

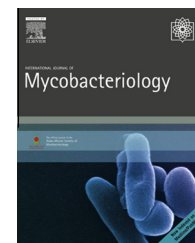


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Full Length Article

Low prevalence of hepatitis B and C among tuberculosis patients in Duhok Province, Kurdistan: Are HBsAg and anti-HCV prerequisite screening parameters in tuberculosis control program?

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ABSTRACT

Objective/background: Viral hepatitis, particularly hepatitis B virus (HBV) and hepatitis C virus (HCV), infections and tuberculosis (TB) are a global public health concern. Co-infection with HBV or HCV among TB patients may potentiate the risk of hepatotoxicity induced by anti-TB drugs. Hence, the aim of this study was to identify the prevalence of HBV and HCV among TB patients included in the Duhok National Tuberculosis Program (NTP). **Methods:** The Duhok NTP Center is a specialized institution in Duhok City, Iraq, concerned with management and follow-up of TB patients. A cross-sectional study was conducted at the center between June 2015 and May 2016. All documented TB patients were analyzed on the basis of socio-demographic and other characteristics. Thereafter, all patients underwent screening for hepatitis B surface antigen (HBsAg), anti-HCV, and anti-HIV using enzyme-linked immunosorbent assay (ELISA). The results obtained were analyzed by entering the data in binary format into a Microsoft Excel spreadsheet. A *p* value of <0.05 was considered to be statistically significant. **Results:** Two-hundred fourteen documented TB patients were recruited in this study, with 127 (59.3%) males and 87 (40.7%) females. The mean age of the patients was 40.34 years (± 20.29). Of the total number of patients, four cases (1.8%) were HBsAg-positive and one case (0.9%) was positive for anti-HCV. The variables significantly associated with HBV were history of surgical dental procedure [odds ratio (OR), 0.04; 95% confidence interval (CI), -0.01 to 0.04; *p* = .03], and nationality (OR, 13.67; 95% CI, 0.46–210.85; *p* = .007). **Conclusion:** The prevalence of HBV and HCV co-infection among TB patients in this study was low. This may be explained by the low rate of blood transfusion among the patients, the very low prevalence of HIV

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infections in Kurdistan, the negative history of injection drug use, and adherence to universal infection-control measures, including vaccination for HBV. Both history of dental intervention and belonging to a Syrian population were independent risk factors for HBV/TB co-infection.

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Introduction

Viral hepatitis, particularly hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, are a global public health concern because they are the leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. HBV infects around one-third of the world population, with 400 million patients that are chronically infected [1]. Chronic HCV infection also affects approximately 170 million individuals, that is, 2.5% of the world population [2]. Hepatitis B and C show great diversity in their prevalence in different parts of the world. The World Health Organization reports a prevalence of HBV and HCV infections in the eastern Mediterranean region of 2–4% and 1–4.6%, respectively [3]. Studies on the general population in Iraq for the years 2006 and 2007 revealed a prevalence of 1.6% and 0.04% for HBV and HCV, respectively [4]. Tuberculosis (TB) has also emerged as a serious public health problem; it is recognized alongside HIV as a leading cause of death worldwide. In 2014, TB caused 9.6 million new cases and killed 1.5 million people [5]. According to a recent report by the World Health Organization, Iraq is a relatively high-TB-burden country in the eastern Mediterranean region, with an estimated incidence rate of 43/100,000 and a case-detection rate of 54% [5]. The war and the unstable security situation in Iraq make access to healthcare facilities difficult. Hence, maintaining treatment and follow-up for TB patients is a priority, especially for patients who have fled their home and subsequently discontinued treatment, and for locations with low case-detection rate. Drug-induced hepatotoxicity is a recognized side effect of anti-TB drugs, particularly rifampicin, isoniazid, and pyrazinamide. TB patients with HBV and/or HCV co-infections have increased susceptibility to the potential hepatotoxic effects of first-line anti-TB drugs and thus may require discontinuation of their treatment [6].

Therefore, chronic liver disease in patients with TB makes TB treatment challenging. Hence, the present cross-sectional study was done to identify the prevalence of HBV and HCV infections in TB patients at the Duhok National Tuberculosis Program (NTP) Center. To our knowledge, this is the first study on the prevalence of HBV and HCV infections among TB patients in Iraq.

