The impact of hepatitis C viremia status on lung functions in chronic hepatitis c patients

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Abstract

Background: Previous trials have investigated the effect of hepatitis C on lung functions; however, the role of viral load levels is unclear. The aim of this study was to investigate the effect of HCV viremia status on lung functions.

Methods: This study was in 60 patients with chronic hepatitis C (CHC). Patients were classified into three groups (non-viremic, low-viremic and high-viremic) based on serum HCV RNA levels. Spirometric parameters (FEV1, FVC, FEV1/FVC) and the proportion of patients with spirometric abnormalities were compared between three groups.

Results: High-viremic and low-viremic patients showed a significantly higher prevalance of spirometric abnormality than observed in non-viremic patients (p=0.02). Moreover, there was a significant moderate correlation between viremia level and the percentage of spirometric abnormalities (Cramer's U value=0.452, p=0.002). High-viremic patients were 14.2 times more likely to exhibiting pulmonary dysfunction than non-viremic patients. Additionally, spirometric parameters FEV1 and FVC were significantly reduced in high-viremic and low-viremic patients compared to those in non-viremic patients (p=0.013 and p<0.001 respectively).

Conclusion: These results indicate that persistent HCV infection may be associated with reduced pulmonary functions, especially in patients with high viremia levels. Therefore, these patients should be carefully monitored for lung function.

Keywords: Chronic hepatitis C infection, viremia, lung function tests.

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Introduction

Hepatitis C virus (HCV) mainly affects the liver, but can also present with extra hepatic manifestations.[1] One of the most important extrahepatic manifestations of HCV is pulmonary involvement. In chronic hepatitis C (CHC) patients, pulmonary involvement may emerge as interstitial pneumonitis and fibrosis, initiation/exacerbation of pre-existing chronic obstructive pulmonary disease (COPD) and asthma.[2]

The pulmonary involvements of HCV infection are mostly asymptomatic and progressive.[3,4] Therefore, the clinical progression of HCV-related pulmonary disorders might contribute to increased mortality and morbidity of CHC infection, which indicates the importance of early diagnosis of HCV-related pulmonary disorders. However, there is no consensus in the literature as to whether routine screening with pulmonary function tests (PFTs) would be beneficial in these patients. In addition, there are no data to identify those at high-risk of lung involvement.

The aim of this study was to explore the influence of viral load level on pulmonary functions in CHC patients. This study may contribute to literature about whether routine screening for lung functions is necessary in CHC patients.

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Patients and methods

Study population and design

This prospective clinical study was carried out among the 60 CHC patients with and without viremia who were admitted to our clinic. The patients were divided into three groups based on serum HCV RNA levels. These groups were non-viremic (HCV RNA: negative), low-viremic (HCV RNA<800.000 IU/ml) and high-viremic (HCV RNA≥800.000 IU/ml) groups.[5] All non-viremic patients had previously received interferon(IFN) therapy for HCV infection. Spirometric PFTs were performed in all three groups. Forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV1) and FEV1/FVC were measured. All the tests were performed in the University hospital pulmonary function laboratory based on the ATS/ERS standard protocol using a Quark PFT device (Cosmed, Italy).[6] All the tests were performed by the same technician using the same spirometer. Spirometric parameters (FEV1, FVC, FEV1/FVC) and the proportion of patients with spirometric abnormalitieswere compared between the three groups. The aspartate aminotransferase to platelet ratio index (APRI) was used to evaluate the liver fibrosis stages of patients, which is a non-invasive alternative to liver biopsy. Blood samples were collected for the following parameters just before the spirometric tests; HCV RNA for viral load, AST level and platelet count. The upper limit of normal (ULN) of AST was 40 IU/L. APRI scores were calculated as [(AST / ULN AST) X 100] / Platelet Count (10^9/L).[7]

Patients coinfected with hepatitis B, current smokers, COPD patients with an episode of exacerbation and patients who were diagnosed as having an acute respiratoryinfection were excluded from the study. To rule out the IFN therapy effect on lung functions, the participants who received IFN therapy within the last one year were also excluded. The presence of previous chronic lung disease and previous smoking habits were also recorded.

Approval for the study was obtained from the ethics Committee of Mustafa Kemal University School of Medicine. Informed consent was obtained from all participants.

Definitions

CHC was defined by the presence of the HCV antibody and the persistence of detectable HCV RNA for at least six months. Patients who were negative for HCV RNA for at least six months were considered as non-viremic.

Spirometric test results were considered normal if the FEV1 and FVC were ≥80% of the predicted value and the FEV1/FVC ratio was≥70%. Spirometric abnormalities were defined as restrictive, obstructive and mixed patterns. An obstructive pattern was defined as an FEV1/FVC ratio below 70% of the predicted value and an FEV1 below 80% of the predicted value. A restrictive pattern was defined as a reduction in FVC and a normal FEV1/FVC ratio. A pattern of combined obstructive and restrictive was defined as a mixed pattern.

