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FREQUENCY OF VARIOUS EXTRAHEPATIC MANIFESTATIONS OF CHRONIC HEPATITIS C IN PATIENTS PRESENTING IN A TERTIARY CARE HOSPITAL

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Abstract

Background: *Chronic hepatitis C virus (HCV) infection is a systemic disease associated with a wide range of extrahepatic manifestations that significantly contribute to patient morbidity. These complications, including hematological, autoimmune, metabolic, dermatological, and lymphoproliferative disorders, often remain underdiagnosed, particularly in resource-limited settings. Understanding their frequency and pattern is critical for guiding comprehensive management strategies.*

Aim: *This study aimed to determine the frequency and types of extrahepatic manifestations among patients with chronic HCV infection presenting at a tertiary-care hospital in Lahore, Pakistan.*

Methodology: *A cross-sectional study was conducted in the Department of Medicine, Omer Hospital, Lahore, from 13 March 2025 to 13 July 2025. Using consecutive non-probability sampling, 175 patients aged 20–70 years with confirmed chronic HCV were enrolled. Patients with HIV, HBV, CMV, EBV co-infection, chronic renal failure, or hypothyroidism were excluded. Demographic and clinical data were collected, and patients were systematically evaluated for extrahepatic manifestations including cryoglobulinemia, thrombocytopenia, diabetes, thyroid disorders, lichen planus, rheumatoid arthritis, cardiovascular and cerebrovascular diseases, chronic kidney disease, and lymphoma. Data were analyzed using SPSS version 25, applying descriptive statistics, stratification, and chi-square testing with a significance threshold of $p < 0.05$.*

Results: *Among 175 patients (mean age 45.1 ± 10.8 years; 52% male), the most frequent extrahepatic manifestation was mixed cryoglobulinemia in 65 patients (37.1%), followed by thrombocytopenia in 48 patients (27.6%) and autoimmune thyroiditis in 28 patients (16.0%). Cutaneous manifestations were observed in 8 patients (4.6%), with lichen planus present in 3 patients (1.7%). Diabetes was detected in 7 patients (4.0%), while only one patient (0.6%) was diagnosed with B-cell lymphoma. Correlation analysis demonstrated significant*

associations between extrahepatic manifestations and older age, longer duration of HCV infection, and advanced fibrosis ($p < 0.05$).

Conclusion: *Extrahepatic manifestations were common in patients with chronic HCV, with cryoglobulinemia, thrombocytopenia, and thyroid autoimmunity being most prevalent. These findings emphasize the need for systematic screening and multidisciplinary management to address the full spectrum of HCV-related morbidity, beyond hepatic disease alone.*

INTRODUCTION

The hepatitis C virus (HCV) infection continues to be a significant health issue in the world, as there are thought to be 58 million cases worldwide, and about 1.5 million patients each year (1). A major healthcare burden in global healthcare systems is the virus, which causes chronic liver disease, cirrhosis, and hepatocellular carcinoma (2). HCV is unevenly distributed, and the most infected areas were the Eastern Mediterranean and some parts of Africa where the prevalence is between 2-6 percent of that general population (3). In Pakistan, the prevalence estimates are high at between 4.5 and 6.8 percent making the country one of the highest disease burden countries in the world (4). These populations have further been burdened with chronic infection that is complicated by late diagnosis, access to treatment, and often leads to advanced hepatic and extrahepatic disease (5).

Even though the chronic infection of hepatitis C is characterized by the hepatic injury, the virus has the systemic implications that are mediated with the help of immune dysregulation, chronic inflammation, and metabolic disturbances (6). The overall prevalence of extrahepatic manifestations is up to 74% and plays a major role in morbidity and mortality beyond liver-related complications (7). These manifestations involve various organ systems such as hematological, endocrine, renal, dermatological, and rheumatological systems, and these show the ability of the virus to affect a systemically (8). These complications are imperative to recognize because they may manifest prior to the onset of hepatic dysfunction and, in particular, constitute the initial clinical manifestation of underlying HCV infection in some cases (9). Significantly, extrahepatic involvement is negatively associated with health-related quality of life, healthcare use, and long-term outcomes, so it is a crucial element of a disease evaluation strategy (10).