Patients and methods

Setting

The Tuberculosis Respiratory Diseases Consultation Center, or NTP center, is a specialized institution in Duhok City concerned with management and follow-up of TB patients. It is

provided with a laboratory, an X-ray unit [i.e., a chest X-ray (CXR) unit], and pharmacy mainly for anti-TB drugs. It is responsible for all TB cases in the governorate, engaging in supervision and implementation of the Directly Observed Treatment, Short-Course (DOTS) program.

Study design and patients

The study was conducted at the NTP Center in Duhok Province between June 2015 and May 2016. All documented pulmonary and extrapulmonary TB patients, who were confirmed by standard protocol using acid-fast-bacilli smear microscopy, GenXpert molecular assay, radiological examination, and/or biopsy, were included in the study. Patients were included in the study after obtaining written informed consent. Information on socio-demographic and other patient characteristics was collected by using a standard questionnaire.

Laboratory diagnostic testing for HBsAg and anti-HCV

All patients underwent screening for hepatitis B surface antigen (HBsAg), anti-HCV, and anti-HIV using enzyme-linked immunosorbent assay (ELISA). Two 5-mL samples of blood for detection of HBV and HCV markers were taken from each participant. Serum specimens were tested for HBsAg and anti-HCV by ELISA (Fortress Diagnostics Limited, Antrim, UK) according to manufacturer instructions [7,8].

Statistical analysis

The results obtained were analyzed by entering the data in binary format into a Microsoft Excel spreadsheet. A *p* value of <.05 was considered to be statistically significant.

Results

A total of 214 patients with TB attending the TB services at the NTP center Duhok were enrolled in this study. The mean age of the patients was 40.34 years (± 20.29); 127 (59.3%) were male and 87 (40.7%) were female, giving a sex ratio of 1.46:1. Of the total patients, 155 (72.4%) were new TB cases and 59 (27.6%) were previously treated patients. The majority of TB patients had pulmonary manifestation (197, 92.1%) and were of Iraqi nationality (97.2, 97.2%; Table 1).

Out of the 214 TB patients recruited in the study, four cases (1.8%) were HBsAg-positive and one case (0.9%) was positive for anti-HCV. None of the TB patients had HBV and HCV co-infection (Table 2, Fig. 1). Table 3 shows the number and crude

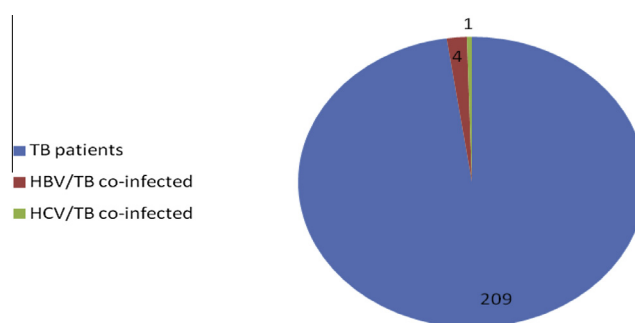
Table 1 – Characteristics of 214 tuberculosis cases in Duhok Province, Kurdistan.

Parameter	Variable	Number	Percentage (%)
Age	Mean age	40.34 ± 20.29	
Gender	Male	127	59.3
	Female	87	40.7
Type of patient	New cases	155	72.4
	Previous TB treatment	59	27.6
Site of disease	Pulmonary	197	92.1
	Extrapulmonary	17	7.9
Region of origin	Iraq	208	97.2
	Others (Syria, Turkey)	6	2.8

odds ratio for HBV patients for each of the variables analyzed. The variables significantly associated with HBV were history of surgical dental procedure [odds ratio (OR), 0.04; 95% confidence interval (CI), –0.01 to 0.04; $p = .03$] and nationality (OR, 13.67; 95% CI, 0.46–210.85; $p = .007$; Table 3).

