doi.org/10.32394/pe.77.46

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PREVALENCE AND RISK FACTORS OF LATENT TUBERCULOSIS INFECTION IN HEMODIALYSIS PATIENTS IN SOUTHWEST IRAN

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ABSTRACT

INTRODUCTION. Tuberculosis (TB) is a significant global health concern, particularly in developing countries. Diagnosing latent tuberculosis infection (LTBI) in hemodialysis patients is crucial because of the risk of developing active tuberculosis in this population due to attenuated immune response. Herein, we assessed the prevalence of LTBI in hemodialysis patients.

METHODS. In this cross-sectional study, we included all patients referred to hemodialysis centers in Kohgiluyeh and Boyer-Ahmad Province, southwest Iran, in 2018 through census sampling. Tuberculin skin test (TST) was utilized to screen the patients for LTBI. All steps were done by trained physicians.

RESULTS. In total, 183 patients (mean age: 59.3, SD= 16.0) were included in the study of which 76 (41.5%) were females, and 107 (58.5%) were males. Neither the patients nor their family members had a history of tuberculosis. Assuming an above 5-millimeter enduration as a positive TST result, 22 patients (12%) had LTBI. None of the demographic or clinical features differed between TST -negative and -positive groups.

CONCLUSION. Hemodialysis patients are prone to LTBI due to several immunological and environmental factors. Screening for LTBI may be beneficial to prevent active tuberculosis in this population.

Keywords: *Latent Tuberculosis, Renal Dialysis, Continuous Renal Replacement Therapy*

Abbreviations

KBP: Kohgiluyeh and Boyer-Ahmad Province;

LMICs: low- and middle-income countries;

LTBI: latent TB infection;

QFT-G: QuantiFERON-TB Gold;

PPD: Purified protein derivative;

TB: Tuberculosis;

TST: Tuberculin skin test;

WHO: World Health Organization;

INTRODUCTION

Tuberculosis (TB) is a significant global health concern, particularly in developing countries. According to the World Health Organization (WHO), in 2020, nearly 1.5 million individuals died as a result of TB (1). Also, after Coronavirus disease 2019, TB is the most lethal infectious organism (1, 2). One of the practical solutions to prevent the transmission of TB is screening for and treating latent TB infection (LTBI), especially for immunocompromised individuals (3).

Hemodialysis is linked to attenuated cellular immune response due to uremia, alterations in the metabolism of immune active proteins, or other specific effects of hemodialysis (4). Compared to healthy individuals and TB-free patients, those on hemodialysis have higher odds of developing active TB, and subsequent mortality (5-7). Also, according to the previous studies, LTBI among hemodialysis patients is more prevalent than in healthy subjects (8, 9).

Several methods have been utilized to diagnose LTBI during the past years, such as tuberculin skin test (TST), T-SPOT.TB, and QuantiFERON-TB Gold (QFT-G) (10, 11). A meta-analysis by Ferguson et al. hinted at the lower sensitivity and almost the same specificity for TST compared to other methods for LTBI diagnosis (10). However, due to the lower accessibility of advanced laboratory tests, TST is an acceptable tool to diagnose LTBI, particularly in low- and middle-income countries (LMICs), where the burden of TB is much higher than in other parts of the world (12, 13).

According to a recent spatio-temporal analysis of TB incidence in Iran, Kohgiluyeh and Boyer-Ahmad (KBP) province, southwest Iran, is one of the high-risk areas for TB. In

the present study, we aimed to determine the prevalence of LTBI among hemodialysis patients in KBP.

MATERIAL AND METHOD

In this descriptive, cross-sectional study, all patients referred to hemodialysis centers in KBP in 2018 were included in the study through census sampling. After obtaining written consent, a complete demographic, occupational and clinical history was obtained from all hemodialysis patients. Variables including age, sex, comorbid disease, education, marital status, residence, cause of renal failure, Bacille Calmette-Guerin (BCG) vaccination, duration of dialysis, use of immunosuppressive drugs, comorbidities history of illness in the individual or family of participants in this study were obtained. In this study, the TST was used to evaluate latent tuberculosis infection using Tuberculin, a sterile solution containing the growth products of or specific substances extracted from the tubercle bacillus. A TST will be positive between three and eight weeks after the initial infection, which is a sign of cellular immunity and increased tissue sensitivity (14). In this research, standard type of 5 units purified protein derivative (PPD) liquid made by Pasteur Institute was prepared and used.

