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## Original Article

# Impact of Hepatitis C Virus Co-Infection on Tuberculous Patients

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## ABSTRACT

**Background:** Tuberculosis [TB] and hepatitis C virus [HCV] infections are both common infectious diseases. Although HCV infection is frequent in patients with TB, few studies have been conducted worldwide and there is still little evidence concerning this topic.

**Aim of the work:** To assess the prevalence of HCV infection among tuberculous patients and to investigate its impact on tuberculosis and its treatment outcome.

**Patients and Methods:** A cross-sectional study was done on 500 tuberculous patients. Socio-demographic data, clinical history and examination, clinical severity, response to drugs, laboratory and radiological investigation, Tuberculin skin test, and HCV screening were done.

**Results:** HCV infection was detected among 54 tuberculosis patients [10.8%]. HCV- positive patients suffered more from almost all clinical presentation than HCV- negative patients but without statistical significant difference. Tuberculin skin test induration and reactions were more in HCV- negative patients with  $17.9 \pm 4.9$  mm compared to  $12.9 \pm 2$  mm in HCV- positive patients. Lung cavitation and lung infiltration were the most predominant radiological finding among HCV- positive patients. CAT [category] IV and modified CAT I were the most treatment regimen used in HCV- positive patients. Failure of treatment was significantly higher among HCV- positive patients [59.3%] compared to 9.9% of their counterparts. Moreover, multidrug resistance [MDR] and rifampicin resistance were significantly higher in HCV- positive group than their comparable group [31.5% and 29.6%, and 9% and 4.3% respectively].

**Conclusion:** Co-infection of HCV in Patients with TB is frequent. It increases the frequency of almost all clinical presentation and had its predominant findings on laboratory and radiological investigations. Co-infection also alters the response to TB treatment and should be screened among tuberculous patients before treatment and closely monitored during treatment to detect early any drug resistance or treatment failure.

**Keywords:** Tuberculosis; Hepatitis c; Multidrug Resistant; Treatment Failure

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\* Main subject and any subcategories have been classified according to the research topic

## INTRODUCTION

Both tuberculosis [TB] and hepatitis C virus [HCV] are threatening infectious diseases and they constitute major health problems, especially in endemic countries. The occurrence of TB/hepatitis co-infection is a considerable clinical and public-health challenge, as it may cause serious health hazards and put a significant burden on the community [1]. Generally, the prevalence of HCV infection in patients with TB has not been extensively studied. Only a limited amount of data on the rates of TB/HCV co-infection exists [2].

HCV has impact on the immune system, as the HCV-positive patients' present relative decline in naïve T cells accompanied by impaired lymphocyte proliferative responses, which is essential in the defense against TB. The deteriorated cellular immune response on account of HCV infection would facilitate the development of intracellular infection [3]. The effect of HCV on TB-specific CD4+ T cells may be a mechanism for accelerated TB disease progression in TB/HCV-co-infected patients. This is because functionally impaired CD4+ T cells may be unable to control TB replication, especially when this is accompanied with an increased level of IL-10 in the serum [4]. Dendritic cells generated in vitro from peripheral blood of individuals with HCV infection appear impaired in their capacity for antigen presentation, which correlates with decrease and dysfunction of dendritic cells. Moreover, HCV core protein could bind to and inhibit the receptor of tumor necrosis factor-alpha [TNF- $\alpha$ ]. As TNF- $\alpha$  is essential cytokines for acute TB control [5].

Chronic liver disease raises the risk of hepatotoxicity during anti-tuberculosis treatment, up to three to five times more than tuberculous patients without a viral infection. This leads to increased complexity in the treatment of this group of TB/HCV patients [6].

## AIM OF THE WORK

Although HCV is globally prevalent, the frequency of co-infection with TB, and the potential impact of this co-infection on the course and treatment outcome of TB disease have received little attention. Thus, the current study was conducted to assess the prevalence of HCV infection among tuberculous patients and to investigate its impact on tuberculosis and its treatment outcome.

## PATIENTS AND METHODS

The current study is a cross-sectional that was conducted on 500 tuberculous patients who were randomly chosen from the attendees of four Chest hospitals [Mansoura Chest Hospital, Abassia chest hospital, Mahalla

Chest Hospital, and Damietta chest hospital] during the period from October 2017 to December 2019.