Discussion

HBV and HCV co-infection among TB patients undergoing anti-TB treatment may increase the risk of drug-induced hepatotoxicity. Hence, we conducted this study to identify the frequency of HBV and HCV infection among TB patients. In our study, four TB cases (1.87%) were found to be co-infected with HBV, and one case (0.47%) with HCV. The prevalence of HBV infection in this study was lower than that reported in most previous studies. Reported prevalence rates are 26.8% in Rio de Janeiro, Brazil [9], and 19.8% in Argentina [10]. Studies in Georgia [11] and Taiwan [6] showed prevalence rates of 13% and 11.7%, respectively. It is noteworthy that a substantial number of TB patients with HBV infection had concomitant HIV infection in the aforementioned studies. Hence, the variations in the prevalence between our study and the studies done abroad may be partially explained by the markedly lower prevalence of HIV infection in our population. An explanation for the low rate of HBV observed in our study is the adherence to universal infection-control measures, including HBV vaccination. Our study also revealed a low HCV sero-prevalence among TB patients. There are wide variations in the prevalence of HCV among HCV co-infected TB patients reported in studies from different countries: An HCV frequency as high as 31% was reported in Thailand [12]. The reported prevalence is 7.5% in Central Brazil [13] and 22% in Georgia and Pakistan [14,15]. Kuniholm et al. [11], Wan et al. [6], and Khalili et al. [16] found prevalence rates of 12%, 6.7%, and 27.45%, respectively. A study by Badawy et al. that involved 135 TB patients revealed an HCV co-infection rate of 6.4% [17]. These variations may reflect

**Fig. 1 – Overall prevalence of HBV and HCV infections among tuberculosis patients (N = 214).**

regional differences in the prevalence of hepatitis C infection, the differential use of diagnostic modalities [ELISA, polymerase chain reaction (PCR), recombinant immunoblot assay (RIBA)], or both. The low HCV sero-prevalence in our study could be explained by the fact that our study population had no history of injection drug use and that only a small number of patients had received a blood transfusion. In agreement with this finding, in 2014 a low HCV sero-prevalence (0.14) was reported among patients who underwent elective surgery at Duhok Emergency Hospital [18].

In general, patients in our study are young, which is in agreement with other studies [19] and confirms that TB is a disease of economically productive age groups. In the study, an age of around 43 years is associated with HBV infection, consistent with a similar study on Iraqi patients [20]. Age is considered to be a cumulative risk factor for HBV infection through blood, blood products, and sexual routes. A patient with HCV aged 35 years had a history of blood transfusion, indicating the possibility of transmission through this route. In the present study, TB clinical manifestations were typical of TB cases for the majority of pulmonary cases (197, 92.1%). The frequency of extrapulmonary TB in this study was lower

Table 2 – Demographic profiles of tuberculosis patients co-infected with HBV and HCV (N = 214).

Serological marker	Number	Mean age	Percentage (%)
HBsAg	4	43.25 ± 12.60	1.87
Anti-HCV	1	35	0.47

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 3 – Factors associated with hepatitis B virus infections among tuberculosis patients in Duhok Province, Kurdistan.

Variable		HCV patients (n)	HBV patients (n)	Total patients (n)	OR (95% CI) (HBV patient)	p value (HBV patients)
Age	Age < 45 y	0	3	127	2.79 (0.28–66.88)	0.52
	Age ≥ 45 y	1	1	87		
Gender	Male	1	3	136	1.78 (0.16–44.12)	0.63
	Female	0	1	78		
Educational status	Uneducated	1	3	117	2.53 (0.23–64.10)	0.40
	Educated	0	1	97		
Marital status	Married	1	2	148	0.44 (0.04–4.47)	0.41
	Unmarried	0	2	66		
Sexual practices	Safe	0	3	202	6.03 (0.22–75.85)	0.09
	Unsafe	1	1	12		
History of blood transfusion	Yes	1	1	25	2.58 (0.10–29.82)	0.09
	No	0	3	189		
History of injection drug use	Yes	0	0	0	–	–
	No	1	4	214		
Smoking	Yes	1	3	145	1.44 (0.13–36.53)	0.75
	No	0	1	69		
Alcohol intake	Yes	1	2	62	2.50 (0.24–25.43)	0.35
	No	0	2	152		
History of surgical operations	Yes	0	2	45	3.88 (0.38–39.10)	0.15
	No	1	2	169		
History of dental intervention	Yes	1	4	99	0.04 (–0.01–0.04)	0.03
	No	0	0	115		
Nationality	Iraqi	1	3	208	13.67 (0.46–210.85)	0.007
	Non-Iraqi	0	1	6		

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio; y, years.

than that in other studies [21]. This difference may be explained by the low prevalence of HIV infection in our locality and the low prevalence of liver cirrhosis induced by viral hepatitis [22].

