

Evaluation of Articular Manifestations in Hepatitis C Virus Infected Patients and its Association with Liver Fibrosis: A Cross-sectional Study from Rural Indian State of Manipur

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ABSTRACT

Introduction: Hepatitis C Virus (HCV) is the main culprit for liver diseases worldwide. In Manipur its incidence is increasing, mainly due to blood borne transmission through intravenous drugs users. Among the extrahepatic manifestations of HCV infection-arthropathy (joint pain, swelling and stiffness) is most common. Exact mechanism of arthropathy are not well elucidated but are probably connected with the participation of the immune system and due to the replicating virus in the affected tissues, organ systems.

Aim: To determine the articular manifestations in HCV infected patients and to study the association between articular manifestations and liver fibrosis.

Materials and Methods: This cross-sectional study enrolled 100 hepatitis C infected patients above 18 years of age who attended Medicine OPD, gastroenterology and liver clinic or admitted in the General Medicine wards, Regional institute of Medical Sciences (RIMS), Imphal, Manipur, India. Blood samples were collected for Complete Blood Count, Erythrocyte Sedimentation Rate, C Reactive Protein, Liver function test, Renal function test, HCV, Rheumatoid Factor (RF), Antinuclear Antibody (ANA), anti-ds DNA. Ultrasound (USG) whole abdomen

and X-rays of involved joints were done when indicated. Markers for liver stiffness/fibrosis, {Aspartate Aminotransferases (AST) to Platelet Ratio Index (APRI)} score, The fibrosis-4 (FIB-4) score and AST/Alanine Transaminase (ALT) ratio were calculated and compared. The Statistical Package for Social Sciences (SPSS) (IBM) version 21.0 was used for statistical analysis. Chi-square and Fischer's-exact test were used.

Results: A total of 100 hepatitis C infected patients were enrolled in the present study. Majority of the study subjects were males (63%) under 40 years of age (69%). Eighty-four (84%) patients were intravenous drug users. Joint pain, swelling and stiffness was present in 37 (37%), 31 (31%) and 24 (24%), respectively. Around 36 (36%), 45 (45%) and 29 (29%) of the participants had significant fibrosis with respect to FIB 4 score, APRI and USG finding, respectively.

Conclusion: The prevalence of joint pain was 37% in this study. Females and younger age group were more associated with articular manifestation. The present study concluded that patient with articular manifestation were seen to have significant fibrosis with respect to FIB 4 score, APRI and USG finding, AST/ALT.

Keywords: Aspartate aminotransferases to platelet ratio index score, Arthropathy, Blood borne transmission, Fibrosis-4 score

INTRODUCTION

The HCV, a hepatotropic RNA virus, transmitted primarily via the blood route, is one of the major causes of liver disease worldwide. It causes acute hepatitis which is mostly subclinical but it gradually evolves into chronic hepatitis in about 80% of the cases [1]. HCV has affected over 150 million people around the world with global prevalence of 2-3% and its prevalence in India is 0.9 to 1.9% [2], while in Manipur, the yearly seroprevalence of hepatitis C infections ranges from 3.91% to 8.17% among the males and from 0.30% to 0.64% among the females [3].

HCV induces clonal B cell expansion causing lymphoproliferative abnormality in liver and other organ systems [4]. The presence of extrahepatic manifestations is a relatively common feature in patients with chronic HCV infections, with a prevalence of more than 74%, among which arthropathy is common, affecting up to 20% of HCV infected individuals [5]. Although hepatitis C related arthropathy symptoms can be disabling, the prognosis typically is benign [6]. HCV-associated arthritis is categorised within the HCV syndrome

as a non-erosive inflammatory, non-deforming arthritis (which can be mono-, oligo-, or polyarticular), with or without RF, but with a negative anti-Cyclic Citrullinated Peptide (CCP) antibody [7], while erythrocyte sedimentation rate is elevated only in about half of the patients and subcutaneous nodules are absent

In about two-thirds of the affected individual's morning stiffness may be severe, resolving after more than an hour [5]. HCV infection causes synovial tissue injury via inflammatory action or by cryoglobulin induced immune complex ultimately leading to arthritis [5,6]. Although arthropathies are the most common extrahepatic manifestations of HCV infection, severity of liver disease does not correlate with their presence or absence [6]. HCV-induced mixed cryoglobulinemia and its complement vessels deposition causes purpura, skin ulcers, and glomerulonephritis [8].