**Sample size:** Sample size [N] was calculated from the following formula:

$$N = Z_{\alpha/2}^2 * p * [1-p] / MOE^2 [7].$$

Where  $Z_{\alpha/2}$  is the critical value of the normal distribution at  $\alpha/2$  [for a confidence level of 95%,  $\alpha$  is 0.05 and the critical value is 1.96], MOE is the margin of error=4%,  $p$  is the prevalence of HCV among tuberculosis patients considering previous study [17%] [8]. Consequently,  $N = [1.96]^2 * 0.17 * 0.83 / [0.04]^2 = 339$ . So, our sample size is 339 eligible patients with TB who were increased to 500 during the field work to compensate for the probable dropout.

**Inclusion criteria:** Patients with Mycobacterium tuberculosis infection [pulmonary and extra pulmonary tuberculosis], aged 14 years and above from both sexes.

**Exclusion criteria:** Tuberculous patients have any malignancies or with history of chemotherapy or radiotherapy exposure.

**Ethical considerations:** The study objectives and tools were explained to the participants. This study was conducted after approval by the institutional review board [IRB], faculty of medicine for girls Al-Azhar University, Cairo, Egypt. Participation was voluntary; informed consent was obtained from each study participant before enrollment in the study. Withdrawal from the study was assured for all participants without giving any reasons and without affecting their rights of medical care. Also, data were anonymous and coded to assure confidentiality of participants.

## Tools and data collection

- Socio-demographic data with special emphasis on age/years, sex, residence, and occupation,
- Clinical history and proper examination were carried out.
- Complete blood count, kidney and liver function tests, erythrocyte sedimentation rate were done using HITACH9-911 TM autoanalyzer.
- All patients underwent a standard single view plain X-ray chest with postero-anterior view to detect any findings suggestive of pulmonary tuberculosis. CT chest was done for the most indicated and suspicious cases.
- Tuberculin skin test: intradermal injection of 0.1 mL of a liquid containing 5 TU of PPD. Proper injection was evaluated by the appearance of a pale and discrete elevation of the skin [6mm-10mm] in diameter. Skin test was interpreted based on the presence or absence and

the amount of induration [localized swelling] after 72 h.

- Sputum smear microscopy was done for all patients. Patients were asked to collect the first sample at the time of the consultation when the patient was identified as a suspected TB case. The second sample was collected in the early morning the day after the initial consultation. The samples were stained by Ziehl-Neelsen stain.
- Sputum or body fluid samples were collected from the patient with suspected TB and Gene Xpert was done using [Cepheid gene Xpert MTB\RIF assay device Sunnyvale, California].
- In all patients, HCV antibody rapid test was done, 3 ml of venous blood samples was drawn were 5 ul of serum was transferred by pipette to the specimen well of the test device then 2 full drops of buffer were added then positive or negative or invalid results were interpreted.
- HCV RNA PCR test was done using [step One Real time PCR System] to confirm a diagnosis of hepatitis c virus infection. A viral load over 800,000 IU/ml was considered high. A low viral load would be less than 800,000 IU/ml.

**Statistical analysis:** Analysis of data was carried out with SPSS version 21. Testing the normality of data was done with one-sample Kolmogorov-Smirnov test. Number and percentage were used to describe qualitative data. Association between categorical variables was tested using chi-square test. Continuous variables were described as mean ± SD [standard deviation] for parametric data and median for non-parametric data. The two groups were compared with student t- test when data were parametric while non- parametric data were compared by Mann–Whitney U test.

**RESULTS**

The prevalence of HCV infections among the studied tuberculous patients was 10.8% [Table 1].

Mean age was significantly higher among HCV- positive than HCV-negative tuberculous patients [49±12.4 and 40.4 ±12.7 respectively P=0.000]. Regarding gender 96.3% of the HCV- positive were male comparing to 81.4% of negative HCV patients [p <0.05]. Concerning occupation, marital status, and residence there were no statistically significant differences between HCV- positive and negative groups [Table 2].

