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Original Article

Rheumatic manifestations of hepatitis C virus infection are associated with autoantibodies but not viremia

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Rheumatoid factor;
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Viral load

Abstract *Background:* To investigate the associations between extrahepatic manifestations, autoantibodies, and viremia in patients with hepatitis C virus (HCV) infection.
Methods: This cross-sectional study recruited patients with HCV infection from the outpatient department of a tertiary medical center in Northern Taiwan between January 2017 and August 2019. Autoantibody profiles and the clinical parameters of HCV infection were evaluated using laboratory tests, and a questionnaire was used to record extrahepatic manifestations. HCV infection status, including inactive HCV infection, active hepatitis, and cirrhosis, was defined according to abdominal ultrasonography findings and alanine transaminase levels.
Results: A total of 77 patients with HCV were recruited, with 19.5% and 16.9% of patients, respectively, presenting with arthritis and dry eyes. Autoantibody screening revealed rheumatoid factor (RF), antinuclear antibody (ANA), anti-Ro antibody, and anti-La antibody positivity in 20.8%, 23.4%, 13.0%, and 2.6% of the patients, respectively. The presence of RF was associated with arthritis, whereas the presence of ANA was associated with dry eyes but not dry mouth. Active hepatitis and HCV-related cirrhosis were associated with viremia, but not autoantibody profiles.
Conclusion: In this single-center study, the prevalence of extrahepatic manifestations and autoantibodies did not differ in patients stratified by the HCV infection status. Rheumatic manifestations were associated with the presence of autoantibodies but not with viremia.

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Introduction

Hepatitis C virus (HCV) is a small (55—65 nm), enveloped, hepatotropic virus of the *Hepacivirus* genus in the family *Flaviviridae* that contains a single-stranded positive-sense RNA genome. HCV is primarily transmitted through a horizontal route, spreading through blood transfusion or body fluid contact, as opposed to a vertical route from parent to offspring. HCV infection is a global health problem and a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma.[1] The all-cause mortality rate of patients with HCV infection is twice that of patients without HCV infection[2]; however, advances in viral eradication therapy using direct-acting antivirals (DAAs) have led to a substantial reduction in all-cause mortality rates.[3,4] Patient-reported outcomes and hepatocellular carcinoma risk have also been improved by DAA therapy.[5,6]

HCV infection is associated with various extrahepatic manifestations, including cardiovascular morbidity and diabetes mellitus.[7] HCV is also a lymphotropic virus that targets B cells,[8] which may contribute to HCV-associated autoimmune features such as sicca syndrome, cryoglobulinemia, thyroid diseases, autoimmune hepatitis, and diabetes mellitus.[7,9] Sicca syndrome is present in 10%—40% of patients with HCV.[10,11] Studies have indicated that 20%—80% of patients with HCV infection also experience arthropathy or arthritis,[10,11] and an association between HCV infection and the development of rheumatoid arthritis (RA) has been suggested.[12] Furthermore, rheumatoid factors (RFs) and antinuclear antibodies (ANAs) have been observed in 20%—75% and 10%—40% of patients with HCV, respectively,[10,13] and are associated with the presence of specific human leukocyte antigen (HLA) alleles.[13,14] However, no consensus exists among studies on associations among autoantibodies, HCV viral load, and hepatic infection status, which can be active hepatitis or cirrhosis.[15—17] Moreover, studies investigating extrahepatic manifestations and their correlation with serological, virological, and hepatic parameters are limited.[18,19]

This study investigated whether extrahepatic manifestations are associated with HCV infection status, HCV viral load, or the presence of autoantibodies.

