 31–40-year age group, accounting for 50% of cases. In contrast, the majority of patients with HIV–HCV co-infection was in the 41–50-year age group, representing 80% of cases.

Extra-hepatic manifestations were observed more frequently in the HIV–HCV co-infected group (73.4%, 22/30) compared to the chronic HCV group (63.4%, 19/30). Additionally, reduced serum albumin levels were significantly more common in the co-infected group, which may explain the higher occurrence of extra-hepatic manifestations in these patients compared to those with chronic HCV alone.

Conclusion: The findings of this study demonstrate a considerable prevalence of extra-hepatic manifestations among patients with chronic HCV infection as well as those with HIV–HCV co-infection in the Manipuri population. Furthermore, the occurrence of these manifestations appears to be associated with decreased serum albumin levels.

Keywords: Hepatitis C virus, Human Immunodeficiency Virus, Extra-hepatic manifestations, Liver function tests.

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Introduction

Hepatitis C virus (HCV) is one of the five recognized hepatitis virus (A-E) that primarily infects the liver. It is an enveloped single-stranded, positive-sense RNA virus classified under the genus Hepacivirus within the family Flaviviridiae. [1] HCV represents a major contributor to liver-related morbidity, particularly among individuals living with HIV infection. [2] In addition to hepatic injury, HCV infection is associated with a broad range of extra-hepatic manifestations (EHM) during its natural course.

The pathogenesis of extra-hepatic complications is multifactorial. HCV is capable of replicating in tissues beyond the liver and expressing viral proteins within extra-hepatic sites, thereby contributing directly to systemic involvement. A key characteristic of HCV infection is its ability to evade immune clearance, which facilitates chronicity. Furthermore, HCV demonstrates lymphotropism in addition to hepatotropism, which plays a significant role in the development of many extra-hepatic disorders [4].

Among the various extra-hepatic conditions, mixed cryoglobulinemia (MC) is the most extensively studied and frequently reported syndrome linked to chronic HCV infection. Patients commonly present with nonspecific symptoms such as fatigue, joint pain, and generalized weakness. Cutaneous involvement occurs in the majority of cases (approximately 95%), typically manifesting as vasculitis. Viral antigens have been identified in nearly 40% of skin lesions. Renal involvement is also common, occurring in 35–60% of patients with cryoglobulinemia related to chronic HCV. The most characteristic renal pathology observed is membranoproliferative glomerulonephritis [4]. Chronic HCV infection has been implicated in the development of several systemic disorders, including type 2 diabetes mellitus, sialadenitis, autoimmune thyroid disorders such as hypothyroidism, B-cell non-Hodgkin lymphoma, thrombocytopenia, idiopathic pulmonary fibrosis, and Mooren's corneal ulcer [4,5].

Because HIV and HCV share similar transmission pathways, co-infection is common; approximately one-third of individuals infected with human immunodeficiency virus type 1 (HIV-1) are also chronically infected with HCV.

The presence of HIV significantly alters the clinical course of HCV-related liver disease [6]. Compared to patients with HCV mono-infection, those with HIV–HCV co-infection tends to experience more rapid progression of hepatic fibrosis. HIV infection contributes to increased viral persistence, accelerated fibrotic changes, earlier onset of cirrhosis, and a greater likelihood of progression to end-stage liver disease. [7]

Manipur is recognized as one of the seven Indian states with a high prevalence of HIV infection. Although many HIV-positive individuals receive free antiretroviral therapy (ART) through designated ART centres, access to HCV-specific treatment remains limited for many patients. Consequently, chronic HCV infection often progresses and leads to significant complications.

Aims and Objectives

1. To document the extra-hepatic manifestations in patients with Chronic HCV infection and HCV-HIV co-infection
2. To determine any correlation between liver function test and the extra-hepatic manifestations.

Materials and Methods

Study Design: Cross sectional study conducted in the Department of General Medicine and ART centre District Hospital Churachandpur in collaboration with Department of Biochemistry, Churachandpur Medical College, and Manipur.

Study Duration: Six months with effect from August 2022 to February 2023

Study population: All chronic HCV patients and all HCV patients co-infected with HIV attending the Department of Medicine Churachandpur Medical College, Manipur and ART centre, District Hospital Churachandpur formed the study population.

Sample Size: A minimum of 60 patients out of which 30 are chronic HCV patients and 30 are HIV-HCV co-infected patients was taken to the study.