HCV- positive patients suffered in more frequencies from all clinical presentation than HCV- negative patients without statistical significant difference except for chest pain [p <0.05] [Figure 1].

Great affection was detected regarding platelet count and liver function tests [including serum albumin, serum bilirubin, ALT and AST] in HCV- positive patients compared with HCV- negative patients with high significant differences [p<0.001]. Positive smear results were noticed more in HCV- positive tuberculous patients [92.5%] compared to their comparable group [78.69%] with a statistically significant difference. Tuberculin skin test was positive among 42.6% of HCV- positive patients compared to 70% of HCV- negative patients with a statistically significant difference [p<0.001]. Tuberculin skin test induration and reaction was significantly lower [12.9 ± 2 mm] in HCV- positive patients than their counterparts [17.9 ± 4.9 mm] [Table 3].

Radiological findings in general were noticed more in HCV- positive tuberculous patients. Both lung cavitation and lung infiltration were more frequent among HCV- positive tuberculous patients compared to HCV- negative ones. Lung masses or nodules and paravertebral abscess were much less common in HCV- positive compared to HCV- negative patients. Lung destruction and pleural effusion were more prevalent among HCV- positive patients compared to HCV- negative patients. All these differences were statistically insignificant [Table 4]

Regarding clinical profile of TB in the patients being studied, it was found that most of HCV- positive and negative patients were presented by pulmonary tuberculosis [77.7% and 84.7% respectively p value >0.05]. Concerning treatment, failure of treatment was higher among HCV- positive patients [59.3%] compared to 9.9% of HCV- negative ones with a high statistically significant difference [p< 0.001]. In addition, CAT IV and modified CAT I were the most treatment regimen used in HCV- positive patients [61.1% and 38.9%] respectively compared to 10.7% and 0.4% in HCV- negative patients with a high statistically significant difference [p<0.001]. High incidence of drug resistance by GENEXERT was detected in HCV- positive patients as about one- third of them [31.5%] showed multidrug resistance [MDR] and 29.6% of them were rifampicin resistance compared to 9% and 4.3% respectively in HCV- negative patients with a high statistically significant difference [p<0.001] [Table 5].

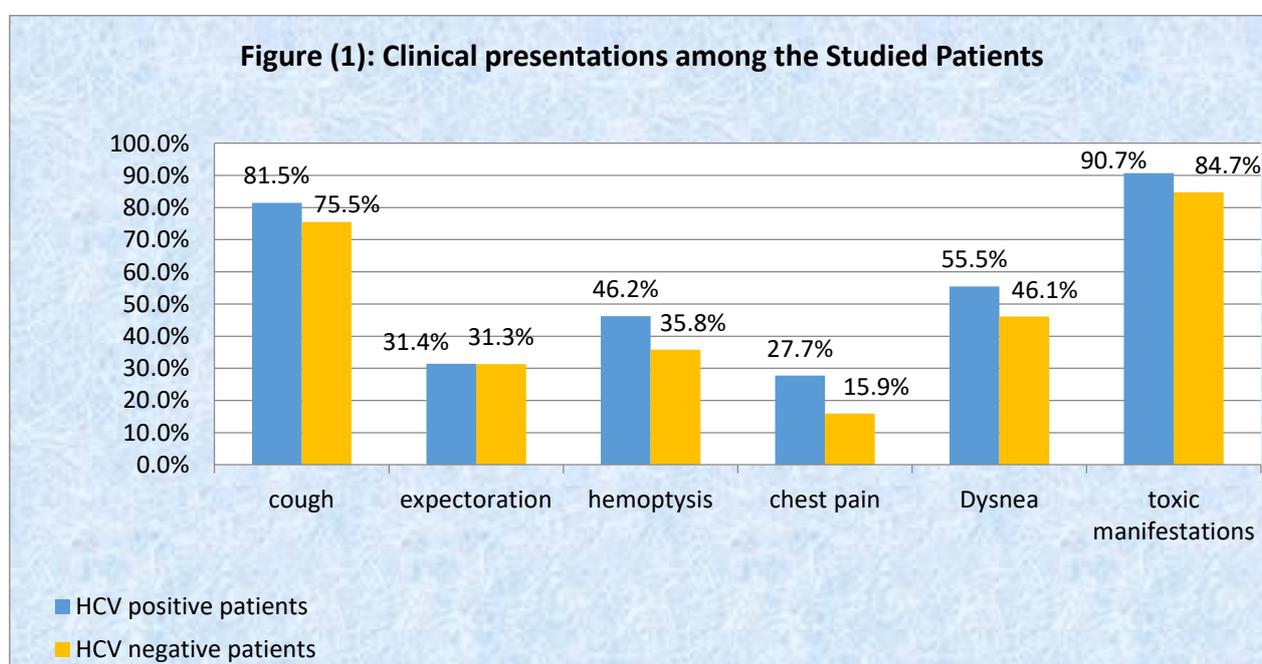
**Table [1]:** Prevalence of HCV among Tuberculous patients