Methods

Patients and data collection

This cross-sectional study was conducted at Far Eastern Memorial Hospital, a tertiary medical center in Northern Taiwan. We recruited patients aged 20 years or older who tested positive for anti-HCV antibodies between January 2017 and August 2019. These patients visited the hospital outpatient department for treatment of active HCV symptoms, through referral after health examination screening, or for regular follow-up after receiving a previous diagnosis of HCV infection. After obtaining written informed consent, we supervised them in completing the study questionnaire and conducted laboratory tests on patients. Extrahepatic manifestations and assessment of joints were recorded in the clinical report form. HCV infection status comprising inactive HCV infection, active hepatitis, and cirrhosis was determined according to abdominal ultrasonography findings and alanine aminotransferase (ALT) levels. Patients with cirrhosis were identified through abdominal ultrasonography and scored using the modified Child-Turcotte-Pugh score.[20] Patients without cirrhosis were divided into two groups: patients with inactive HCV infection (ALT levels $<$ twice the normal limit [41 U/L in men and 31 U/L in women]) and patients with active hepatitis (ALT levels $\geq$ twice the upper normal limit). Patients coinfected with hepatitis B virus or human immunodeficiency virus (HIV) and patients with underlying malignancies were excluded from the study. The presence of autoantibodies and HCV viral loads in the patients was analyzed. The study protocol was approved by the Ethics Committee of Far Eastern Memorial Hospital (105099-E). All procedures adhered to the ethical standards of the study institution, the national committee on human experimentation, and the Declaration of Helsinki.

Extrahepatic manifestations

The questionnaire included questions covering basic demographic characteristics, comorbidities, HCV infection mode, and clinical manifestations (dry eyes, dry mouth, arthritis, skin rashes, photosensitivity, numbness). Details regarding the prevalence of cardiovascular disease, cerebrovascular disease, thyroid disease, diabetes mellitus, and the history of antiviral therapy were obtained from an electronic chart review. Joint swelling and tenderness were also assessed. Oligoarthritis was defined as the involvement of two to four joints, and polyarthritis was defined as the involvement of five or more joints.

Laboratory tests

Venous whole blood (15 mL) was peripherally obtained from each of the patients. Serum samples were collected to analyze ANA, RF, anti-Ro, and anti-La autoantibody levels; albumin, globulin, ALT, total bilirubin, creatinine, and α-fetoprotein (AFP) levels; and complete blood count data. RF was detected using an RF II test (Roche Diagnostics GmbH, Mannheim, Germany). ANA was detected using ANAFAST HEp-2 kit (DiaSorin, Stillwater, MN, USA). Anti-Ro and anti-La autoantibodies were detected using an AtheNA Multi-Lyte ANA-II Plus Test System (ZEUS Scientific, Branchburg, NJ, USA). Positive results were defined according to the manufacturers' instructions. HCV viral loads

were measured using the Abbott Real-Time HCV viral load assay (Abbott Molecular, Des Plaines, IL, USA). Abdominal ultrasonography was performed to identify cirrhosis.

Statistical analysis

Parametric results were expressed as mean ± standard error of the mean (SEM). Comparisons between two groups were performed using a Student's *t*-test, and comparisons between three group were performed using an analysis of variance (ANOVA) and the post hoc Tukey test. The chi-square test was used to compare categorical variables, and the Bonferroni-adjusted post hoc test was used for the comparisons between three groups. All statistical analyses were performed using SPSS Statistics for Windows (version 22.0; IBM corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

Results

Clinical manifestations of the patients with HCV infection

We enrolled 77 patients with HCV infection and analyzed their clinical manifestations to investigate the effects of HCV infection on clinical manifestations. To examine whether extrahepatic manifestations were associated with different HCV infection status, the patients were divided into three subgroups: those with inactive HCV infection (n = 41), those with active hepatitis (n = 18), and those with cirrhosis (n = 18; Table 1). We included 12 patients in class A, 5 in class B, and 1 in class C in the cirrhosis group. The average ages (mean ± SEM) of the patients with inactive HCV infection, active hepatitis, and cirrhosis were 58.07 ± 2.07, 56.94 ± 2.20, and 67.72 ± 2.73 years, respectively. The patients with cirrhosis were significantly older ($p = 0.011$; ANOVA test with post hoc Tukey test). The proportion of HCV viremia was the lowest in those with inactive HCV infection ($p < 0.001$; ANOVA test with post hoc Tukey test). Dry eyes were present in 16.9% of the patients, and dry mouth and arthritis were present in 11.7% and 19.5% of the patients, respectively. Among the patients with arthritis, 6 had monoarthritis or oligoarthritis and 9 had polyarthritis. RF was observed in two (33.3%) of the six patients with monoarthritis or oligoarthritis and in four (44.4%) of the nine patients with polyarthritis. Photosensitivity, numbness, cardiovascular disease, and diabetes mellitus were observed in more than 10% of the patients. In patients with cirrhosis, albumin levels, hemoglobin levels, and platelet counts were significantly lower; globulin and total bilirubin levels were significantly higher (Supplementary Table).