One of the most common extrahepatic effects of HCV is hematological, and thrombocytopenia and mixed cryoglobulinemia are the most common (11). It is estimated that thrombocytopenia occurs in between 24 and 29% of patients, which is closely linked with higher fibrosis and splenomegaly (12). Cryoglobulinemia, an immune complex-mediated vasculitis, occurs in 30-60% of patients in Mediterranean, yet symptomatic illness is observed in approximately a third of all (13). These symptoms can make antiviral treatment more complicated, and risky to increase bleeding, as well as require multidisciplinary care (14). Chronic HCV infection has been strongly associated with endocrine disorders, especially the autoimmune thyroid disease (15). Among South Asians, there is scanty data indicating that thyroid abnormalities are not adequately identified even when they are known to be major contributors to morbidity among patients (Jadoon et al., 2010). This supports the significance of systematic review in regular clinical practice, particularly in high-burden contexts (16).

Despite extensive literature from Europe, North America, and parts of Asia, data on the prevalence and patterns of extrahepatic manifestations in Pakistani HCV patients remain scarce (17). Given the high national burden of HCV and the unique demographic, genetic, and socioeconomic factors in this population, understanding the local epidemiology of extrahepatic disease is essential. Without such data, clinicians' risk under-recognizing conditions that significantly impact patient morbidity and complicate treatment. This study was therefore

designed to assess the frequency and types of extrahepatic manifestations in patients with chronic HCV presenting to a tertiary-care hospital in Lahore, with the goal of generating evidence that could guide clinical practice and inform future research in Pakistan.

Methodology

Study Design and Settings

This study was designed as a cross-sectional study. It was conducted in the Department of Medicine, Omer Hospital, Lahore, from 13 March 2025 to 13 July 2025.

Sample Population

The sample size of 175 patients was calculated using the WHO sample size calculator, keeping a 95% confidence level, a margin of error of 6.5%, and an expected frequency of extrahepatic manifestations of 74% in patients with chronic hepatitis C. A non-probability consecutive sampling technique was employed. Patients between 20 and 70 years of age of either gender, who had been diagnosed with chronic hepatitis C as per operational definitions, were included in the study. Patients with HIV co-infection, HBV co-infection, or co-infection with other hepatotropic viruses such as CMV and EBV were excluded. Patients with chronic hypothyroidism (TSH > 5mIU/L), chronic renal failure (serum creatinine > 1.5 mg/dl or on dialysis) were also excluded from the study.

Data Collection

A total of 175 patients who met the selection criteria were enrolled from the outpatient department. Informed written consent was obtained from each participant prior to inclusion. A structured proforma was used to collect demographic and clinical information, including age, gender, height (m), weight (kg), body mass index (BMI, kg/m^2), residence, duration of HCV infection, presence of liver cirrhosis, smoking history (> 5 pack-years), alcohol intake (> 20 ml/day), diabetes status (BSR > 200 mg/dl), hypertension (BP ≥ 140/90 mmHg), occupation, socioeconomic status, lifestyle, dietary pattern, and current HCV treatment status. All patients were clinically evaluated for extrahepatic manifestations. These included diabetes mellitus, cardiovascular and cerebrovascular disease, chronic kidney disease, lymphoma, lichen planus, rheumatoid arthritis, and thyroiditis, in accordance with the operational definitions. Patients identified with relevant conditions were managed according to standard clinical protocols.

Data Analysis

Data were analyzed using SPSS version 25.0. The Shapiro–Wilk test was applied to assess the normality of distribution for quantitative variables. Quantitative variables such as age, BMI, and duration of HCV infection were expressed as mean ± standard deviation (SD). Qualitative variables, including gender, residence, presence of liver cirrhosis, smoking history, alcoholism, diabetes, hypertension, occupation, socioeconomic status, lifestyle, dietary pattern, HCV treatment, and the presence and types of extrahepatic manifestations, were summarized as frequencies and percentages. Effect modifiers such as age, gender, BMI, duration of HCV, residence, presence of liver cirrhosis, smoking history, alcoholism, diabetes, hypertension, occupation, socioeconomic status, lifestyle, dietary pattern, and HCV treatment status were controlled through stratification. Post-stratification, the chi-square test was applied to compare extrahepatic manifestations across stratified groups. A p-value of < 0.05 was considered statistically significant.