Tuberculous patients [n=500]	
HCV results	No. [500]
Positive	54 [10.8%]
Negative	446 [89.2%]

**Table [2]:** Comparing between both groups regarding laboratory data

		HCV- positive Patients [n=54]	HCV- negative Patients [n=446]	Test	P value
<b>Age in years:</b>	≤ 20	1 [1.9%]	20 [4.48%]	29.1	<b>0.000**</b>
	21-40	11 [20.4 %]	216 [48.4%]		
	4-60	31 [57.4%]	188 [42.1%]		
	61-75	11 [20.4%]	22 [4.9 %]		
	Mean ± SD	49±12.4	40.4 ±12.7		
<b>Gender</b>	Male	52 [96.3%]	363 [81.4%]	7.5	<b>0.004*</b>
	Female	2 [3.7%]	83 [18.6%]		
<b>Marital status</b>	Single	3 [5.6%]	105 [23.5%]	11.15	<b>0.006*</b>
	Married	49 [90.7%]	313 [70.2%]		
	Divorced	0 [0%]	9 [2%]		
	Widowed	2 [3.7%]	19 [4.3%]		
<b>Residence</b>	Upper Egypt	8 [14.8%]	68 [15.2%]	0.46	0.794
	Delta	37 [68.5%]	307 [68.8%]		
	Cairo	8 [14.8%]	55 [12.3%]		
	Frontiers	1 [1.9%]	16 [3.6%]		
<b>Occupation</b>	Workers	33 [61.1%]	307 [68.8%]	1.32	0.28
	Non-workers	21 [38.9%]	139[31.2%]		

\*significant difference [p value&lt;0.05].

**Table [3]:** Laboratory findings among the studied patients

	HCV- positive Patients [n=54]	HCV- negative Patients [n=446]	Test	P value
<b>HB</b>	11.9 ±1.7	11.6 ±1.7	11166	0.382
<b>WBCs</b>	8.9±3.4	9.4± 4.0	11329.5	0.477
<b>PLT</b>	252± 111.0	335± 122.0	7012	<b>.000**</b>
<b>ESR</b>	67±29.0	69.18±29.0	11327.5	0.476
<b>Albumin</b>	3.33±0.4	4.06±.49.0	2696	<b>.000**</b>
<b>Bilirubin</b>	1.5 ±0.56	.87±.19.0	1933.5	<b>0.000**</b>
<b>ALT</b>	49.9± 27.4	21±11.1	3009	<b>0.000**</b>
<b>AST</b>	52.9±31	22.6±13	2803	<b>0.000**</b>
<b>S. creatinine</b>	.87 ±.18	0.83 ±0.18	10776	0.2
<b>Positive Smear result</b>	50 [92.5%]	351 [78.69%]	5.85	<b>.017*</b>
<b>Tuberculin skin test</b>	23 [42.6%]	312 [70%]	16.3	<b>0.000*</b>
Negative	31 [57.4%]	134 [30%]		
<b>Tuberculin Skin Test mean ± SD</b>	12.9 ± 2.0	17.9 ± 4.9	1178.5	<b>0.000*</b>

\*significant difference [p value&lt;0.05].