We analyzed the clinical manifestations in accordance with the presence or absence of HCV viremia (Table 2). AFP, globulin, total bilirubin, ALT, and creatinine levels were significantly higher in the patients with HCV viremia, whereas albumin levels and platelet counts were significantly higher in those without viremia. In sum, all these biochemistry data were compatible with the hepatitis C viremia status. We did not observe any significant association between HCV viremia and extrahepatic manifestations.

Autoantibodies and extrahepatic manifestations of patients with HCV infection

When investigating autoimmunity in HCV infection, we observed that 16 (20.8%), 18 (23.4%), 10 (13.0%), and 2 (2.6%) patients tested positive for RF, ANA, anti-Ro, and anti-La autoantibodies, respectively (Table 1). No significant difference in age or sex was observed between the

Table 1 Clinical characteristics of patients stratified by HCV infection status.

	Inactive HCV (N = 41)	Active hepatitis (N = 18)	Cirrhosis (N = 18)	All (N = 77)	*p*
Age (year)	58.07 ± 2.07	56.94 ± 2.20	**67.72 ± 2.73**	60.06 ± 1.44	0.011[a]
Male sex n (%)	20 (48.8)	13 (72.2)	6 (33.3)	39 (50.6)	0.062
Dry eye n (%)	7 (17.1)	3 (16.7)	3 (16.7)	13 (16.9)	0.999
Dry mouth n (%)	4 (9.8)	1 (5.6)	4 (22.2)	9 (11.7)	0.254
Arthritis n (%)	11 (26.8)	2 (11.1)	2 (11.1)	15 (19.5)	0.221
Photosensitivity n (%)	6 (14.6)	6 (33.3)	1 (5.6)	13 (16.9)	0.072
Dermatitis n (%)	3 (7.3)	1 (5.6)	0 (0)	4 (5.2)	0.505
Numbness n (%)	12 (29.3)	5 (27.8)	8 (44.4)	25 (32.5)	0.461
Cardiovascular disease n (%)	6 (14.6)	1 (5.6)	1 (5.6)	8 (10.4)	0.428
Cerebrovascular disease n (%)	0 (0)	1 (5.6)	2 (11.1)	3 (3.9)	0.117
DM n (%)	8 (19.5)	2 (11.1)	5 (27.8)	15 (19.5)	0.451
Thyroid disease n (%)	3 (7.3)	0 (0)	1 (5.6)	4 (5.2)	0.505
RF + n (%)	9 (22.0)	4 (22.2)	3 (16.7)	16 (20.8)	0.886
ANA + n (%)	10 (24.4)	6 (33.3)	2 (11.1)	18 (23.4)	0.282
Anti-Ro + n (%)	6 (14.6)	1 (5.6)	3 (16.7)	10 (13.0)	0.551
Anti-La + n (%)	1 (2.4)	1 (5.6)	0 (0)	2 (2.6)	0.575
Viremia n (%)	**17 (41.5)**	16 (88.9)	15 (83.3)	48 (62.3)	<0.001[b]
VL (10^6 IU/mL)	2.68 ± 0.90	10.11 ± 4.5	6.39 ± 2.62	5.28 ± 1.33	0.070

ANA, antinuclear antibody; DM, diabetes mellitus; HCV, hepatitis C virus; RF, rheumatoid factor; VL viral load.
[a,b]Values with statistically significant differences are marked in bold.

Table 2 Comparison of patient characteristics according to HCV viremia status.