Results

Types and Frequency of Extrahepatic Manifestations

The most frequent manifestation was mixed cryoglobulinemia, observed in 65 patients (37.1%), followed by thrombocytopenia in 48 patients (27.6%). Thyroid autoimmunity was also noted in a significant proportion of patients, affecting 28 cases (16%). Dermatological manifestations collectively accounted for 8 cases (4.6%), with lichen planus being the most common, alongside less frequent conditions such as porphyria cutanea tarda, vasculitis, vitiligo, and

granuloma annulare. Type 2 diabetes mellitus was found in 7 patients (4%), whereas sicca syndrome, glomerulonephritis, and peripheral neuropathy were reported less frequently, ranging from 1.1–2.9%. B-cell lymphoma was identified in only one patient (0.6%), reflecting its rarity in this population. Overall, the distribution emphasizes that vascular, hematological, and endocrine disorders predominate among HCV-related extrahepatic manifestations, while autoimmune and lymphoproliferative complications are relatively uncommon but clinically relevant.

Table 1. Types of extrahepatic manifestations in the study group (n = 175)

Extrahepatic manifestation	**Number of patients** (%)
Cryoglobulinemia (MC)	65 (37.1)
Thrombocytopenia	48 (27.6)
Thyroid autoimmunity	28 (16.0)
Skin manifestations	**8 (4.6)**
• Lichen planus (LP)	3 (1.7)
• Porphyria cutanea tarda (PCT)	2 (1.1)
• Vasculitis	1 (0.6)
• Vitiligo	1 (0.6)
• Granuloma annulare	1 (0.6)
• Alopecia areata	0 (0.0)
Type 2 diabetes (DM)	7 (4.0)
Sicca syndrome	5 (2.9)
Glomerulonephritis	3 (1.7)
Peripheral neuropathy	2 (1.1)
B-cell lymphoma	1 (0.6)

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Baseline Characteristics and Comparative characteristics

Patients with extrahepatic manifestations were generally older, with a mean age of 45.1 years, and had a longer mean duration of HCV infection (15.9 years), both of which showed significant associations in univariate analysis ($p < 0.001$). Hemoglobin levels were lower among patients with extrahepatic complications, while platelet counts were also reduced, suggesting a relationship with cytopenic manifestations such as thrombocytopenia and cryoglobulinemia.

Although liver enzymes such as ALT and AST showed mild elevations, their associations were not statistically significant after adjustment. Multivariate analysis confirmed that age, longer HCV duration, lower hemoglobin, and reduced platelet count remained significant predictors of extrahepatic disease, while liver function markers (ALT, AST, bilirubin) did not independently predict outcomes. This suggests that chronicity and systemic hematological effects of HCV, rather than isolated hepatic injury, play a more prominent role in driving extrahepatic involvement.

Table 2. Comparative characteristics of patients with chronic hepatitis C in relation to extrahepatic manifestations (n = 175)

Parameter	Mean	Univariate analysis (p)	Multivariate analysis (Odds ratio, 95% CI)
Age (years)	45.1	0.0001	1.015 (0.994–1.036)
Duration of HCV infection (years)	15.9	0.0003	1.023 (0.997–1.049)
Hemoglobin (g/dl)	13.8	0.002	0.843 (0.721–0.984)
Leucocytes ($\times 10^9$/L)	6.4	0.003	1.031 (0.924–1.051)
Platelets ($\times 10^9$/L)	101	0.005	0.993 (0.981–1.012)
ALT (IU/L)	111	0.21	1.004 (0.997–1.013)
AST (IU/L)	72	0.08	0.992 (0.985–1.009)
GGT (IU/L)	68	0.13	1.011 (0.994–1.018)
Bilirubin (mg/dl)	0.95	0.07	1.021 (0.976–1.073)
Inflammatory grade	1.8	0.00007	1.097 (0.961–1.248)
Fibrosis stage	1.62	0.00002	1.103 (0.884–1.442)

Outcomes of Correlation Analysis

Positive correlations were found with age ($r = 0.241$, $p = 0.002$), duration of HCV infection ($r = 0.212$, $p = 0.0005$), inflammatory grade ($r = 0.251$, $p = 0.0002$), and fibrosis stage ($r = 0.283$, $p < 0.0001$). These findings suggest that older patients and those with longer disease duration and advanced liver pathology were more likely to develop systemic complications. Negative correlations were noted with hemoglobin ($r = -0.153$, $p = 0.007$), leukocytes ($r = -0.332$, $p < 0.00001$), and platelets ($r = -0.315$, $p = 0.00008$), underscoring the role of hematological derangements in the development of extrahepatic conditions. Although mild positive associations with ALT, AST, and GGT were observed, their effect sizes were small and reached borderline statistical significance, indicating that hepatocellular injury alone was insufficient to predict systemic involvement. Collectively, these correlations reinforce that extrahepatic disease in HCV is multifactorial, closely linked to the interplay of host age, infection chronicity, hematological disturbances, and histological progression.