Inclusion Criteria:

- Age ≥ 18years
- All Chronic HCV infected patients
- All HCV patients co-infected with HIV and those patients who give informed consent

Exclusion Criteria:

- Patients co-infected with HBV infection.
- Patients known to have malignancy, cardiovascular disease.

Materials and Methods

The research was conducted after obtaining approval from the Institutional Ethics Committee, and written informed consent was secured from

every participant. All enrolled participants underwent a detailed clinical assessment. The following information and investigations were recorded and performed:

Routine Laboratory investigations included: Random Blood Glucose (RBG), Fasting Blood Glucose (FBG), Postprandial Blood Glucose (PPBG), Liver Function Tests (LFT), Renal Function Tests (RFT) along with serum electrolytes, Complete Blood Count (CBC), Prothrombin Time/International Normalized Ratio (PT/INR)

Additional investigations: Lipid profile, Thyroid Stimulating Hormone (TSH) estimation, Routine urine examination, Antinuclear antibody (ANA) test, Rheumatoid factor (RF), Chest radiography, Ultrasonography (USG) of the abdomen, Fine Needle Aspiration Cytology (FNAC) of lymph nodes, when indicated, Bone marrow biopsy, if clinically required and Renal biopsy, if necessary.

Study Variables: HIV Infection Status: The presence of HIV infection was established in accordance with the National AIDS Control Organization (NACO) guidelines (2008). Diagnosis was confirmed using three different rapid/ELISA-based test kits. The testing kits employed were:

CombAids – Based on the dot immunoassay principle, Tridot – Based on immunofiltration, SD Bioline HIV 1/2 3.0 – Based on immunochromatographic method.

Hepatitis C Virus (HCV) Infection: HCV infection was determined by detecting anti-HCV antibodies using a third-generation ELISA method (Flaviscreen).

Statistical Analysis: The collected data were processed and analysed using SPSS software (version 16). Descriptive statistical measures, including mean, standard deviation, and percentages, were applied. For inferential analysis, the chi-square test and Fisher's exact test were utilized where appropriate. A p-value of less than 0.05 was regarded as statistically significant.

Results and Observation

Table 1: Distribution of respondents by age

Age in years	HCV	HCV+HIV infection	Total	Fisher exact test
31-40*	15 (50.0)	0 (0.0)	15 (25.0)	Value=1.18 p-0.47
41-50*	12 (40.0)	24 (80.0)	36 (60.0)	
>50	3 (10.0)	6 (20.0)	9 (15.0)	
	30 (100.0)	**30 (100.0)**	**60 (100.0)**	
Mean ±SD	43.3±5.6	45±5.3	44.5 ±5.58	t= -1.691, p-0.09

Majority of the HCV infected patients were from the age group 31-40 years which accounted for 50% of cases while majority of the HIV/HCV co-infection were from the age group 41-50 years which accounted for 80% of cases as shown in table 1 and figure 1. The mean age of the study population was 43.3±5.6 for chronic HCV group and 45±5.3 for HCV/HIV co-infection group. Age group in the two groups were comparable as the difference observed is insignificant (p>0.05).

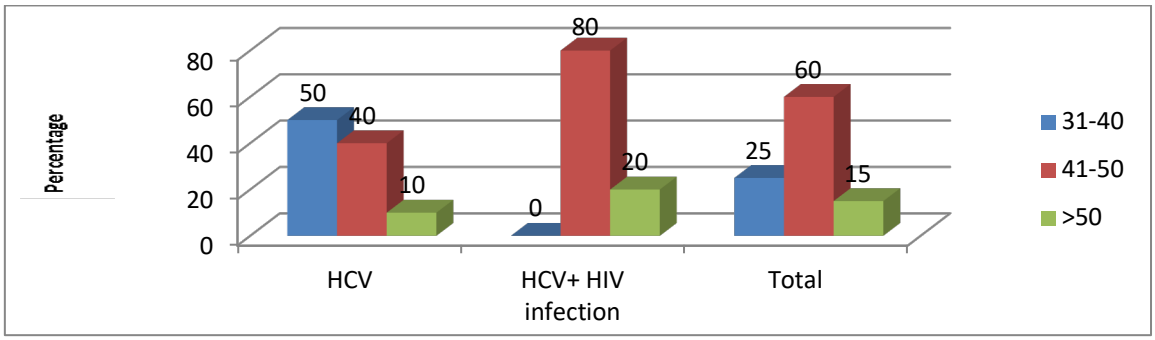

Figure 1: Bar diagram showing age distribution of the respondents

Table 2: Distribution of respondents by sex

Sex	HCV (%)	HCV+HIV infection (%)	Total (%)	Chi square test
Male	21 (70.0)	18 (60.0)	39 (65.0)	Value=0.417 p-0.589
Female	9 (30.0)	12 (40.0)	21 (35.0)	
	30 (100.0)	**30 (100.0)**	**60 (100.0)**	