Statistical analysis

Statistical analyses were performed using the SPSS software version 21(SPSS Inc., Chicago, IL, USA). Normality tests were done by using Kolmogorov-Smirnov and Shapiro-Wilk's tests. Categorical variables were compared by the Chi-square test or Fisher's exact test, where appropriate, between the groups. To determine an association between lung functions (FEV1, FVC, FEV1/FVC) / APRI scores and HCV viremia level (non-viremic, low-viremic or high-viremic) the Kruskal-Wallis test was used.The correlation between HCV viremic status/viremia level and the percentage of spirometric abnormalities was tested using the Chi-Square independence test. A Spearman's Rank-Order Correlation was run to the relationship between APRI scores and lung functions. In all tests, p values <0.05 were considered to be statistically significant.To identify the predictive factor for spirometric abnormality, binary logistic regression analysis was performed. The Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. The Wald test was used to determine statistical significancefor each of the independent variables. Charts were plotted using GraphPad Prism v7.0d for Mac (GrapPad Software, San Diego, CA, USA).

Results

The study included 31 patients without viremia, 15 patients with low viremia and 14 patients with high viremia. Of the 60 patients, 48.3% were female and 51.7% were male. The median age of the patients was 64.5 (range: 38-74) years. The characteristics of each group are shown in Table 1.

Table 1. Comparison of chronic hepatitis C patient groups according to epidemiological and pulmonary function tests (N=60)

[a] Chronic obstructive pulmonary disease, 9; Bronchial asthma, 6.

Characteristics	**Non-viremic group (n=31)**	**Low-viremic group (n=15)**	**High-viremic group (n=14)**	***P* value**
Median (IQR) age, yr	62 (10.0)	67 (10.0)	66 (9.0)	0.106
Male sex, n (%)	13 (41.9)	6 (40.0)	10 (71.4)	0.141
Ex-smokers, n (%)	11 (35.5)	5 (33.3)	5 (35.7)	0.935
Median (IQR) Pack-years	8.9 (12.3)	11 (17.6)	14.8 (21.3)	0.866
Median (IQR) BMI, Kg/m^2	28.5 (4.9)	29.3 (6.0)	28.8 (4.2)	0.823
History of previous pulmonary disease, n (%) [a]	5 (16.1)	4 (26.7)	6 (42.9)	0.157
Pulmonary function tests				
Median (IQR) FEV1 [b]	86 (23.0)	76 (36.0)	67 (39.0)	0.013
Median (IQR) FVC[b]	86 (19.0)	79 (34.0)	65 (19.0)	<0.001
Median (IQR) FEV1/FVC[b]	103 (28.0)	84 (35.0)	103 (47.5)	0.432
Spirometric abnormality, n (%)	9 (29.0)	8 (53.3)	12 (85.7)	0.02
Median (IQR) APRI	0.2 (0.12)	0.7 (0.65)	0.3 (0.6)	<0.001

[b] Percent of predicted value

Abbreviations: BMI, Body-mass index; FVC, Forced vital capacity; FEV1, Forced expiratory volume in 1stsecond; APRI, Aspartate aminotransferase to platelet index.

There was no significant difference regarding age, gender and body mass index (BMI) among the non-viremic, low-viremic and high-viremic groups ($p>0.05$ for all comparisons). The proportions of ex-smokers and previous pulmonary disease history were similar across the three groups ($p=0.935$ and $p=0.157$ respectively).

The most striking result to emerge from the data was that of the 60 CHC patients, 29 (48.3%) had abnormal PFTs results, while only 15 (25%) had a history of previous lung disease (9 patients with COPD and 6 patients had asthma).

The proportion of patients with spirometric abnormalities was significantly lower in the non-viremic group than in the low-viremic and high-viremic groups ($p=0.02$)(Table 1). Compared with patients without viremia, the percentages of spirometric abnormalities increased gradually from low-viremic to high-viremicpatients (29%, 53.5% and 85.7% respectively). The Chi-Square Independence test showed a significant moderate correlation between viremia level and the percentage of spirometric abnormalities (Cramer's U value=0.452, $p=0.002$). A normal PFT result was determined in only a minority (14.3%) of high-viremic patients.

As shown in Figure 1 and Figure 2, the spirometric parameters FEV1 and FVC were significantly reduced in high-viremic and low-viremic patients compared to those in non-viremic patients ($p=0.013$ and $p<0.001$respectively). There were no significant differences in FEV1/FVC ratio between the three groups ($p=0.432$)(Table 1).

PFT results showed a predominantly restrictive pulmonary dysfunction (26.6%) followed by mixed pulmonary dysfunction (5%). The distribution of pulmonary function patterns in the three groups is shown in Figure 3.