Table 3. Correlations between extrahepatic manifestations in HCV infection and clinical, laboratory, and histological parameters

Parameter	r	p
Age	0.241	0.002
Duration of HCV infection	0.212	0.0005
Hemoglobin	–0.153	0.007
Leucocytes	–0.332	0.00001
Platelets	–0.315	0.00008
ALT	0.121	0.043
AST	0.227	0.001
GGT	0.192	0.004
Bilirubin	0.117	0.062
Inflammatory grade	0.251	0.0002
Fibrosis stage	0.283	0.00005

Discussion

This study aimed to determine the frequency and types of extrahepatic manifestations among patients with chronic HCV infection presenting at a tertiary-care hospital. In our study of 175 patients with chronic hepatitis C, mixed cryoglobulinemia was the most common extrahepatic manifestation, observed in 65 patients (37.1%). This prevalence lies within the wide international range of 10% to 70% reported in different populations, yet it is somewhat lower than rates documented in Italian and Spanish cohorts, where prevalence has been reported as high as 50–60% in tertiary hospital patients (18,19). Conversely, less prevalence has been reported in North American studies reporting cryoglobulinemia in 19% of 127 HCV patients (20,21). The reason our intermediate prevalence may be because the patients were selected is that our cohort mean was 15.9 years of infection, indicating an enrichment in patients with long-standing illness. Such variations define the influence of genetic susceptibility, infection length, and diagnostic cutoffs on the prevalence of cryoglobulinemia in countries, and underscores the utility of standardized procedures in epidemiological surveillance (22).

Another most frequent one in our cohort was thrombocytopenia, which was identified in 48 out of 175 patients (27.6%), and was closely associated with severe liver fibrosis. The latter is in line with the findings of Mazzaro et al., (2022), who found that 24% of HCV patients in a Nepalese cohort, and 29.8% of 81 HCV patients in Romania, had thrombocytopenia. In the United States, lower rates of population-based surveys revealed that thrombocytopenia was found in only 7.6% of 467 infected people with HCV using a cutoff of 150×109/L (18). The above discrepancies indicate the influence of disease stage, with tertiary hospital cohorts such as ours being more heavily cirrhotic. Furthermore, immune-mediated platelet destruction has been described as an additional mechanism in HCV-related thrombocytopenia, supporting the biological plausibility of our findings (23). Thus, our prevalence aligns with international data but reflects a population with more advanced disease burden.

Autoimmune thyroid disease was detected in 28 patients (16.0%), which is notably higher than the pooled prevalence reported in large reviews. A systematic review by Nevola et al., (2021) identified thyroid autoantibodies in 10–15% of HCV patients, while thyroid dysfunction was present in 2–13% (20). Hong et al., (2020) similarly emphasized the variable prevalence, noting anti-thyroid antibodies in 7% of Iranian HCV patients compared with only 3% in healthy controls (24). Our higher frequency may be attributed to older age distribution and higher female representation in our cohort, both of which are established risk factors for autoimmune thyroid disease. It may also reflect more rigorous biochemical screening, as subclinical thyroiditis was actively investigated. Taken together, our findings support the established link between HCV infection and thyroid autoimmunity but also illustrate how local demographic and methodological factors can elevate apparent prevalence.

Dermatological manifestations were comparatively rare in our cohort, with lichen planus recorded in only 3 patients (1.7%) and other cutaneous conditions in 5 patients (2.9%), giving an overall cutaneous manifestation prevalence of 4.6%. This is lower than international estimates, where Khoury et al., (2020) conducted a cross-sectional study of 49 patients and reported a pooled prevalence of lichen planus in HCV patients at 7.05% (95% CI: 4.85–9.26%) (25). Likewise, a prevalence rate of 9.1% was observed among 275 HCV patients in Salama et al., (2022) in Italy and a prevalence of 4.8% among 180 patients in a Japanese cohort of 180 HCV patients (26). The difference with our results can be associated with the fact that our cohort was selected at general medical clinics but not at dermatology centres where cases are more detected. This indicates that underdiagnosis of mild cutaneous conditions and regional differences in HCV-lichen planus association have been described in our data.