TST evaluation was done with the Mantoux method by trained physicians, (15) in which for all patients who participated in the study, 0.1 ml of PPD fluid was injected with insulin syringe (number 26) intradermally in the anterior part of the forearm which was not used for dialysis. The results were evaluated and recorded 48-72 hours later. Enduration and stiffness less than 5 mm was considered as negative, between 5 mm and 10 mm as suspicious, and above 10 mm as a positive test result. An enduration and stiffness of above 5mm were also considered positive in immunosuppressive patients (14, 16).

Data were imputed and analyzed using SPSS 23 software (IBM Corp., Armonk, N.Y., USA). Descriptive statistics including frequency, mean and standard deviation (SD) were used to report the findings. Then, independent sample t-test was used to compare the groups with each other for quantitative variables and Chi-square test was used for nominal qualitative variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 183 patients were evaluated, with ages ranging from 16 to 88 years old (mean: 59.3, SD= 16.0). None of the patients had a history of TB in themselves or their family members. Regarding education, 142 (77.6%) were illiterate, while 41 (22.4%) were educated (diploma or higher). The majority (76%) of TSTs were evaluated after 72 hours.

Based on the TSTs results, 15 (8.2%) of the patients were positive and 7 (3.8%) were intermediate. By combining these two groups, a total of 22 (12%) patients were positive for latent tuberculosis. Table 1 demonstrates the demographic and clinical features of the patients in our study.

DISCUSSION

This study showed the prevalence of LTBI among hemodyalisis patients in KBP, Iran. No significant relationship was observed between the variables. The prevalence of LTBI among hemodialysis patients was reported in several studies (8, 9, 17-26), with a recent meta analysis (27) reporting a pooled prevalence of 34.8% (95%CI; 29.1,- 40.5). Specifically for Iran, two of the previous reports indicated the prevalence of LTBI to be between 19.6-25.5% (25, 26), while one study reported a high prevalence of 81.5% (21), which should be interpreted in light of their limitations. Also, two of the most recent studies (23, 24) found a significant association between higher age and LTBI in hemodyalisis patients. This heterogeneity between the studies may stem from the endemicity of TB in the region where studies have taken place or different methodology and laboratory methods have been used to diagnose LTBI, including TST, Interferon-Gamma Release Assays and tuberculosis antigen-based skin tests.

Our study found a lower prevalence of LTBI among hemodialysis patients compared to the global estimates. The prevalence of LTBI among Iranian healthcare workers was 27.13% (28), which is relatively similar to the age standardized estimate for Iran in 2019, which stands at 26.03% (29). This variance in LTBI prevalence could be attributed to the sensitivity and specificity of TST in hemodialysis patients and variations in TB endemicity across different regions in Iran.

In addition, it should be borne in mind that TST may exhibit false negatives, for example, in immunocompromised individuals, or false positives in those with prior BCG vaccination (15). However, we found no difference in our study regarding prior BCG vaccination.

Of note, one of the United Nations' sustainable development goals is to end the worldwide TB epidemic by 2030 (1). To achieve this goal, providing feasible, accessible, and cost-effective tests to diagnose TB is indispensable. Further studies should focus on the cost-effectiveness of diagnostic methods and screening programs for high-risk individuals, particularly in LMICs, which account for 98% of TB cases (1).

Our study provided an evaluation of LTBI in hemodialysis patients in KBP through census sampling. We invited trained physicians to perform and interpret TST results. However, this study has several limitations. Firstly, we acknowledge the shortcomings of TST in diagnosing LTBI. Although, TST is still an acceptable tool to screen for LTBI in LMICs, other methods such as Interferon-Gamma Release Assays and tuberculosis antigen-based skin tests may have achieved more accurate results. Secondly, the study's cross-sectional design makes it impossible to establish causation between the variables. Thirdly, due to the small sample size of the study, there may be a lack of statistical power to evaluate associations between LTBI prevalence and other covariates. Additionally, we were unable to perform chest X-rays to evaluate patients for TB-related lung sequelae.

CONCLUSION

Given the endemicity of TB in Iran, risk of LTBI among hemodialysis patients, and the likelihood of progression to active TB in this population, proactive measures and screening programs are necessary in various regions to assess the prevalence of LTBI and its determinants.

Ethics approval and consent to participate

The present study was approved by the medical ethics committee of the Yasuj Universitiy of Medial Sciences.

Availability of data and materials

SPSS data of the participants can be requested from the authors. Please write to the corresponding author if you are interested in such data.

Competing interests

The authors declare that they have no competing interests.

Funding

No financial support was received for this report.