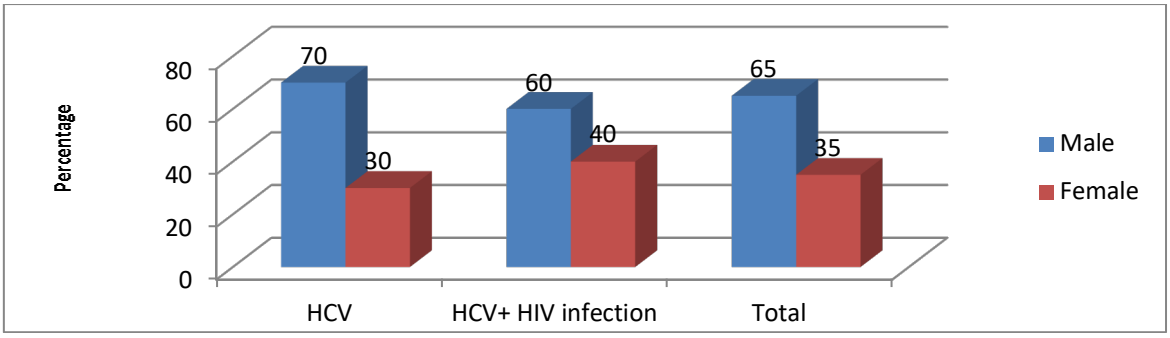

Figure 2: Bar diagram showing sex distribution of the respondents

Of the total 60 patients 39 were male and 21 were female, M: F ratio of 1.8:1. In the chronic HCV group 21 (70%) were male and 9 (30%) were female and in HCV/HIV co-infection group 18 (60%) were male and 12 (40%) were female. Table 2 and figure 2 showed that there is no significant difference in sex wise distribution between the two groups.

Table 3: Distribution of respondents by alcohol consumption stratified by co-infection

Alcohol consumption	HCV	HCV+ HIV infection	Total	Chi square test
Yes	19 (63.3)	12 (40.0)	31 (51.6)	Value=3.27
No	11 (36.7)	18 (60.0)	29 (48.4)	p-0.07
	30 (100.0)	**30 (100.0)**	**60 (100.0)**	

There is some difference observed in alcohol consumption between the two groups (63.3% vs. 40%) but it is found to be statistically insignificant (p>0.05).

Table 4: Prevalence of extra-hepatic manifestations

Groups	Extrahepatic manifestations	No extrahepatic manifestations	Total
HCV only	19 (63.4)	11 (36.6)	30 (100.0)
HCV/HIV co infection	22 (73.4)	8 (26.6)	30 (100.0)
	41 (68.3)	**19 (31.7)**	**60 (100.0)**

Chi-square=0.693, p=0.405

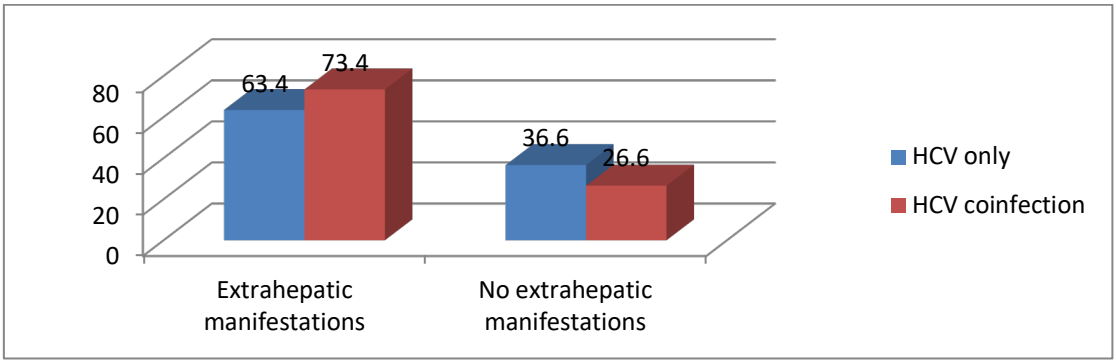

Figure 3: Bar diagram showing prevalence of extrahepatic manifestations

At least one extra-hepatic manifestation was identified in 63.4% (19/30) of the patients in the chronic HCV group and 73.4 % (22/30) of the patients in the HCV/HIV co-infection group. The difference between the prevalence of extra-hepatic manifestations between the two group was not statistically significant with p = 0.405.