**Table [4]:** Radiological findings among the studied patients

		HCV- positive Patients [n=54]	HCV- negative Patients [n=446]	Test	P value
<b>Radiology</b>	Normal	0 [0%]	10 [2.24%]	1.23	0.61
	No	17 [31.4%]	155 [34.75%]		
<b>Cavitary lesion</b>	The right lung	14 [25.9%]	73 [16.36%]	4.86	0.23
	The left lung	1 [1.85]	33 [7.39%]		
	Bilateral	22 [40.7%]	185 [41.47%]		
<b>Lung infiltrate</b>	No	17 [31.4%]	155 [34.75%]	4.57	0.22
	The right lung	14 [25.9%]	75 [16.8%]		
	The left lung	1 [1.85]	33 [7.39%]		
	Bilateral	22 [40.7%]	183 [41.03%]		
<b>Paravertebral abscess</b>		0 [0%]	4 [0.89%]	0.488	0.485
<b>Lung mass</b>		0 [0%]	6 [1.34%]	0.735	0.391
<b>Destroyed lung</b>	No	48 [88.88%]	403 [90.35%]	0.637	0.611
	The right lung	4 [7.4%]	34 [7.62%]		
	The left lung	2 [3.7]	9 [2.01%]		
<b>Pleural effusion</b>	The right lung	4 [7.4]	29 [6.5%]	0.41	0.834
	The left lung	2 [3.7%]	13 [2.91%]		
	Bilateral	0 [0%]	2 [0.44%]		

**Table [5]:** Tuberculosis profile and treatment outcome among the studied patients

		HCV- positive Patients [n=54]	HCV- negative Patients [n=446]	Chi square	P value
<b>The type of TB</b>	pulmonary	42 [77.7%]	378 [84.7%]	1.87	0.391
	Extra pulmonary	10 [18.5%]	59 [13.2%]		
	Pulmonary and extra pulmonary	2 [3.7%]	9 [2%]		
<b>TB category</b>	New	19 [35.2%]	308 [69.1%]	91.1	<b>0.000*</b>
	Relapse	2 [3.7%]	60 [13.5%]		
	Defaulter	1 [1.9%]	34 [7.6%]		
	Failure	32 [59.3%]	44 [9.9%]		
<b>TB Treatment</b>	CAT I	0 [0.0%]	298 [66.8%]	250.0	<b>0.000*</b>
	Modified CAT I	21 [38.9%]	2 [0.4%]		
	Cat II	0 [0.0%]	91 [20.4%]		
	Cat IV	33 [61.1%]	55 [10.7%]		
<b>Drug resistance</b>	Non- resistant	21 [38.9%]	387 [86.8%]	79.2	<b>0.000*</b>
	Rifampicin resistance	16 [29.6%]	19 [4.3%]		
	Multidrug resistant	17 [31.5%]	40 [9%]		

\*: significant difference [p value<0.05].

## DISCUSSION

Tuberculosis and HCV are still among the most life-threatening infectious agents. They have a high mortality rate in adults especially in developing countries where these two diseases have similar epidemiological risk factors [9]. However, the causal link between HCV infection and TB risk is still unclear. Prevention, care, and treatment of TB and HCV can be successful, and both diseases can be cured. Inadequate disease screening, limited and insensitive diagnosis, difficult treatment regimens with varying toxicities, and complicated pharmaco-kinetic and pharmaco-dynamic drug interactions; these could result in delayed diagnosis, acknowledged treatment initiation, and low rates of completion, with the possibility for generation and spread of drug resistant organisms [10].

Thus, the current study was done to assess the prevalence of HCV infection among tuberculous patients and to investigate its impact on tuberculosis and its treatment outcome. The prevalence of HCV among patients with TB varies internationally. HCV prevalence was reported by Reis *et al.* [11] to be 7.5% while in Thailand, a study revealed a very high prevalence of HCV [31%] [12]. Another study carried out in Georgia, Richards *et al.* [13] found that 22% were HCV seropositive, and Kuniholm *et al.* [14] revealed 12% HCV-positives, while Wang *et al.* [7] showed HCV 6.7%, Khalil *et al.* [15] documented HCV co-infections in TB were 28 [27.45%]. We studied five Hundred patients with tuberculosis either pulmonary or extra pulmonary, and found that 10.6% of them were positive for HCV, most of HCV- positive and negative patients were presented by pulmonary tuberculosis [77.7% and 84.7% respectively].