	Viremia− (N = 29)	Viremia+ (N = 48)	p
Age (year)	57.93 ± 2.55	61.35 ± 1.72	0.270
Male sex n (%)	14 (48.3)	25 (52.1)	0.746
Dry eye n (%)	8 (27.6)	5 (10.4)	0.051
Dry mouth n (%)	4 (13.8)	5 (10.4)	0.655
Arthritis n (%)	8 (27.6)	7 (14.6)	0.163
Photosensitivity n (%)	5 (17.2)	8 (16.7)	0.948
Dermatitis n (%)	2 (6.9)	2 (4.2)	0.601
Numbness n (%)	10 (34.5)	15 (31.3)	0.769
Cardiovascular disease n (%)	4 (13.8)	4 (8.3)	0.447
Cerebrovascular disease n (%)	0 (0)	3 (6.3)	0.170
DM n (%)	6 (20.7)	9 (18.8)	0.835
Thyroid disease n (%)	0 (0.0)	4 (8.3)	0.110
RF + n (%)	3 (10.3)	13 (27.1)	0.079
ANA + n (%)	7 (24.1)	11 (22.9)	0.902
Anti-Ro n (%)	6 (20.7)	4 (8.3)	0.118
Anti-La n (%)	2 (6.9)	0 (0)	0.065
AFP (ng/mL)	3.56 ± 0.62	**14.96 ± 5.15**	0.033[a]
Albumin (g/dL)	**4.33 ± 0.10**	4.03 ± 0.09	0.028[b]
Globulin (g/dL)	3.29 ± 0.14	**3.74 ± 0.11**	0.016[c]
T-Bil (mg/dL)	0.61 ± 0.08	**0.99 ± 0.16**	0.037[d]
ALT (U/L)	31.76 ± 4.21	**106.23 ± 20.11**	0.001[e]
Cre (mg/dL)	0.82 ± 0.03	**1.65 ± 0.39**	0.039[f]
WBC (k/μL)	6.14 ± 0.37	6.11 ± 0.31	0.947
Hb (g/dL)	13.75 ± 0.32	13.84 ± 0.37	0.857
Platelet (k/μL)	**234.34 ± 12.34**	168.65 ± 9.43	<0.001[g]

AFP, α-fetoprotein; ALT, alanine amino transferase; ANA, antinuclear antibody; T-Bil, total bilirubin; Cre, creatinine; DM, diabetes mellitus; Hb, hemoglobin; HCV, hepatitis C virus; RF, rheumatoid factor.
[a,b,c,d,e,f,g]Significantly higher values are marked in bold.

patients with and without RF or ANA presence. In the analysis of the association between autoantibodies and clinical symptoms, we noted that RF presence was positively associated with the presence of arthritis ($p = 0.041$; chi-square test, Table 3). ANA presence was associated with dry eyes ($p = 0.033$, chi-square test) and lower creatinine levels ($p = 0.046$; Student t-test, Table 4). A summary of the associations between ANA presence, RF presence, arthritis, and dry eyes is illustrated in Fig. 1. Other extrahepatic manifestations, including dry mouth, photosensitivity, dermatitis, numbness, cardiovascular disease, cerebrovascular disease, thyroid disease, and diabetes mellitus, were not associated with serological markers.

Discussion

In our patients with HCV infection, we determined that RF presence was associated with arthritis, and that ANA presence was associated with dry eyes but not with dry mouth. In addition, we previously hypothesized that extrahepatic manifestations would be associated with HCV infection status, such as active hepatitis with activated host immunity. However, our results do not support this hypothesis. We also determined that arthritis and dry eyes were not correlated with the presence of HCV viremia. Therefore, our results demonstrated that autoantibody status but not HCV infection status or viral load was associated with rheumatic manifestations, indicating the interaction between an environmental factor and autoimmunity, and suggesting that rheumatic manifestations are not directly associated with HCV viremia—driven immune responses but with infection-induced autoimmunity.