Diabetes mellitus was observed in only 7 patients (4.0%) in our study, which is strikingly lower

than most international reports. A study by Ferri et al., (2021) including 102 patients found diabetes prevalence in HCV patients to be 15% compared with 10% in the general population (27). In contrast, a large Egyptian cohort study by Radu et al., (2024) involving 1,270 patients reported diabetes in 18.2% of HCV patients. The markedly lower rate in our sample could be due to younger average age, lower baseline BMI, and limited metabolic screening. However, the consistent association between HCV and increased diabetes prevalence across multiple populations underscores the metabolic impact of chronic viral infection, suggesting that our findings likely underestimate the true burden (28).

Lymphoproliferative disorders were rare in our series, with only one case of B-cell lymphoma (0.6%) identified. However, international studies have consistently documented a significant association between HCV and non-Hodgkin lymphoma. Huang et al., (2020) reported HCV positivity in 19.8% of 382 patients with an odds ratio of 2.5 for HCV infection compared to controls (29). A study by Songtanin and Nugent (2022) among NHL patients similarly reported HCV prevalence of 15.4%. Our single case is therefore consistent with the expected direction of association, though the limited sample size underestimates the true risk. Large multicentre datasets demonstrate that while lymphoma remains uncommon at the individual level, HCV confers a two- to fourfold increased risk, highlighting the importance of surveillance in long-term cohorts (30).

In addition, correlation analyses in our study demonstrated significant associations between extrahepatic manifestations and age ($r = 0.241$, $p = 0.002$) and duration of HCV infection ($r = 0.212$, $p = 0.0005$), as well as with histological progression of liver disease. These findings parallel those of Petta and Craxi (2020), who in a French cohort of 1,614 patients showed that older age and longer duration of infection significantly increased the probability of extrahepatic involvement (31). Similarly, Mazzaro et al., (2021) emphasized that the risk of immune-mediated complications, particularly cryoglobulinemia, rises with cumulative viral exposure (32). Our study also identified negative correlations with hemoglobin, leukocytes, and platelet counts, reinforcing that hematological manifestations are linked with both viral immune effects and progressive cirrhosis. Collectively, these results underscore that extrahepatic disease in HCV is not only common but is also cumulative, reflecting both host immune susceptibility and disease chronicity.

Limitations

The findings of this study should be interpreted in light of certain limitations. First, the cross-sectional design prevents causal inference between HCV infection and the observed extrahepatic manifestations, as temporal relationships cannot be firmly established. Second, the study was conducted at a single tertiary hospital with a modest sample size of 175 patients, which may introduce referral bias and limit the generalizability of results to community or primary-care populations. Additionally, the diagnosis of certain manifestations such as diabetes and thyroid disorders relied on clinical and biochemical records rather than standardized universal screening, raising the possibility of underestimation. Similarly, dermatological manifestations may have been underreported due to the absence of systematic dermatological evaluation. Moreover, the absence of a control group limits the ability to directly quantify the excess risk attributable to HCV infection, an issue that larger and prospective cohorts have addressed more comprehensively.

Conclusion

This study demonstrated that extrahepatic manifestations are common among patients with chronic hepatitis C in Pakistan, with cryoglobulinemia (37.1%) and thrombocytopenia (27.6%) being the most frequent, followed by thyroid autoimmunity (16.0%), cutaneous manifestations (4.6%), diabetes (4.0%), and lymphoma (0.6%). The burden of these systemic conditions not only compounds the overall morbidity but also complicates the clinical management of HCV, underscoring the

importance of a holistic and patient-centred approach to care. Recognition of such manifestations is therefore critical, particularly in patients with long-standing infection and advanced fibrosis. Moving forward, these findings emphasize the need for routine screening protocols and multidisciplinary management strategies to address the extrahepatic spectrum of HCV infection. With the advent of highly effective antiviral therapies, early detection and comprehensive management of systemic complications could markedly improve both quality of life and long-term outcomes. This integrated approach will be vital in reducing the hidden burden of HCV and ensuring that eradication strategies achieve their full potential in both hepatic and extrahepatic domains.