With regard to risk factors, the history of dental intervention and nationality in the present study were independent risk factors for HBV/TB co-infection. We found that dental treatment is a potential risk factor for HBV infection (OR, 0.04; 95% CI, –0.01 to 0.04; $p = .03$). In concordance with this study, other works have documented similar findings [23,24]. Viral hepatitis particles are well known to be present in oral fluids; hence, they can be transmitted via saliva [25]. Generally, dental intervention by a professional dentist is not a risk factor for HBV transmission; however, intervention by an uncertified dentist can pose a risk [26]. Unqualified dentists are allegedly allowed to work in developing countries [24]; standard precautionary measures are therefore needed in dental treatment to reduce the risk of transmission. In our study, Syrian nationality (data not shown) was significantly associated with HBV/TB co-infection (OR, 13.67; 95% CI, 0.46–210.85; $p = .007$). Syria is a country of intermediate HBV endemicity [27]. Following internal conflict in Syria in 2011, many Syrian immigrants have fled its towns to the Kurdistan region. These displaced refugees pose a potential risk for HBV transmission in Kurdistan, particularly Duhok Province. Similarly, Radun showed increased prevalence of HBV in some parts of northern Europe due to migration of people from intermediate- or high-HBV-prevalence countries [28]. It is worth mentioning that TB patients with HBV/HCV co-infection can develop complications due to chronic liver disease, which in turn can lead to interrupted TB treatment.

Of particular concern are rifampicin, isoniazid, and pyrazinamide, which are among the first-line drugs. These are hepatotoxic drugs, which should be discontinued by patients with deteriorated liver function due to liver disease [6]. Such patients remain infectious and are more likely to experience treatment failure and relapse, which may eventually threaten the TB control program. Therefore, screening TB patients for hepatotropic viruses that induce chronic liver disease may be a valuable measure for reducing the side effects of hepatotoxic anti-TB drugs.

The main limitation in this study was the small sample size; furthermore, we did not determine whether patients were in an active hepatitis state. The presence of significant liver abnormality can result in deferred treatment and, subsequently, to poor treatment outcome. Another limitation was the exclusion of HBV DNA and HCV RNA tests for patients included in the study. This may affect the study results, as it would allow early diagnosis of hepatitis infections, particularly in cases of occult hepatitis and, furthermore, in cases before HBsAg or anti-HCV antibodies were detectable in blood.

In conclusion, the prevalence of HBV and HCV co-infection among TB patients in this study was low. This may be explained by the low rate of blood transfusion among the patients, the very low prevalence of HIV in Kurdistan, the negative history for injection drug use, and adherence to universal infection-control measures, including vaccination for HBV. Both history of dental intervention and nationality were independent risk factors for HBV/TB co-infection. Further prospective studies with larger sample size are needed to ascertain the need for routine screening for HBsAg and anti-HCV for HIV testing in TB patients.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