Arthritis was prevalent in our patients (19.5%), which is similar to the finding regarding arthralgia in 23% of the patients with HCV in another study.[11] The prevalence of RF in our patients (20.8%) was at the lower end of values reported in other studies but similar to the prevalence of 18.1% reported in another study conducted in Taiwan.[13] Silosi et al. reported that serum RF levels were similar between an early RA cohort and an HCV-related arthropathy cohort, and that both RF levels were significantly higher in these two groups than in the control group.[21] Unlike RA, HCV-related arthritis is not associated with articular bony erosions. However, RF may be present in HCV-associated arthritis and precede RA onset.[22,23] Furthermore, a population-based study comparing patients with or without HCV revealed that the risk of developing RA was greater in patients with HCV infection.[12] In summary, HCV is among the environmental factors that trigger RF production,[23] which may contribute to the subsequent development of RA.

Dry eyes were also prevalent and associated with the presence of ANA in our patients and are a well-known sign of HCV-associated sicca syndrome as demonstrated by multicenter studies.[9,11] ANA positivity ranges from 10 to 40% in patients with HCV infection.[10,11] Studies have

Table 3 Comparison of characteristics of patients with HCV infection according to RF serostatus.

	RF− (N = 61)	RF+ (N = 16)	p
Age (year)	60.11 ± 1.64	59.88 ± 3.09	0.946
Male sex n (%)	33 (54.1)	6 (37.5)	0.237
Dry eye n (%)	12 (19.7)	1 (6.3)	0.202
Dry mouth n (%)	7 (11.5)	2 (12.5)	0.910
Arthritis n (%)	9 (14.8)	**6 (37.5)**	0.041[a]
Photosensitivity n (%)	10 (16.4)	3 (18.8)	0.823
Dermatitis n (%)	4 (6.6)	0 (0.0)	0.293
Numbness n (%)	21 (34.4)	4 (25.0)	0.474
Cardiovascular disease n (%)	7 (11.5)	1 (6.3)	0.542
Cerebrovascular disease n (%)	3 (4.9)	0 (0)	0.366
DM n (%)	13 (21.3)	2 (12.5)	0.428
Thyroid disease n (%)	3 (4.9)	1 (6.3)	0.831
ANA + n (%)	16 (26.2)	2 (12.5)	0.248
Anti-Ro + n (%)	7 (11.5)	3 (18.8)	0.441
Anti-La + n (%)	1 (1.6)	1 (6.3)	0.302
HCV viremia n (%)	35 (57.4)	13 (81.3)	0.079
VL (10^6 IU/mL)	5.17 ± 1.59	5.71 ± 2.17	0.841
AFP (ng/mL)	8.24 ± 2.67	21.82 ± 13.31	0.336
Albumin (g/dL)	4.15 ± 0.07	4.06 ± 0.19	0.665
Globulin (g/dL)	3.51 ± 0.08	3.93 ± 0.31	0.220
T-Bil (mg/dL)	0.84 ± 0.13	0.95 ± 0.17	0.615
ALT (U/L)	80.97 ± 16.01	67.56 ± 19.00	0.593
Cre (mg/dL)	1.09 ± 0.15	2.38 ± 1.10	0.265
WBC (k/μL)	6.00 ± 0.29	6.55 ± 0.34	0.224
Hb (g/dL)	13.80 ± 0.29	13.81 ± 0.62	0.987
Platelet (k/μL)	196.72 ± 9.66	180.69 ± 15.44	0.386

AFP, α-fetoprotein; ALT, alanine amino transferase; ANA, antinuclear antibody; T-Bil, total bilirubin; Cre, creatinine; DM, diabetes mellitus; Hb, hemoglobin; HCV, hepatitis C virus; RF, rheumatoid factor; VL, viral load.
[a]The significantly higher value is marked in bold.