HCV-associated arthritis is poorly aggressive responding to low doses of steroids, hydroxychloroquine [7] and Rituximab used in patients with more aggressive disease in the setting of mixed cryoglobulin [9]. Though further research is needed; available

data suggest that HCV eradication is often associated with the improvement of extrahepatic symptoms including arthropathy [10].

The severity of liver disease in chronic viral hepatitis [11,12] is best indicated by liver fibrosis and can be diagnosed by liver biopsy (gold standard) though invasive. Acoustic Radiation Force Impulse (ARFI) [12] is sensitive and specific for diagnosis of significant fibrosis in liver cirrhosis. FIB-4 index [13] and APRI [14] are promising non-invasive alternative to liver biopsy for detecting hepatic fibrosis. An AST/ALT ratio ≥ 1 is highly suggestive of the presence of cirrhosis in these patients [15].

Lack of literature about articular manifestations in hepatitis C patients in our state prompted us to determine the frequency of articular manifestations in HCV infected patients and its association with liver fibrosis.

MATERIALS AND METHODS

This cross-sectional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from December 2020 to November 2022. The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal, Manipur, India. (Reference No- A/206/REB-Comm (SP)/RIMS/2015/711/53/2020).

All hepatitis C infected patients who attended Medicine Outpatient Department (OPD), Gastroenterology and Liver clinic or admitted in the General Medicine wards were enrolled following the criteria.

Inclusion criteria: It include confirmed HCV infected patients aged 18 years and above.

Exclusion criteria: It exclude patients with co-existing hepatitis B infection, HIV co-infection, known systemic disease like rheumatoid arthritis, Systemic Lupus Erythematosus (SLE), gout and diabetes, alcoholic liver disease, auto-immune hepatitis, pregnant women and those not giving consent for the study.

Sample size calculation: was done according to the formula:

Sample size [16], $N = 1.96^2 PQ/L^2$

Taking, Prevalence of HCV infection in Manipur as 2.3% [3]

Precision (L)=3%

Alpha=1.96

Therefore, N=100

Procedure

A detailed structured proforma which included information of a detailed history of presenting symptoms (joint pain, swelling, stiffness) were recorded along with age, sex, Body Mass Index (BMI), mode of HCV infection and proper clinical examination. Blood samples were collected for RF, ANA and anti-dsDNA. USG whole abdomen and X-rays of involved joints if indicated were done.

Articular symptoms such as pain, swelling or stiffness at any joint were evaluated. If the number of joint involvement is one joint only then it is categorised as "monoarthritis". If 2-4 joints involved then "oligoarthritis" and ≥ 5 joints then "polyarthritis" [17].

The cut-off values of 3.25 for FIB-4 were used for significant fibrosis in liver [18]. Fibrosis index based on four factors (FIB-4) was first developed to access liver fibrosis in HIV/HCV co-infection comprised of age, AST, ALT, and platelet [18].

Formula for FIB-4 score [18]: $\text{Age (years)} \times \text{AST (U/L)} / \text{Platelet (} 10^9/\text{L)} \times \{\text{ALT (U/L)}\}^{1/2}$

Aspartate Aminotransferase to Platelet Ration Index (APRI): The APRI is used for assessment of liver fibrosis [18]. The cut-off values of 1.5 was used for APRI for significant fibrosis in liver [18]. Formula for APRI score [18]: $\{\text{AST (IU/L)} / \text{Upper normal limit of AST (IU/L)}\} / \text{Platelet count (} 10^9/\text{L)}$

Coarse echo texture or nodular surface or reduced size of liver was termed as significant fibrosis [19].

