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Original Article

Epidemiology of latent tuberculosis and associated risk factors in Al-Madinah, Saudi Arabia: A hospital-based cross-sectional study

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الملخص

أهداف البحث: تهدف هذه الدراسة لوصف وبائيات وعوامل الخطورة المرتبطة بمرض السل غير النشط (الكامن) لدى المرضى البالغين بمستشفى الأمير محمد بن عبد العزيز بالشؤون الصحية بالحرس الوطني بالمدينة المنورة.

طرق البحث: تم إجراء هذه الدراسة المقطعية في مستشفى الأمير محمد بن عبد العزيز بالمدينة المنورة في الفترة من يناير 2021 إلى ديسمبر 2022. تم فحص المشاركين الذين تزيد أعمارهم عن 14 عامًا بحثًا عن مرض السل الكامن باستخدام اختبار كوانتيفيرون. تم استبعاد المصابين بالسل النشط. تم تحليل البيانات المتعلقة بالتركيبة السكانية والأمراض المصاحبة وعوامل الخطورة باستخدام الانحدار اللوجستي متعدد المتغيرات لتحديد العوامل المرتبطة بمرض السل الكامن.

النتائج: تم تضمين 773 مشاركًا، وكان الإختبار(إيجابيًا في 291 حالة (37.6%) لمرض السل الكامن. أظهر التحليل متعدد المتغيرات أن العمر الأكبر والذكور ومرض السكري واضطرابات النسيج الضام هي عوامل خطورة مهمة لمرض السل الكامن. ارتبطت الجنسية غير السعودية بارتفاع احتمالات الإصابة بمرض السل الكامن (نسبة الأرجحية المعدلة 3.86) مقارنة بالمواطنين السعوديين.

الاستنتاجات: تسلط هذه الدراسة الضوء على عبء السل الكامن في المدينة المنورة، مع عوامل الخطر الديموغرافية والطبية من عامل كبر السن والإصابة بمرض السكري والقدوم من بلدان ذات معدل إصابات مرتفع بمرض الدرن.

الكلمات المفتاحية: عدوى السل الكامنة؛ اختبار إطلاق الإنترفيرون

Abstract

Objectives: To investigate the epidemiology of latent tuberculosis infection (LTBI) and associated risk factors among adults in Al-Madinah, KSA, and to identify vulnerable populations for targeted interventions.

Methods: This hospital-based cross-sectional study was conducted at Prince Mohammed Bin Abdulaziz Hospital, Al-Madinah, from January 2021 to December 2022. Participants aged >14 years were screened for LTBI using the QuantiFERON®-TB Gold In-Tube test. People with active tuberculosis were excluded. Data on demographics, comorbidities, and risk factors were

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analyzed using multivariate logistic regression to identify factors associated with LTBI.

Results: In total, 773 participants were included and 291 (37.6 %) tested positive for LTBI. Multivariate analysis identified greater age, male sex, diabetes mellitus, and connective tissue disorders as significant risk factors for LTBI. Non-Saudi nationality was associated with higher odds of LTBI (adjusted odds ratio [aOR], 3.86; 95 % confidence interval (95 % CI), 1.80—8.27), whereas the risk was lower for Saudi nationals (aOR, 0.34; 95 % CI, 0.25—0.47).

Conclusions: This study highlights the burden of LTBI in Al-Madinah, and specific demographic and medical risk factors. These findings underscore the importance of personalized public health strategies and preventive measures for controlling LTBI progression in high-risk populations.

Keywords: Interferon-gamma release assay; Latent tuberculosis infection; QuantiFERON®-TB Gold In-Tube test

Introduction

Tuberculosis (TB) poses a considerable global health challenge, burdening healthcare systems and societies.[1] Despite notable advancements in TB control, its prevalence needs to be controlled further, necessitating the development of novel strategies to mitigate its impact and curb transmission rates. In particular, identifying the risk factors associated with latent TB infection (LTBI) is an essential component of TB control.[2]

Al-Madinah in KSA presents a unique epidemiological setting for LTBI research due to its role as a major religious pilgrimage destination.[3] Pilgrims and visitors come from diverse geographical regions, including many TB-endemic countries, and thus the city is affected by several distinct challenges in terms of TB control.[4] The annual influx of visitors from countries with high TB burdens creates unique conditions that could potentially influence TB transmission patterns.[5] The present study is the first to comprehensively analyze LTBI and associated risk factors in this unique setting, providing insights that may be particularly relevant to healthcare planning in cities with high international visitor traffic.[2]

LTBI is characterized by the survival of *Mycobacterium tuberculosis* bacterium (MTB) in the body without symptoms, acting as a reservoir for future TB cases, particularly in patients with compromised immune systems.[6] Therefore, understanding the risk factors associated with LTBI is crucial for developing focused preventive measures that break the chain of TB transmission.