revealed that the presence of autoantibodies is associated with specific HLA alleles, including the positive association of autoantibodies with HLA-DR4,[24] or their negative associations with HLA-DR2 and HLA-DR11,[13,14] suggesting that environmental factors, such as HCV infection, contribute to autoimmunity because of the presence of specific HLA alleles. Lymphotropic viral infections other than HCV, such as Epstein–Barr virus, HIV, or human T-lymphotropic virus type 1, have been associated with sicca syndrome, which should be excluded for the diagnosis of primary Sjogren's syndrome.[25,26] This may indicate a possible link between lymphotropic viral infection and lymphoid tissue infiltration in sicca syndrome. Additionally, HCV is prevalent in ocular adnexal non-Hodgkin lymphoma,[27] indicating an association between HCV infection and ocular lymphatic tissue dysplasia. Direct infection of salivary glands by HCV has been suspected to be a trigger of glandular inflammation, but this claim is controversial.[28,29]

When analyzing the correlations between autoantibodies and hepatitis C infection statuses, our results do not reveal any association of active hepatitis or HCV-related cirrhosis with autoantibodies, which is consistent with the other studies.[15,19] In addition, a previous study showed that the presence of autoantibodies had no impact on the natural history of hepatitis C infection.[18] Although globulin levels were higher in patients with cirrhosis, hypergammaglobulinemia was not automatically associated with the presence of autoantibodies. However, some studies have demonstrated an association between autoantibodies and liver tissue fibrosis;[16,17] therefore, pathology study may reveal additional information than clinically defined cirrhosis and provide an insight into the pathogenesis of autoantibodies.

Between patients with or without HCV viremia, the positivity rates of RF, anti-Ro, and anti-La autoantibodies were not significantly different. We observed a lower prevalence of anti-Ro and anti-La autoantibodies in our patients than in patients with primary Sjögren syndrome.[9,14] Notably, HCV viral loads were not statistically significant but lower in our patients with positive ANA, supporting the result of another study that reported the presence of ANA to be associated with lower HCV RNA levels.[17] This result suggests a relationship between ANA and viral clearance, but the underlying mechanism remains unclear. In contrast, the effect of positive ANA on the treatment response to interferon-based therapy is inconclusive.[18,30] HCV clearance has been reported to improve patient survival and reduce the incidence of end-stage renal disease, acute coronary syndrome, ischemic stroke, and type 2 diabetes.[4,31] Patients with HCV eradication and a sustained virological response also had a lower risk of developing mixed cryoglobulinemia vasculitis and B-cell non-Hodgkin lymphoma.[32] Nevertheless, long-term, complete clearance of cryoglobulin is reported in only 29–66% of cases after DAA therapy, reflecting the

Table 4 Comparison of characteristics of patients with HCV infection according to ANA serostatus.

	ANA− (N = 59)	ANA+ (N = 18)	p
Age (year)	59.41 ± 1.78	62.22 ± 1.98	0.296
Male sex n (%)	30 (50.8)	9 (50)	0.950
Dry eye n (%)	7 (11.9)	**6 (33.3)**	0.033[a]
Dry mouth n (%)	7 (11.9)	2 (11.1)	0.931
Arthritis n (%)	13 (22.0)	2 (11.1)	0.306
Photosensitivity n (%)	9 (15.3)	4 (22.2)	0.490
Dermatitis n (%)	4 (6.8)	0 (0)	0.257
Numbness n (%)	18 (30.5)	7 (38.9)	0.506
Cardiovascular disease n (%)	8 (13.6)	0 (0)	0.099
Cerebrovascular disease n (%)	3 (5.1)	0 (0)	0.329
Diabetes mellitus n (%)	14 (23.7)	1 (5.6)	0.088
Thyroid disease n (%)	4 (6.8)	0 (0)	0.257
RF + n (%)	14 (23.7)	2 (11.1)	0.248
Anti-Ro + n (%)	7 (11.9)	3 (16.7)	0.596
Anti-La + n (%)	1 (1.7)	1 (5.6)	0.367
HCV viremia + n (%)	37 (62.7)	11 (61.1)	0.902
VL (10^6 IU/mL)	6.13 ± 1.70	2.51 ± 0.93	0.067
AFP (ng/mL)	9.51 ± 2.88	15.25 ± 10.90	0.617
Albumin (g/dL)	4.13 ± 0.08	4.14 ± 0.14	0.943
Globulin (g/dL)	3.46 ± 0.08	3.96 ± 0.23	0.055
T-Bil (mg/dL)	0.87 ± 0.13	0.84 ± 0.16	0.905
ALT (U/L)	78.86 ± 16.46	75.94 ± 18.13	0.906
Cre (mg/dL)	**1.51 ± 0.33**	0.84 ± 0.05	0.046[b]
WBC (k/μL)	6.13 ± 0.28	6.08 ± 0.46	0.930
Hb (g/dL)	13.77 ± 0.31	13.91 ± 0.46	0.802
Platelet (k/μL)	190.32 ± 10.24	203.44 ± 11.61	0.401