Generally, in chronic viral hepatitis B and C, AST/ALT ratio is < 1.0 . However, in a known case of chronic viral hepatitis if the AST/ALT ratio becomes > 1.0 , it indicates progression to fibrosis and cirrhosis stage. The raised AST/ALT ratio correlates with fibrosis rather than necro inflammatory activity especially in chronic hepatitis C. The AST/ALT ratio is also considered to be the "best routine marker" of hepatic fibrosis [20].

STATISTICAL ANALYSIS

SPSS (IBM) version 21.0 was used for statistical analysis. Mean, standard deviation and percentages. Chi-square test and Fisher's-exact test were employed to test the association between two proportions of outcome variables and variables of interest like sex, age, etc. The p-value of less than 0.05 was taken as statistically significant.

RESULTS

A total of 100 hepatitis C infected patients were included in the study. Baseline characteristics of the study subjects are given in [Table/Fig-1]. Majority of them were males (63%) and under 40 years (69%). Intravenous Drug Users (IVDU) was the most common mode of HCV infection (84%). RF was positive in 14% of the patients but none of them fulfilled criteria of Rheumatoid arthritis (2010 ACR criteria) [21] thereby Rheumatoid arthritis disease were ruled out. ANA was positive in 5%, ds DNA in 3% of the patents, 37 (37%) patients had joint pain, out of which 30 (81.1%) patients had polyarthritis, 6 (16.2%) had oligoarthritis and only 1 (2.7%) had monoarthritis Joint swelling was present in 31% of the patients; joint stiffness was present in 24% of them.

Characteristics	Study patients (N=100), n (%)
Age (in years)	
<40	69 (69%)
≥ 40	31 (31%)
Gender	
Male	63 (63%)
Female	37 (37%)
Modes of HCV infection	
Blood transfusion	3 (3%)
IVDU	84 (84%)
Multiple partners	5 (5%)
Others	8 (8%)
Body mass index (BMI in kg/m²)	
<18.5	2 (2%)
18.5-22.9	10 (10%)
23-24.9	9 (9%)
25-29.9	28 (28%)
>30	51 (51%)
Pain in joints	
Yes	37 (37%)
No	63 (63%)
Distribution of joints (N=37)	
Monoarthritis	1 (2.7%)
Oligoarthritis	6 (16.2%)
Polyarthritis	30 (81.1%)
Joint swelling	
Yes	31 (31%)
No	69 (69%)
Joint stiffness	
Yes	24 (24%)
No	76 (76%)

RF positivity	
Positive	14 (14%)
Negative	86 (86%)
ANA positivity	
Positive	5 (5%)
Negative	95 (95%)
Anti-ds DNA positivity	
Positive	3 (3%)
Negative	97 (97%)
Ultrasound (USG) findings	
Significant fibrosis	
Yes	29 (29%)
No	71 (71%)
APRI score	
≥1.5	45 (45%)
<1.5	55 (55%)
FIB 4 score	
≥3.25	36 (36%)
<3.25	64 (64%)
AST/ALT ratio	
≥1	27 (27%)
<1	73 (73%)

[Table/Fig-1]: Baseline characteristics of the study subjects (N=100).

There was a significant association between joint pain and gender (p=0.022). Females were seen more commonly associated with articular manifestation than male patients. Joint pain was seen more among the participants below the age of 40 years than those above 40 years and it was found to be statistically significant (p=0.044). Joint pain was not associated with RF [Table/Fig-2]. A 29% of patients had detected significant fibrosis by USG. Significant association of joint pain with USG finding for liver fibrosis was seen (p<0.001) [Table/Fig-3]. A 36% of patients were detected with fibrosis using FIB 4 score ≥3.25. A 45% of patients had fibrosis using APRI score ≥1.5. There was a significant association between swelling of joints with FIB 4 score (p-value 0.029), USG finding of fibrosis (p-value 0.001) and AST/ALT ratio (p-value 0.024) other articular manifestations like stiffness were not associated with FIB 4, APRI, USG findings and AST/ALT ratio [Table/Fig-4].

