

## FREQUENCY OF RHEUMATOID FACTOR IN PATIENTS WITH HEPATITIS C INFECTION ASSOCIATED POLYARTHROPATHY

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### ABSTRACT

**Objective:** To determine the frequency of Rheumatoid Factor (RF) in patients with Hepatitis C infection (HCV) associated polyarthropathy at Combined Military Hospital Quetta.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Department of Medicine, Combined Military Hospital Quetta, from 1<sup>st</sup> Oct 2012 to 31<sup>st</sup> Mar 2013.

**Material and Methods:** Two hundred and seven patients having confirmed Hepatitis C infection (positive anti HCV antibodies and positive HCV RNA by Qualitative PCR) with polyarthropathy were included in this study. These patients were screened for RF by immunonochromatography based RF Latex assay kit.

**Results:** Out of 207 patients, 138 (66.67%) were males and 69 (33.33%) were females. The age among all subjects ranged from 21–55 years and mean age of all subjects was  $44.29 \pm 4.61$  years, the youngest patient was 21 years old and eldest was 55 years old. Most of the patients 97 (47%) were in the age group of 36–45 years. RF was positive in 88 (42.51%) patients and it was negative in 119 (57.49%) patients suffering from hepatitis C infection associated polyarthropathy. The frequency of RF in female patients was 66 (48%) and in male patients was 22 (32%) and it was significantly ( $p\text{-value}=0.0367$ ) greater in female patients as compared to male patients.

**Conclusion:** The detection of Rheumatoid Factor (RF) is of little utility as a diagnostic tool for concurrent RA in patients of chronic HCV infection because a high percentage of them were having serum RF reactivity.

**Keywords:** Arthropathy, Hepatitis C, Rheumatoid factor.

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### INTRODUCTION

More than 180 million people are infected with hepatitis C virus (HCV) infection with global prevalence of 2%<sup>1</sup>. Many patients are asymptomatic and are diagnosed incidentally by serology test or once they develop end stage liver disease. However in 70% of patients, infection is associated with wide range of clinical manifestations affecting various systems and organs referred as extrahepatic manifestations of chronic HCV infection (EHM). Among these extrahepatic manifestations, rheumatological manifestation is most common<sup>2</sup>.

There is no specific pattern of HCV related

arthropathy (HCVRa) and it ranges from polyarthralgias to arthritis. The latter usually present clinically in two subsets; intermittent mono-oligoarthritis (IMO) and symmetrical polyarthritis (SP). IMO is associated with cryoglobulinemia and has classical presentation of medium and large joints involvement particularly hip and knee joints along with Raynaud's phenomenon and palpable purpura<sup>3</sup>. In contrast polyarthritis has clinical presentation similar to rheumatoid arthritis. The clinical course of RA is prolonged with intermittent exacerbations and remissions<sup>4</sup>. In most of the cases, classic clinical picture of RA is not entirely helpful in diagnosis and unfortunately there is no single clinical, radiological, or serologic test that enables a diagnosis of RA to be made with certainty. So as with other rheumatic diseases, the

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diagnosis depends upon the constellation of characteristic symptoms and signs including morning stiffness, swelling and tenderness of joints, raised ESR and detection of Rheumatoid Factor (RF)<sup>5,6</sup>. Similar clinical finding are also present in HCVrA. Predominant clinical findings of HCVrA include tenosynovitis, small joint synovitis, symmetrical arthritis, involvement of small joints of hand and wrist. Erythrocyte Sedimentation Rate is elevated in about half of the patients and morning stiffness in two third of patients resolving after more than an hour<sup>7</sup>. Increased interleukin (IL)-6 levels are increased in both rheumatoid and HCV-related arthritis, which are considered to play the main role in both rheumatoid and HCV-related arthritis. However in contrast of RA, HCVrA runs benign

## MATERIAL AND METHODS

This cross sectional study was carried out from 1<sup>st</sup> October 2012 to 31<sup>st</sup> March 2013 at department of Medicine, Military Hospital Quetta, which is a tertiary care hospital. Sample size was calculated by using WHO sample size calculation formula  $n=z^2 pq/e^2$  with confidence level of 95%, absolute precision of 5% and anticipated prevalence of 60%.