AFP, α-fetoprotein; ALT, alanine amino transferase; ANA, antinuclear antibody; T-Bil, total bilirubin; Cre, creatinine; DM, diabetes mellitus; Hb, hemoglobin; HCV, hepatitis C virus; RF, rheumatoid factor; VL, viral load.
[a,b]Significantly higher values are marked in bold.

persistence of a B-lymphocyte clone in a substantial percentage of patients.[7] The previous study result suggests that cryoglobulin could be produced in the absence of persistent HCV infection, indicating a complex interaction among viral infection, immune activation, and autoimmunity. Additionally, sustained viral remission in patients with chronic HCV infection is not always followed by normalization of serological markers such as RF.[33] DAAs have demonstrated efficacy in treating HCV-associated cryoglobulinemia. However, evidence of the benefits in terms of HCV clearance from using a DAA on autoantibodies and autoimmune manifestations, such as arthropathy or sicca syndrome, is lacking.[34]

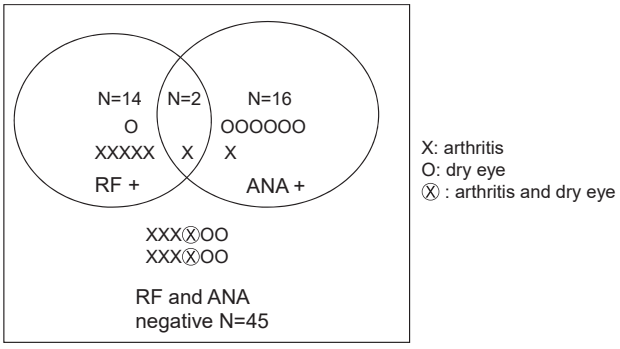

Figure 1. Associations between autoantibodies and symptoms of arthritis or dry eyes. Sixteen patients were positive for RF, and 18 patients were positive for ANA; moreover, two patients were positive for both RF and ANA. Forty-five patients were negative for both RF and ANA. Arthritis was more prevalent in the RF-positive population and dry eyes were more prevalent in ANA-positive population.

In this study, clinical presentations obtained by a predefined checklist and the prevalence of autoantibodies were relatively high, which revealed significant associations despite a small case number. Although a few studies investigated the extrahepatic manifestations and measured autoantibodies as well as viral loads simultaneously, these studies did not disclose the association between autoantibody and clinical manifestation, probably due to ethnic differences in the prevalence of autoantibodies,[19] or different definitions of clinical manifestations.[18] However, our study has several limitations. First, only five of our patients completed antiviral treatment at the time of recruitment (Supplementary Table), as a result, we could not determine whether extrahepatic manifestations and autoantibody profiles would be affected by the treatment. Second, we had limited patients who were positive for autoantibodies; hence, we could not conduct further subgroup analysis. However, this study included real-world data in the form of comprehensive clinical and laboratory information, and thus has value in that regard.

In conclusion, our study demonstrated that the prevalence of extrahepatic manifestations and autoantibodies did not differ in patients with variable HCV infection status. Rheumatic manifestations of HCV were associated with autoantibodies but not with viremia, whereas active hepatitis and HCV-related cirrhosis were both associated with viremia.

Author contributions

Conceptualization: M-T Weng and C-S Wu; acquisition of data: M-T Weng, T-H Chang; data analysis: M-T Weng and T-H Chang; drafting and critical revision: M-T Weng, T-H Chang, and C-C Lin. All authors contributed and approved the final manuscript.

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Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.03.007.