Table 5: Distribution of respondents by signs and symptoms

Signs and symptoms	HCV (%)	HCV+ HIV coinfection (%)	Number	Chi square test/ Fisher exact test
Fatigue	20 (66.7)	27 (90.0)	47 (78.3)	Value=4.812 p-0.028
Arthralgia	15 (50.0)	12 (40.0)	27 (33.0)	Value=0.606 p-0.604
Peripheral neuropathy	10 (33.3)	12 (40.0)	22 (36.7)	Value=0.287 p-0.789
Bleeding gum	4 (13.3)	6 (20.0)	10 (16.7)	Value =0.480

				p-0.488
Decreased urine output	6 (20.0)	3 (10.0)	9 (15.0)	Value=1.17 p-0.278
Skin lesions	0 (0.0)	4 (13.3)	4 (6.7)	Value=4.2 p-0.038
Sicca syndrome	0 (0.0)	3 (10.0)	3 (5.0)	Value=3.15 p-0.076
Weight loss	0 (0.0)	3 (10.0)	3 (5.0)	Value=3.15 p-0.076
Epistaxis	0 (0.0)	3 (10.0)	3 (5.0)	Value=3.15 p-0.076

The commonest presenting symptom in patients with chronic HCV infection was fatigue present in 66.7% of cases followed by arthralgia (50%), peripheral neuropathy (33.3%) and decreased urine output (20%). While in the HCV/HIV co-infection group they were fatigue (90%), arthralgia (40%), peripheral neuropathy (40%), skin lesions (13.3%) and decreased urine output (10%). Chance of skin lesion was statistically more among the HCV/HIV co infection group than the chronic HCV group (p = 0.038).

There was no statistically significant difference between the two groups in case of other signs and symptoms.

Table 6: Distribution of respondents by hemogram finding

Hemogram	HCV (%)	HCV/HIV coinfection (%)	Chi-square test/ fisher exact test
Hemoglobin			
Low	27 (90.0)	29 (96.6)	Value=1.07
Normal	3 (10.0)	1 (3.4)	p-0.6
Platelet			
Low	6 (22.2)	14 (46.7)	Value=4.72
Normal	24 (72.7)	16 (53.3)	p-0.029
	30 (100.0)	30 (100.0)	

27 out of the 30 patients (90%) of the chronic HCV group had low haemoglobin (Hb < 12 g/dl) while 29 out of 30 patients (96.6%) of the HCV/HIV co-infection group had low haemoglobin. The difference between the two groups was not statistically significant (p>0.05). 22.2 % of the patients with chronic HCV only and 46.7% of the patients with HCV/HIV co-infection had thrombocytopenia.

Platelet count was significantly lower in HCV/HIV co infection group than HCV group (p<0.05).

Table 7: Distribution of respondents by liver function test

Liver function test	HCV infection (%)	HCV-HIV coinfection (%)	Chi-square test/fisher exact test
Serum bilirubin			
High	27 (90.0)	30 (100.0)	Value=0.076
Normal	3 (10.0)	0 (0.0)	p-0.237
SGOT			
High	20 (66.6)	26 (86.6)	Value=3.35
Normal	10 (33.4)	4 (13.4)	p-0.12
SGPT			
High	19 (63.3)	22 (73.3)	Value=0.69
Normal	11(36.7)	8 (26.7)	p-0.57
Serum albumin			
Low	11 (63.3)	25 (83.3)	Value=13.6
Normal	19 (36.7)	5 (16.7)	p-0.000

Table 7: showed that percentage of patients with raised serum bilirubin and SGPT were almost comparable in both the two groups but patients with raised SGOT was higher in case of HCV/HIV co infection group compared to chronic HCV group but the finding was statistically insignificant (p>0.05). In case of serum albumin number of patients with low serum albumin were higher in case of HCV/HIV co infection group and the finding was statistically significant (p<0.05).