The APRI scores were significantly lower in the non-viremic group than in the low-viremic and high-viremic groups ($p<0.001$). However, there was no correlation between APRI scores and spirometric parameters FEV1, FVC, FEV1/FVC (Spearman correlation coefficients were -0.065, -0.081 and -0.170 respectively).

Logistic regression analysis was applied to ascertain the effects of viremia level, age, BMI, gender and smoking history on the likelihood of developing pulmonary dysfunction. The model explained 37% (Nagelkerke R 2) of the variance in pulmonary dysfunction and correctly classified 70% of cases. High viremic patients were 14.2 times more likely to exhibiting pulmonary dysfunction than non-viremic patients. A high viremia level [odds ratio (OR)=14.202, confidence interval (CI)=2.324-86.805; $p=0.004$] was found to be a significant predictive factor for the occurrence of pulmonary dysfunction.

Discussion

There is increasing evidence suggesting that CHC infection can play an important role in interstitial pneumonitis, pulmonary fibrosis, the initiation/exacerbation of pre-existing asthma and COPD.[2] Previous research has demonstrated that HCV-related pulmonary disorders are mostly asymptomatic, which means that these disorders are mostly underdiagnosed or delayed.[3,8] On the other hand, pulmonary fibrosis causes a progressive and devastating loss of pulmonary functions.[4] Therefore, diagnosis of pulmonary involvement in the early stages is of great importance. To examine all HCV infected patients for lung function would not be cost-effective, so it is important to identify HCV-infected patients who are at increased risk of pulmonary involvement. As, the prognostic relevance of baseline HCV RNA levels is known,whether or not there was a causal relationship between viral load levels and pulmonary involvement was investigated in this study.[9]

The results of the current study showed that the presence of viremia is associated with an increased rate of pulmonary disorders, especially at high levels of viremia. Surprisingly, patients with high viremia were found to be 14.2 times more likely to have a spirometric abnormality than non-viremic patients.Moreover, there was a moderate significant association between viral load level and the rate of spirometric abnormalities. This association may be explained by the greater number of patients in the high-viremic group and low-viremic group with advanced hepatic fibrosis compared to the non-viremic groups. However, there was no association between APRI scores and lung functions. In accordance with the present results,recent studies using PFTs have failed to find any association between the severity of hepatic disease and the presence of interstitial lung changes.[8,10] Another possible explanation for this is that if HCV induces chronic inflammation in the lung, higher levels of viremia might be associated with a higher degree of inflammation and may contribute to the high rates of pulmonary disorders.[11] This hypothesis was supported by the findings of a prospective study conducted by Kanazawa et al who found that lung damage in viremic CHC patients can be reversed or returned to normal with successful eradication of the HCV infection.[12]

In reviewing the literature, pulmonary dysfunction in CHC patients was predominantly restrictive as shown by Abbas et al.[13] Similarly, in the current study, the most commonly detected spirometric abnormalities wererestrictive and mixed patterns.This result also supports previous research into this issue which has linked CHC infection and interstitial lung disease.[8,14]

Another important finding in this study was that the spirometric parameters, FEV1 and FVC, were significantly lower in high-viremicand low-viremic groups compared to thenon-viremic group. These findings suggested that a high viremia level is associated with reduced lung functions in patients with CHC, and are consistent with those of Ezzeldin et al who reported an association between the presence of CHC infection and decline in lung functions and also stated that treatment of the CHC infection may improve pulmonary functions.[15] Similarly, a 6- year follow up study,which confirmed this finding in asthmatic patients with CHC infection, showed that the annual decline in DLCO was higher in IFN non-responders than IFN responders.[4] However, the results of that study were not compatible with those of Foster et al who found no association between lung functions and viral load levels in CHC patients.[16]

In the current study, 48.3% of the patients had an abnor-

mal PFT result, while only 25% had a history of previous lung disease, which indicates that a large proportion of CHC patients have subclinical pulmonary disorders. This result is consistent with the findings of a study by Erturk et al, which showed a high rate(75%) of pulmonary disorders in CHC patients without pulmonary symptoms.[3]
There were a number oflimitations in this study.First of all, the sample size is very small. This limitation means that study findings need to be interpreted cautiously. In addition, we have no histologic data for determine the stageof liver fibrosis which might affect pulmonary functions. Therefore, we used APRI to evaluate liver fibrosis stages in CHC patients. Despite these limitations, this research has highlighted the importance of careful monitoring of high-viremic CHC patients for lung functions, even if they have no pulmonary symptoms.

Conclusion

The results of this study indicate that active HCV infection may be associated with reduced pulmonary functions, especially in patients with high viremia levels.In addition, the results of this study further support the idea that CHC patients may have sub-clinical pulmonary disorders. Therefore, these patients should be carefully monitored with regular PFTs for sub-clinical pulmonary disorders. Nevertheless, larger, prospective trials are needed to determine whether there is a definitive causal relationship between HCV viral load levels and pulmonary disorders.

Conflict of interest

None declared.

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