HCV-positive patients were found to be more prevalent among the age group 41-60 years with male predominance. Supporting to the current study, Merza *et al.* [16] found male predominance with 127 [59.3%] males and 87 [40.7%] females. The mean age of the patients was 40.34 years  $\pm$ 20.29. In the same line, Behzadifar *et al.* [17] showed that men had a higher risk of HCV than women. In disagreement with the current study, Kuniholm *et al.* [14] showed that HCV seropositivity in patients with TB did not differ significantly by gender.

Concerning laboratory findings among tuberculosis patients, there was a statistically significant difference among HCV-positive and HCV-negative tuberculous cases in terms of PLT, albumin, bilirubin, ALT, AST [ $p < 0.001$ ] for each of them and positive smear result [ $p = 0.017$ ]. An important note must be considered, significant variations in blood parameters of pulmonary TB and TB-associated co-infected patients [such as HCV] suggest the investigation of associated abnormalities in patients with TB to rule out the co-infection before the start of TB treatment therapy. Similarly, Javed *et al.* [18] stated that there were statistically significant differences among control, cases with TB only and Co-infection TB/HCV cases in terms of RBCs, HB, WBCs, platelet, neutrophil, monocytes, and ESR [ $P < 0.001$ ].

In the current study the Tuberculin skin test was done for all patients, it was positive in 42.6% of HCV- positive patients compared to 70% in HCV- negative patients with statistical significance [ $p < 0.001$ ], and there was a significant smaller tuberculin skin test induration in HCV positive patients with induration  $12.9 \pm 2$  mm compared to  $17.9 \pm 4.9$  in HCV-negative patients [ $p < 0.001$ ]. Compared to Some authors reported the induration mean of the tuberculin skin test to be  $14.7 \pm 6.9$  mm in patients with a viral etiology and  $6.1 \pm 5.4$  mm in those with a non-viral etiology [ $p < 0.05$ ]. Another two studies found insignificant difference between the two groups regarding the tuberculin test [19, 20].

Another important finding of the current study is failure of treatment which was higher among HCV- positive tuberculous patients [59.3%] compared with HCV- negative patients [9.9%] with a high statistically significant difference [ $p < 0.001$ ]. Tuberculous patients with multidrug-resistant co-infected with HCV are more likely to develop drug-induced liver injury [3], one of the most common adverse events during treatment of MDR-TB with reported rates at 9.7%–22.3%. Hence, the treatment of HCV co-infection patients with MDR-TB could be beneficial [21]. Our study showed a high incidence of drug resistance by GENEXERT in HCV-positive patients as about one- third of them showed multidrug resistance [MDR] and 29.6% were rifampicin resistant compared to 9% and 4.3% respectively, in HCV-negative tuberculous patients with a statistically significant value [ $p < 0.001$ ]. Seung *et al.* [22] supported this finding as

they revealed high prevalence of hepatitis C infection among multidrug resistant tuberculous patients.

As regards radiological findings in tuberculous patients, our study illustrated that radiological affection was noticed more frequently in HCV- positive patients. Both lung cavitation and lung infiltration were more frequent among HCV- positive compared to HCV- negative tuberculous patients without a statistically significant difference [ $p = 0.2$ ]. Also there were no statistical significant differences among HCV- positive and HCV- negative tuberculosis cases in paravertebral abscess [ $p = 0.485$ ], lung mass [ $p = 0.391$ ], destroyed lung [ $p = 0.611$ ] and Pleural effusion [ $p = 0.834$ ].

In the same line with our study, Darwish *et al.* [23] studied the effect of HCV infection on patients with pulmonary tuberculosis. They found that diffuse infiltration and cavitory lesion were the predominant findings in HCV patients.

## CONCLUSION

Co-infection of HCV in Patients with TB is frequent. It increases the frequency of almost all clinical presentation and had its predominant findings on laboratory and radiological investigations. Co-infection also alters the response to TB treatment and should be screened among tuberculous patients before treatment and closely monitored during treatment to detect early any drug resistance or treatment failure.

## Financial and Non-financial Relationships and Activities of Interest

None

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