Two hundred and seven patients of age 21 to 55 having confirmed Hepatitis C infection (positive anti HCV antibodies and positive HCV RNA by Qualitative PCR) with polyarthropathy were included in this study. All patients presenting to medical OPD fulfilling the inclusion criteria selected through consecutive sampling. Written informed consent was obtained from the

**Table: Comparison of Rheumatiod Factor in infection associated Polyarthropathy.**

Rheumatoid Factor	Male n(%)	Female n(%)	Total n(%)	
Positive	22 (32)	66 (48)	88 (42.51)	0.0367
Negative	47 (68)	72 (52)	119 (57.49)	
Total	69 (33.33)	138 (6.67)	207 (100)	

course and sub cutaneous nodules, joint erosion and deformities are not present<sup>8</sup>.

HCV infection also results in the production of autoantibodies including Rhematoid Factor (RF) which is part of diagnostic criteria and commonly used serological marker for RA. Frequency of RF reactivity increases with the articular involvement and is found in 37-81% of HCV patients. However, RF is also present in 9.7% of patients with HCV in the absence of arthropathy<sup>9,10</sup>. Thus differentiating HCV related polyarthritis and recent-onset concurrent RA, in which articular damage and deformities have not yet occurred is clinically difficult and in some cases is a diagnostic challenge.

The rationale of study is to find the frequency and clinical relevance of RF in Pakistani patients with chronic hepatitis C related polyarthropathy to avoid erroneous diagnoses of concurrent RA.

patients participating in this study. Every patient was assigned a serial number. Detailed history and careful physical examination were taken and all information including name, age, and hospital ID number were entered in the Performa. Serums of the patients of HCV infection reporting to Medicine department with polyarthropathy were screened for RF by immunonochromatography based RF Latex assay kit. All data collected were entered in SPSS version 18. For quantitative variables, mean and standard deviation were calculated. Frequencies and percentages were presented for qualitative variables like gender and Rheumatioid factor. Chi-square test was applied for the comparison of catagorical variables. A *p*-value of less than 0.05 was considered significant.

## RESULTS

Out of 207 patients, 138 (66.67%) were males and 69 (33.33%) were females. The age among all subjects ranged from 21-55 years and mean age

was  $44.29 \pm 4.61$  years, the youngest patient was 21 years old and eldest was 55 years old.

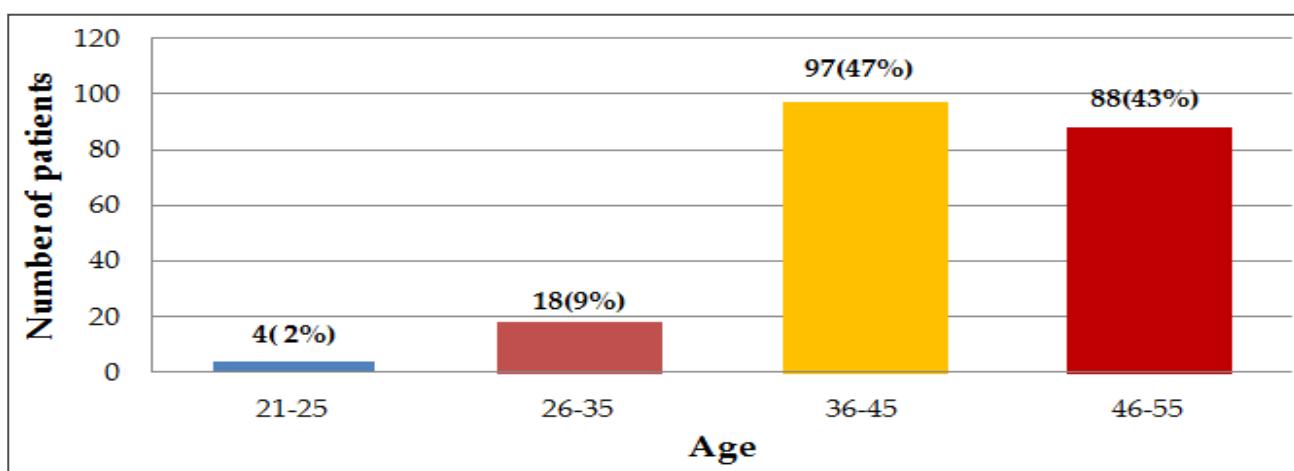
Figure shows the age distribution of all patients selected in the study. Most of the patients 97 (47%) were in the age group of 36-45 years, followed by 88 (43%) patients who belonged to the age group of 46-55 years.