Parameters	Joint pain, n (%)		p-value
	Yes (n=37)	No (n=63)	
Age in years			
<40	28 (41%)	41 (59%)	0.044
≥40	9 (29%)	22 (71%)	0.022
Gender			
Male	18 (28.5%)	45 (71%)	0.019
Female	19 (51.3%)	18 (48.7%)	
AST/ALT ratio			
≥1	15 (55.56%)	12 (44.4%)	0.019
<1	22 (17.4%)	51 (82.6%)	
Rheumatoid Factor (RF)			
Positive	6 (42.8%)	8 (57.2%)	0.624
Negative	31 (36.1%)	55 (63.9%)	

[Table/Fig-2]: Association of joint pain with baseline characteristics (N=100).

Joint pain	USG findings for significant fibrosis, n (%)		p-value
	Yes	No	
Yes	18 (48.6%)	19 (51.4%)	<0.001
No	11 (17.4%)	52 (82.6%)	

	APRI score group, n (%)		0.025
	≥1.5	<1.5	
Yes	22 (59.4%)	15 (40.6%)	0.043
No	23 (36.5%)	40 (73.5%)	
	FIB 4 score group		0.043
	≥3.25	<3.25	
Yes	18 (48.6%)	19 (51.4%)	0.043
No	18 (28.5%)	45 (71.5%)	

[Table/Fig-3]: Association of joint pain and parameters for liver fibrosis.

S. No.	Characteristics	Swelling of joints*	Stiffness**	p-value	
1.	FIB 4	≥3.25	16 (44.4)	8 (22.2)	0.029*
		<3.25	15 (23.4)	16 (25.0)	0.754**
2.	APRI	≥1.5	18 (40.0)	11 (24.4)	0.078*
		<1.5	13 (23.6)	13 (23.6)	0.925**
3.	USG finding of significant fibrosis	Yes	16 (55.1)	9 (31.0)	0.001*
		No	15 (21.1)	15 (22.7)	0.390**
4.	AST/ALT ratio	≥1	13 (48.1)	10 (37)	0.024*
		<1	18 (24.6)	14 (19.2)	0.063**

[Table/Fig-4]: Association between other articular manifestation and liver fibrosis (N=100).

DISCUSSION

In this study, 100 hepatitis C infected patients were enrolled. Out of which 63 were males and remaining 37 were females. This difference in proportion can be explained by the difference in prevalence of male (5.4%) and female (0.5%) in a study by Lafangbam S et al., [3]. Another study by Kujur KK et al., reported 78.57% of the hepatitis C patients were males [22]. Similarly, Zuckerman E et al., reported 71% of the study population to be male [23]. But in a similar study by Ferucci ED et al., females dominated their study population with 59.8% [24]. This variation may be due to the mode of HCV infection, where males are usually involved in intravenous drug and this route was reported to be one of the main routes of HCV infection in Manipur [25].

Agewise, in this study most of the participants were under the age of 40 years (69%) and 31% of them were above 40 years. As most of the HCV infection in Manipur occurs through needle sharing among intravenous drug user [25], they are usually younger, thus most of the patients were young in this study compared to other study by Zuckerman E et al., and Ferucci ED et al., [23,24]. Another study by Kujur KK et al., reported most of the patients were above 40 years [22].

Regarding BMI in present study, a little more than half of all the patients were obese with 30 kg/m² and above BMI followed 28% of the study population in the range of 25 to 29.9 kg/m² BMI. Only two patients had BMI <18.5 kg/m². Ferucci ED et al., reported the median BMI among the participants to be an above 30 kg/m² [24].