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Received: 02.12.2023
Accepted for publication: 06.03.2024

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Table 1. demographic, socioeconomic, and clinical features of the hemodialysis patients

Variable		Total; *N=183*	TST Results		P-value*
			Positive; *n=22*	**Negative**; *n=161*	
Residence; n (%)	Kohgiloye	63 (34.4)	6 (9.5)	57 (90.5)	0.73
	Boyer ahmad	72 (39.3)	10 (13.9)	62 (86.1)	
	Gachsaran	48 (26.2)	6 (12.5)	42 (87.5)	
Age (years); mean ± SD		59.3 ± 16.0	61.1 ± 11.8	59.04 ± 16.5	0.47
Age groups (years); n (%)	≤ 25	3 (1.6)	0 (0)	3 (100)	0.62
	26 – 45	34 (18.6)	2 (5.9)	32 (94.1)	
	46 – 65	80 (43.7)	12 (15.0)	68 (85.0)	
	> 65	66 (36.1)	8 (12.1)	58 (87.9)	
Gender; n (%)	Male	107 (58.5)	14 (13.1)	93 (86.9)	0.60
	Female	76 (41.5)	8 (10.5)	68 (89.5)	
Marital status; n (%)	Single	20 (10.9)	0 (0)	20 (100)	0.21
	Married	144 (78.7)	19 (13.2)	125 (86.8)	
	Divorced or widowed	19 (10.4)	3 (15.8)	16 (84.2)	
Number of children; n (%)	0	9 (4.9)	1 (11.1)	8 (88.9)	0.40
	1 - 3	32 (17.5)	5 (15.7)	27 (84.3)	
	4 – 6	62 (33.9)	6 (9.7)	56 (90.3)	
	7 – 9	61 (33.3)	7 (11.5)	54 (88.5)	
	> 9	19 (10.4)	3 (15.8)	16 (84.2)	
Education; n (%)	Illiterate/Reading & writing	142 (77.6)	21 (14.8)	121 (85.2)	0.03
	Educated	41 (22.4)	1 (2.4)	40 (97.6)	
Occupation; n (%)	Housewife	60 (32.8)	4 (6.7)	56 (93.3)	0.20
	Unemployed	49 (26.8)	7 (14.3)	42 (85.7)	
	Freelance	47 (25.7)	5 (10.6)	42 (89.4)	
	Employed	27 (14.8)	6 (22.2)	21 (77.8)	
Cause of renal failure; n (%)	Acute renal failure	43 (23.5)	6 (14.0)	37 (86.0)	0.77
	Hypertension	54 (29.5)	8 (14.8)	46 (85.2)	
	Diabetes mellitus	32 (17.5)	3 (9.4)	29 (90.6)	
	Renal stone	25 (13.7)	4 (16.0)	21 (84.0)	
	Primary kidney disease	21 (11.5)	1 (4.8)	20 (95.2)	
	Other	8 (4.4)	0 (0)	8 (100)	
Duration of dialysis (months); median [IQR]		24 [40]	12 [20]	24 [39]	0.13
Comorbid disease; n (%)	Hypertension	79 (43.2)	9 (11.4)	70 (88.6)	0.38
	Kidney cyst	52 (28.4)	5 (9.6)	47 (90.4)	
	Diabetes mellitus	33 (18.0)	4 (12.1)	29 (87.9)	
	ischemic heart disease	8 (4.4)	1 (12.5)	7 (87.5)	
	Cancer	4 (2.2)	2 (50)	2 (50)	
	Rheumatic arthritis	3 (1.6)	1 (33.3)	2 (66.7)	
	Cardiovascular accident	2 (1.1)	0 (0)	2 (100)	
	Spinal cord injury	1 (0.5)	0 (0)	1 (100)	
	Gouts	1 (0.5)	0 (0)	1 (100)	
BCG vaccination; n (%)	Positive	99 (54.1)	14 (14.1)	85 (85.9)	0.34
	Negative	84 (45.9)	8 (9.5)	76 (90.5)	
Immunosuppressive medication; n (%)	Total	15 (8.3)	1 (6.7)	14 (93.3)	1.00
	Prednisolone	12 (80.0)	1 (8.3)	11 (91.7)	1.00
	Cellcept	6 (40.0)	0 (0)	6 (100)	1.00
	Hydrocortisone	2 (13.3)	0 (0)	2 (100)	1.00
	Tacrolimus	1 (6.7)	0 (0)	1 (100)	1.00

BCG: Bacillus Calmette–Guérin; IQR: Interquartile range; TST: tuberculin skin test; SD: Standard deviation;
* Independent sample t-test/ Mann-Whitney test or Chi-square/ Fisher's exact test