Table 8: Distribution of respondents by other biochemical tests

Other laboratory findings	HCV infection (%)	HCV+ HIV co infection (%)	Chi-square test/fisher exact test
Proteinuria	3(10.0)	1 (3.3)	Value = 3.15 p-0.076
Serum creatinine			
High	9 (30.0)	7(23.0)	Value = 0.287
Normal	21 (70.0)	23 (77.0)	p-0.789
Serum TSH			
High	2 (6.6)	3 (10.0)	Value = 0.22
Normal	28 (93.4)	27 (90.0)	p-1.00
Random blood sugar/ type 2 diabetes mellitus			
High	11 (36.7)	13 (43.3)	Value = 0.28
Normal	19 (63.3)	17 (56.7)	p-0.79
ANA			
Positive	24 (80.0)	27 (90.0)	Value = 1.18
Negative	6 (20.0)	3 (10.0)	p-0.47

There was no statistically significant difference between the groups in terms of number of patients with raised random blood sugar level, positive ANA, proteinuria and high serum TSH level with $p > 0.05$. The difference was statistically insignificant with $p > 0.05$.

Table 9: Distribution of respondents by Rh factor positivity

Rh factor	HCV (%)	HCV+ HIV infection (%)	Chi-square test
Positive	9 (30.0)	18 (60.0)	Value = 5.45
Negative	21 (70.0)	12 (40.0)	p-0.03
	30 (100.0)	**30 (100.0)**	

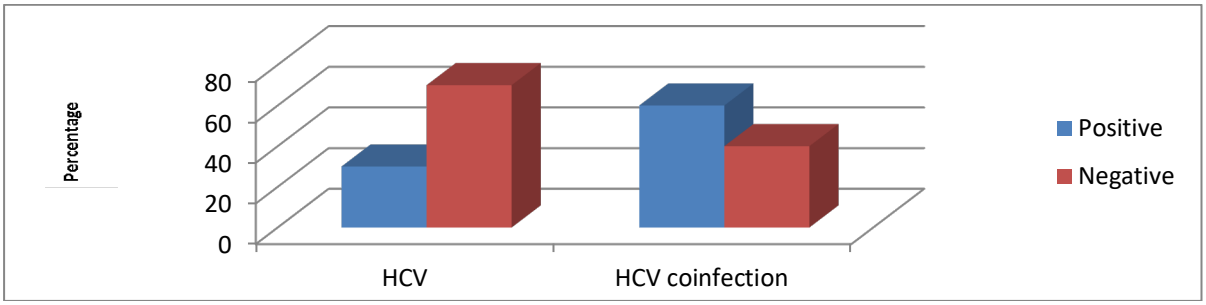

Figure 4: Bar diagram showing distribution of the respondents by Rh factor positivity

Table 10: Distribution of respondents by USG finding

USG finding	HCV (%)	HCV+ HIV coinfection (%)	Chi-square test
Hepatic parenchymal	24 (80.0)	24 (80.0)	**Not applicable**
Fatty liver	6 (20.0)	0 (0.0)	
Splenomegaly	0 (0.0)	6 (20.0)	
	30(100.0)	**30(100.0)**	

Hepatic parenchymal disease was common in both the groups. Fatty liver was more in HCV only group but splenomegaly was more in HCV/HIV co infection.

Table 11: Relation between EHMs and selected liver function parameters

Liver function parameters	Extra hepatic manifestations		Chi-square test/ fisher exact test
	Yes (%)	No (%)	
SGOT			Value=0.54
High	25 (61)	14 (73.7)	p-0.65
Normal	16 (39)	5 (26.3)	
SGPT			Value =0.00
High	21 (51.3)	13 (68.4)	p-0.80
Normal	20 (48.7)	6 (31.6)	
Serum albumin			Value=3.97
Low	34 (83)	12 (63)	p-0.046
Normal	7 (17)	7 (37)	
	41 (68.3)	**19 (31.7)**	

Table 11. Showed that most of the patients in the study group overall had low serum albumin i.e., < 3.5 mg/dl. In that 83% of the patients with presence of at least one extrahepatic manifestation had low serum albumin while 63% of patients without any extrahepatic manifestation had low serum albumin. Low serum albumin was associated more with patients with extrahepatic manifestation compared to patients without extrahepatic manifestation and it was found to be statistically significant (p=0.046). Raised SGOT and SGPT was found more in patients without extrahepatic manifestation compared to patients with extrahepatic manifestation. But the difference was found to be statistically insignificant (p>0.05).