- [1] A.S. Lok, B.J. McMahon, Chronic hepatitis B, *Hepatology* 45 (2007) 507–539.
- [2] European Association for Study of Liver, EASL clinical practice guidelines: management of hepatitis C virus infection, *J. Hepatol.* 60 (2014) 392–420.
- [3] World Health Organization, Global policy report on the prevention and control of viral hepatitis, from <http://www.who.int/csr/disease/hepatitis/global_report/en/> (accessed 17.05.16).
- [4] World Hepatitis Alliance Viral Hepatitis: Global Policy, from <http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=18148&Itemid> (accessed 14.05.16).
- [5] World Health Organization, Global Tuberculosis Report 2015, from <http://www.who.int/tb/publications/global_report/en/> (accessed 14.05.16).
- [6] J.Y. Wan, C.H. Liu, F.C. Hu, et al, Risk factors during anti tuberculous treatment and implications of hepatitis virus load, *J. Infect.* 62 (2011) 448–455.
- [7] Fortress Diagnostics Limited, HBsAg ELISA (CE 1293), Revision No. 2 MAY/14 V. 2012-02. Antrim, United Kingdom, from <www.fortressdiagnostics.com> (accessed 20.05.16).
- [8] Fortress Diagnostics Limited, Anti-HCV ELISA (CE 1293), Revision No. 2 MAY/14 V. 2013-01. Antrim, United Kingdom, from <www.fortressdiagnostics.com> (accessed 20.05.16).
- [9] C.A. Lal, S.R. Passos, C. Horn, et al, High prevalence of hepatitis B virus infection among tuberculosis patients with and without HIV in Rio de Janeiro, Brazil, *Eur. J. Clin. Microbiol. Infect. Dis.* 24 (2005) 41–43.
- [10] M.A. Pando, C. De Salvo, C.T. Bautista, et al, Human immunodeficiency virus and tuberculosis in Argentina: prevalence, genotypes and risk factors, *J. Med. Microbiol.* 57 (2008) 190–197.
- [11] M.H. Kuniholm, J. Mark, M. Aladashvili, et al, Risk factors and algorithms to identify hepatitis C, hepatitis B, and HIV among Georgian tuberculosis patients, *Int. J. Infect. Dis.* 12 (2008) 51–56.
- [12] C. Sirinak, W. Kittikraisak, D. Pinjeesekikul, et al, Viral hepatitis and HIV-associated tuberculosis: risk factors and TB treatment outcomes in Thailand, *BMC Public Health* 8 (2008) 245.
- [13] N.R. Reis, C.L. Lopes, S.A. Teles, et al, Hepatitis C virus infection in patients with tuberculosis in Central Brazil, *Int. J. Tuberc. Lung Dis.* 15 (2011) 1397–1402.
- [14] D.C. Richards, T. Mikiashvili, J.J. Parris, et al, High prevalence of hepatitis C virus but not HIV co-infection among patients with tuberculosis in Georgia, *Int. J. Tuberc. Lung Dis.* 10 (2006) 396–401.
- [15] M. Ul-Haq, A.S. Arshad, A. Hakeem, et al, High prevalence of hepatitis B & C in TB patients – will it be the next threat to tuberculosis control?, *JSZMC* 4 (2013) 427–431.
- [16] H. Khalili, S. Khavidaki, R. Mehrnaz, et al, Anti-tuberculosis drugs related hepatotoxicity: incidence, risk factors, pattern of changes in liver enzymes and outcome, *J. Pharm. Sci.* 17 (2009) 163–167.
- [17] M. Badawy, M. Taha, L. Mohamed, et al, Hepatitis C virus infection among tuberculosis patients in Sohag Governorate: seroprevalence and associated risk factors, *Eur. Respir. J.* 38 (2011) 4896.
- [18] M.A. Merza, W.M. Hassan, A.S. Muhammad, Frequency of HBV and HCV among patients undergoing elective surgery in a tertiary care referral hospital in Duhok, Iraqi Kurdistan, *JMSCR* 2 (2014) 1810–1815.
- [19] R. Bahl, B. Singh, R. Singh, Prevalence of HIV infection among patients of pulmonary tuberculosis attending chest diseases hospital, Jammu (Jammu and Kashmir), *Indian J. Community Med.* 32 (2007) 288–289.
- [20] A.M. Tarky, W. Akram, A.S. Al-Naaimi, et al, Epidemiology of viral hepatitis B and C in Iraq: a national survey 2005–2006, *Zanco, J. Med. Sci.* 17 (2013) 370–380.
- [21] H.M. Peto, R.H. Pratt, T.A. Harrington, et al, Epidemiology of extrapulmonary tuberculosis in the United States, 1993–2006, *Clin. Infect. Dis.* 49 (2009) 1350–1357.
- [22] Y.J. Cho, S.M. Lee, C.G. Yoo, et al, Clinical characteristics of tuberculosis in patients with liver cirrhosis, *Respirology* 12 (2007) 401–405.
- [23] M.R. Ghadir, M. Belbasi, A. Heidari, et al, Distribution and risk factors of hepatitis B virus infection in the general population of Central Iran, *Hepat. Mon.* 12 (2012) 112–117.
- [24] W.A. Hayajneh, H.A. Masaadeh, Y.A. Hayajneh, A case-control study of risk factors for hepatitis B virus infection in North Jordan, *J. Med. Virol.* 82 (2010) 220–223.
- [25] N. Mahboobi, S.R. Porter, P. Karayiannis, et al, Oral fluid and hepatitis A, B and C: a literature review, *J. Oral Pathol. Med.* 41 (2012) 505–516.
- [26] S. Sali, R. Bashtar, S.M. Alavian, Risk factors in chronic hepatitis B infection: a case-control study, *Hepat. Mon.* 5 (2005) 109–115.
- [27] D. Lavanchy, Chronic viral hepatitis as a public health issue in the world, *Best Pract. Res. Clin. Gastroenterol.* 22 (2008) 991–1008.
- [28] D. Radun, Epidemiology of hepatitis B in Germany, *Viral Hepat.* 12 (2004) 13–14.