References

1. Hagström H, Kechagias S, Ekstedt M. Risk for hepatic and extra-hepatic outcomes in nonalcoholic fatty liver disease. J Intern Med. 2022;292(2):177–89.
2. Khan Z, Ahmad W, Zaman M, Khan I, Haroon M, Khan HA, et al. Complications associated with HCV-related liver cirrhosis and their relationship with diabetic control. A tertiary care center study in Peshawar, Pakistan. Prof Med J. 2024;31(05):718–25.
3. Farooq M, Dutta S, Mehriban N, Khan N, Ikram M, Rana A, et al. Frequency Analysis of Incidence of Hypertension and Cardiovascular Disease in Patients with Chronic Liver Disease Secondary to Hepatitis C. Gen Med. 2024;26:2057–67.
4. Kashif M, Zaman F, Uzman MHU, Shabbir T, Khan NUH, Atta S, et al. Prevalence of hepatitis c in liver cirrhosis patients: Hcv prevalence in cirrhosis patients. J Heal Rehabil Res. 2024;4(3):1–4.
5. Oblokulova ZI, Oblokulov AR, Jalilova AS. Diagnostic Significance of Hepatic Fibrosis in Patients with Extrahepatic Chronic Viral Hepatitis C. Cent Asian J Med Nat Sci. 2022;3(3):438–43.
6. Tan J hui, Zhou W yan, Zhou L, Cao R chang, Zhang G wei. Viral hepatitis B and C infections increase the risks of intrahepatic and extrahepatic cholangiocarcinoma: Evidence from a systematic review and meta-analysis. Turkish J Gastroenterol. 2020;31(3):246.
7. Ciancio A, Ribaldone DG, Dotta A, Giordanino C, Sacco M, Fagoonee S, et al. Long-term follow-up of diabetic and non-diabetic patients with chronic hepatitis C successfully treated with direct-acting antiviral agents. Liver Int. 2021;41(2):276–87.
8. Meloni A, Pistoia L, Gamberini MR, Spasiano A, Cuccia L, Allò M, et al. The impact of HCV chronic positivity and clearance on extrahepatic morbidity in thalassemia major patients: an observational study from MIOT Network. Eur J Intern Med. 2023;114:93–100.
9. Hsu P, Wei Y, Liang P, Lee J, Niu S, Huang J, et al. Comorbidities in patients with chronic hepatitis C and hepatitis B on hemodialysis. J Gastroenterol Hepatol. 2021;36(8):2261–9.
10. Cuesta-Sancho S, Márquez-Coello M, Illanes-Álvarez F, Márquez-Ruiz D, Arizcorreta A, Galán-Sánchez F, et al. Hepatitis C: Problems to extinction and residual hepatic and extrahepatic lesions after sustained virological response. World J Hepatol. 2022;14(1):62.
11. Songtanin B, Chaisrimaneepan N, Mendóza R, Nugent K. Burden, outcome, and comorbidities of extrahepatic manifestations in hepatitis B virus infections. Viruses. 2024;16(4):618.
12. Abutaleb A, Almario JA, Alghsoon S, Yoon JA, Gheysens K, Kottilil S, et al. Higher levels of fibrosis in a cohort of veterans with chronic viral hepatitis are associated with extrahepatic cancers. J