The prevalence of HCV-associated articular manifestation has been described in previous studies, ranging from 2-20% [10,24-26]. In this study, the prevalence of joint pain, swelling of joints and joint stiffness were seen in is 37%, 31% and 24%, respectively. Similar to this was reported by Ferucci ED et al., who reported 71%, 29% and 55% of joint pain, joint swelling and joint stiffness in their study population respectively [24]. Out of those 37 patients with HCV related arthritis in this study, no erosions were noted in the radiographic images while maximum had polyarthritis (81.1%), followed by oligoarthritis (16.2%) and monoarthritis (2.7%). Similar findings were mentioned by Ferucci ED et al., where 62.5% had polyarthritis, 37.5% had oligoarthritis with nil radiographic erosion [24]. Zuckerman E et al., also reported 68% polyarthritis, 32% oligoarthritis and none had

radiological erosions [23]. Plausible mechanisms of involvement of multiple joints may be viral attack or immune response of viral attack within synovial tissue and cryoglobulin induced immune complex deposition within synovium [10,23]. HCV virus thrives in extrahepatic tissues causing varied manifestations [25,26].

Although extrahepatic/articular symptoms of HCV infection were less but cannot be ignored completely. The treatment should include for such symptoms to have a complete successful recovery. Researchers have reported significant extrahepatic/rheumatic manifestations (arthralgia, arthritis, cryoglobulinemia, sicca symptoms, cutaneous vasculitis, polymyositis, anti-phospholipid syndrome [10], though it does not showed significant association with severity of liver disease. In present study, predominant symptoms reported were joint pain, swelling of joints and joint stiffness.

HCV related arthritis can mimic RA; therefore, it was mandatory to distinguish HCV related arthropathy from RA because the prognosis and therapeutic strategies can be fairly different [5]. In this study, RF was positive in 14% of the participants and among the patient with articular manifestation 42.8% were positive for RF which was consistent with the studies by Zuckerman E et al., Ferucci ED et al., (37.6%), and Tarantino G et al., (42%) [23-25]. A 61(61%) of the HCV related arthritis patients were positive for RF. Thus, RF was detected in almost half of the hepatitis C infected patient with articular manifestation (which may be due to cryoglobulinemia). But there was no significant relation between presence of RF and articular manifestation in present study and this was consistent with those of other researchers [24,25]. In the present study, ANA was positive in 5%, ds DNA in 3% of the patients which is similar to studies by Ferucci ED et al., (24.7% positive for ANA) [24].

In this study, severity of liver disease was categorised as significant fibrosis and normal texture according to FIB 4 score, APRI score and USG findings. APRI and FIB-4 scores are non-invasive methods that can diagnose advanced fibrosis and cirrhosis with high accuracy in hepatitis C patients compared to liver biopsy [27]. The present study found significant liver fibrosis in 36%, 45% and 29% of the study population according to FIB 4 score, APRI and USG, respectively. In a study by Rungta S et al., FIB 4 was reported to be superior in identifying significant fibrosis among hepatitis C patients than APRI score [18].

The authors reported statistically significant association between patients with joint pain, swelling of joints with significant fibrosis of their liver according to FIB 4, APRI, AST/ALT ratio and USG finding. On other hand, joint stiffness was not associated with FIB 4, APRI and USG findings. A relevant search in National library of medicine or Pubmed yielded dearth of such association. In this study, patients with AST/ALT ratio ≥ 1 were seen more among the FIB 4 score ≥ 3.25 than those with FIB 4 score < 3.25 , thus it may be said that AST/ALT ratio ≥ 1 can be said to have a relation on the fibrosis of liver. Similar correlation of AST/ALT Ratio with FIB 4 score in detection of fibrosis in chronic hepatitis patients were reported by Moosavy SH et al., [28].

Limitation(s)

Severity of liver fibrosis were non-invasively measured and associated with articular symptoms. Fibroscan association was not done due to its unavailability in our setup in rural India. Although liver biopsy (histopathological) is the gold standard, it more invasive with risk of bleeding and hence was not done in this study.

CONCLUSION(S)

In this study, prevalence of joint pain was 37%, joint swelling was 31% and stiffness was 24% in HCV patients. These patient with

articular manifestation (joint pain, joint swelling) were seen to have significant fibrosis with respect to FIB 4 score, APRI and USG finding while no association was found with joint stiffness. Hence, early recognition of HCV infection and understanding its associated arthropathy will greatly influence the treatment. Further researches are needed, in collaboration with arthroscopic findings to strengthen this association comprehensively.

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