Rheumatoid Factor (RF) was positive in 88 (42.51%) patients and it was negative in 119 (57.49%) patients suffering from hepatitis C infection associated polyarthropathy (table).

The frequency of RF in female patients was 66 (48%) and in male patients was 22 (32%) as given in table. The frequency of Rheumatoid

auto antibodies including RF which is associated with genetic predisposition but independent of viral load and does not affect antiviral treatment<sup>12,13</sup>. These antibodies production is due to cross reactive immune reactions between epitopes on the viral polyprotein which has resemblance with human antigen and human proteins promoting inflammation and tissue injury<sup>8</sup>. There is increased risk of developing RA in patients with HCV infection<sup>14</sup>.

Our study showed that RF was positive in 88 (42.51%) patients and it was negative in 119 (57.49%) patients suffering from hepatitis C infection associated polyarthropathy. Important



**Figure: Age distribution.**

Factor was found significantly ( $p\text{-value}=0.0367$ ) greater in female patients as compared to male patients.

## DISCUSSION

Extrahepatic manifestations are quite common feature in HCV infected patients and its prevalence is up to 70%<sup>3</sup>. Articular manifestations are most frequent complications that may present as chronic polyarthritis that mimic RA<sup>8,11</sup>. This clinical presentation has led to several studies to ascertain whether HCV is linked with pathogenesis of RA. However this association between RA and HCV was found casual as HCV found only in 0.45% of patient with RA.

HCV infection also induce immunological disorders in the host resulting in formation of

risk factor associated with increase probability of RF in our study was female gender that is consistent with previous study done by Mohammad et al 2010<sup>15</sup>.

Our results reconfirm the previous finding that RF was positive in sera of 44% patients with HCV related arthropathy the positive RF values<sup>16</sup>. Our study also supports the earlier findings that 81.8% HCV infected patients with articular involvement showed positive result for RF reactivity in their sera<sup>9</sup>. Similarly, in a study conducted at Cairo university, Egypt revealed that RF was found positive in 60% of HCV patients with polyarthropathy<sup>17</sup>. The difference in our result and this study might be due to fact that all patients in this study were of HCV genotype

IV, whereas the common genotype in Pakistan is II and III. This is supported by study of Brito-Zeron et al. (2015) in which RF was present in 37% and 55% of sera containing HCV genotype Ia and Ib respectively compared with 20% of sera with other genotypes<sup>18</sup>.

There is also an alternate interpretation of our study. Any patient presenting with rheumatic symptoms with positive RF, a clinician should keep in mind the possibility of HCV infection presenting with rheumatic manifestations as part of differentials of diagnosis on case to case basis which will facilitate in early diagnosis and treatment. Clues in such cases can be history of blood transfusion, raised liver enzymes and can be confirmed by PCR for HCV RNA.

To summarize, our study has focused on strong association and relationship between Rheumatoid Factor and chronic hepatitis C related polyarthropathy and has discussed its clinical relevance and reconfirms that RF is frequently present in the sera of these patients which can be confusing as well as misleading. This limits its diagnostic reliability in distinguishing HCV-associated rheumatic symptoms with positive rheumatoid factor from patients with possible concurrent RA. So it may be prudent in clinical practice to carefully interpret RF in patients suffering from the Hepatitis C with polyarthropathy. This is of clinical importance as arthritis occurring in HCV infected patients might be cured by antiviral treatment. On other hand treating these patients for concurrent RA will result in aggravation of liver disease as disease modifying anti-Rheumatic drugs are well documented causative agents for Hepatitis and fibrosis of Liver.

However in contrast to RF, anti-cyclic citrullinated peptide (anti-CCP) antibodies lack any associations with RF and HCV related polyarthropathy and display a high specificity for RA accompanied by a reasonable high sensitivity and is recommended to differentiate HCV from concurrent true Rheumatoid arthritis.

## CONCLUSION

The detection of Rheumatoid Factor (RF) is of little utility as a diagnostic tool for concurrent RA in patients of chronic HCV infection because a high percentage of them display serum RF reactivity.

## CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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