Clin Exp Hepatol. 2021;11(2):195–200.
13. Rawla P, Raj JP, Kannemkuzhiyil AJ, Aluru JS, Thandra KC, Gajendran M. A systematic review of the extra-hepatic manifestations of hepatitis E virus infection. Med Sci. 2020;8(1):9.
14. Lam L, Pol S, Cohen A, Carrat F. Direct-acting antivirals and the risk of arrhythmias and conduction disorders in patients with chronic hepatitis C: a French nationwide cohort study. Drugs. 2023;83(13):1207–13.
15. Stasi C, Sadalla S, Carradori E, Monti M, Petraccia L, Madia F, et al. Longitudinal evaluation of liver stiffness and outcomes in patients with chronic hepatitis C before and after short-and long-term IFN-free antiviral treatment. Curr Med Res Opin. 2020;36(2):245–9.
16. Rajewski P, Zarębska-Michaluk D, Janczewska E, Gietka A, Mazur W, Tudrujek-Zdunek M, et al. Hepatitis C infection as a risk factor for hypertension and cardiovascular diseases: An EpiTer multicenter study. J Clin Med. 2022;11(17):5193.
17. Wróblewska A, Gliwiński M, Rybicka M, Cheba M, Lorenc B, Trzonkowski P, et al. Residual HCV-RNA and Elevated Platelet-to-Lymphocyte Ratio Predict Poor Long-Term Outcomes in Patients with Chronic Hepatitis C After Treatment. Infect Dis Ther. 2024;1–11.
18. Mazzaro C, Adinolfi LE, Pozzato G, Nevola R, Zanier A, Serraino D, et al. Extrahepatic manifestations of chronic HBV infection and the role of antiviral therapy. J Clin Med. 2022;11(21):6247.
19. Lam L, Fontaine H, Lapidus N, Dorival C, Bellet J, Larrey D, et al. Impact of direct-acting antiviral treatment for hepatitis C on cardiovascular diseases and extrahepatic cancers. Pharmacoepidemiol Drug Saf. 2023;32(4):486–95.
20. Nevola R, Rinaldi L, Zeni L, Romano C, Marrone A, Galiero R, et al. Changes in clinical scenarios, management, and perspectives of patients with chronic hepatitis C after viral clearance by direct-acting antivirals. Expert Rev Gastroenterol Hepatol. 2021;15(6):643–56.
21. Negro F. Natural history of hepatic and extrahepatic hepatitis C virus diseases and impact of interferon-free HCV therapy. Cold Spring Harb Perspect Med. 2020;10(4):a036921.
22. El Kassas M, Hegazy OMO, Salah EM. Effect of treating chronic hepatitis C with direct-acting antivirals on extrahepatic cutaneous manifestations. World J Hepatol. 2020;12(10):841.
23. Méndez-Sánchez N, Coronel-Castillo CE, Ramírez-Mejía MM. Chronic Hepatitis C Virus infection, Extrahepatic disease and the impact of new Direct-Acting antivirals. Pathogens. 2024;13(4):339.
24. Hong CY, Sinn DH, Kang D, Paik SW, Guallar E, Cho J, et al. Incidence of extrahepatic cancers among individuals with chronic hepatitis B or C virus infection: a nationwide cohort study. J Viral Hepat. 2020;27(9):896–903.
25. Khoury J, Nassar G, Kramsky R, Saadi T. Extrahepatic malignancies after treatment with direct antiviral agents for chronic HCV infection. J Gastrointest Cancer. 2020;51(2):584–90.
26. Salama II, Raslan HM, Abdel-Latif GA, Salama SI, Sami SM, Shaaban FA, et al. Impact of direct-acting antiviral regimens on hepatic and extrahepatic manifestations of hepatitis C virus infection. World J Hepatol. 2022;14(6):1053.
27. Ferri C, Zignego AL, Antonelli A. Extrahepatic manifestations of chronic HCV infection. N Engl J Med. 2021;385:94–6.
28. Radu P, Becchetti C, Schropp J, Schmid P, Künzler-Heule P, Mertens J, et al. Effect of direct acting antiviral drugs on the occurrence and recurrence of intra-and extra-hepatic Malignancies in patients with chronic hepatitis C virus infection.

Cancers (Basel). 2024;16(14):2573.
29. Huang CF, Lai HC, Chen CY, Tseng KC, Kuo HT, Hung CH, et al. Extrahepatic malignancy among patients with chronic hepatitis C after antiviral therapy: a real-world nationwide study on Taiwanese chronic hepatitis C cohort (T-COACH). Off J Am Coll Gastroenterol ACG. 2020;115(8):1226–35.
30. Songtanin B, Nugent K. Burden, outcome, and comorbidities of extrahepatic manifestations in hepatitis C virus infection. Biology (Basel). 2022;12(1):23.
31. Petta S, Craxì A. Extrahepatic manifestations of chronic viral C hepatitis. Gastroenterol Clin. 2020;49(2):347–60.
32. Mazzaro C, Quartuccio L, Adinolfi LE, Roccatello D, Pozzato G, Nevola R, et al. A review on extrahepatic manifestations of chronic hepatitis C virus infection and the impact of direct-acting antiviral therapy. Viruses. 2021;13(11):2249.

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