Discussion

In this cross-sectional analysis, the majority of individuals with chronic HCV infection belonged to the 31–40 years age group (50%). In contrast, most patients in the HCV/HIV co-infected group were between 41–50 years of age (80%). HCV infection is often identified later during the course of HIV disease. The mean age was 43.3 ± 5.6 years in the chronic HCV group and 45 ± 5.3 years in the co-infected group. The two groups were comparable with respect to age distribution (p = 0.09). Similar findings were reported in a study by Shaikh MK et al. [8], where the average age among chronic HCV patients was 44.65 ± 8.66 years.

Extrahepatic manifestations were identified in 63% of patients with chronic HCV infection. In the HCV/HIV co-infected group, at least one extrahepatic manifestation was documented in 22 patients (73.4%), indicating a higher proportion compared to the HCV mono-infected group. However, this difference did not reach statistical significance (p > 0.05).

Fatigue emerged as the most commonly reported non-specific symptom among individuals with chronic HCV infection. In this study, 67% of patients in the chronic HCV group experienced fatigue. Similar observations have been documented in another research. Stefanova-Petrova DV et al [9]. Reported fatigue in 60% of patients with chronic HCV. However, the prevalence observed in the present study was considerably higher than that reported by Shaikh MK et al. [8], who found fatigue in only 20% of chronic HCV patients. The frequency of peripheral neuropathy in the present study was lower than that reported by Lee HY et al. [12], who documented paraesthesia in 44% of chronic HCV cases, and Abdelkader NA et al. [15], who reported a 46% prevalence among patients with HCV-related chronic liver disease. However, our findings were higher than those described in studies by Cacoub P et al. [9] (17%) and Stefanova-Petrova DV et al. [19] (20%).

Three patients exhibited demyelinating involvement—two with severe demyelination and one with a mixed axonal demyelinating pattern. Previous research by Cerry CL et al. [16] has suggested that HCV co-infection may play a significant role in the development of sensory neuropathy among individuals with HIV. Type 2 diabetes mellitus, defined as a random blood glucose level exceeding 200 mg/dL or documented diabetes under treatment, was identified in 36.7% of patients with chronic HCV infection [9,17,18,19]. The prevalence has been shown to be even higher up to 50% in patients with HCV-related liver cirrhosis [20,21].

The development of diabetes in HCV infection is thought to result from a complex interplay of insulin resistance, hepatic steatosis, and pro-inflammatory cytokine activity [23]. Studies have indicated an association between insulin resistance and increased liver stiffness [22]. In this study cohort, 10% of patients with chronic HCV exhibited proteinuria (urinary protein excretion exceeding 30 mg in 24 hours). Elevated serum creatinine levels (>1.3 mg/dL) were detected in 30% of patients, while 20% showed reduced urine output (<500 mL/day).

Elevated serum TSH levels (>5.00 mU/L), indicating thyroid dysfunction, were identified in 6.6% of individuals with chronic HCV infection and in 10% of those with HCV/HIV co-infection. The variation between the two groups was not statistically significant. Hypothyroidism has been documented in nearly 3.5% to 13% of patients with chronic HCV infection.

In the present study, analysis of liver function parameters demonstrated a statistically significant association (p<0.05) between extrahepatic manifestations and reduced serum albumin levels.

Conclusion

Out of the 30 individuals diagnosed with chronic HCV infection, 63.4% exhibited at least one extrahepatic manifestation. The most frequently reported symptom in this group was fatigue, followed by joint pain, peripheral neuropathy, diabetes mellitus, thrombocytopenia, and renal dysfunction.

Similarly, among the 30 patients with HCV/HIV co-infection, 73.4% presented with one or more extrahepatic features. In this group as well, fatigue was the predominant complaint. Other commonly observed conditions included thrombocytopenia, arthralgia, peripheral neuropathy, diabetes mellitus, dermatological lesions, and sicca syndrome.

The occurrence of extrahepatic manifestations showed a significant association with decreased serum albumin levels; however, no meaningful correlation was found with elevated SGOT or SGPT

levels. In summary, extrahepatic complications are commonly encountered in both chronic HCV infection and HCV/HIV co-infection. Furthermore, reduced serum albumin levels appear to be linked with the presence of these extrahepatic manifestations.

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