LTBI is diagnosed based on evidence of TB infection detected by using either the tuberculin skin test (TST) or interferon-gamma release assay (IGRA) in the absence of clinical symptoms.[6] QuantiFERON-TB Gold In-Tube (QFT-GIT), an IGRA, is widely used for LTBI diagnosis. This test measures interferon-gamma production by T-cell lymphocytes upon exposure to known MTB antigens, such as early secreted antigenic target 6 (ESAT-6) or culture filtrate protein 10 (CFP-10).[7,8]

Similar to several other countries, the KSA has experienced TB-related challenges.[3,9] Some LTBI risk factors are universal, whereas others may be specific to the Saudi Arabian population due to its distinct sociocultural context and migration patterns. Al-Madinah City, a holy city for Muslims, annually attracts many visitors and pilgrims from around the world, potentially increasing the risk of exposure for residents. However, data regarding the epidemiology of LTBI and associated risk factors are lacking for Al-Madinah. Therefore, the present study aimed: (1) to describe the prevalence of LTBI among adults attending Prince Mohammed Bin Abdulaziz Hospital, National Guard Health Affairs, Al-Madinah, KSA; and (2) to identify the specific demographic and clinical risk factors associated with LTBI, including comorbidities, nationality, and age.

Materials and Methods

Study design and patient selection

A retrospective cross-sectional design was utilized in this study to describe the epidemiology of LTBI and identify the associated risk factors. Data were obtained from the electronic medical records of patients tested at Prince Mohammed Bin Abdulaziz Hospital, National Guard Health Affairs, Al-Madinah, KSA, from January 1, 2021, to December 31, 2022. Formal sample size calculation was not performed due to the retrospective nature of the study. All patients who underwent testing for LTBI using QFT-GIT were included. We included participants aged 14 years and above in accordance with institutional guidelines that define the adult population as aged 14 years and above. Direct consent was not obtained from participants because this retrospective study used anonymized medical records. This study was conducted under the ethical approval of the Institutional Review Board (IRB), which waived the requirement for informed consent due to the use of de-identified retrospective data for patients who underwent IGRA using QFT-GIT. Patients with suspected or confirmed active TB disease were excluded from the study. Active TB was excluded based on a comprehensive review of clinical, radiological, and laboratory findings. The criteria for exclusion were: presence of symptoms suggestive of active TB (e.g., persistent cough, fever, weight loss, or night sweats); radiological findings consistent with active TB, such as cavitation or miliary patterns on chest X-rays or computed tomography (CT) scans; or positive microbiological results, including sputum smear or culture positivity for *M. tuberculosis*, where available. The exclusion process ensured that the study population only represented patients with LTBI.

Data collection

Data were collected retrospectively from electronic health records at Prince Mohammed Bin Abdulaziz Hospital, National Guard Health Affairs. Data were extracted following a standardized protocol to ensure accuracy and consistency. The variables collected included demographic details (age,

sex, and nationality), clinical history (comorbidities and prior TB exposure), laboratory results (IGRA outcomes), and imaging findings (chest X-rays and CT scans, if available). A data collection sheet was developed and piloted before data abstraction to ensure comprehensive and systematic data capture.

Definitions of the comorbidities were based on the Charlson comorbidity index (CCI) definitions. The CCI is traditionally used to estimate survival in patients with chronic diseases and it provides standardized definitions for comorbidities, which were used in this study to capture the overall comorbidity burden and its association with LTBI.[10]

QFT-GIT testing

Blood samples were collected from participants and processed according to the guidelines for the QFT-GIT procedure using specialized tubes containing antigens specific to MTB (i.e., ESAT-6 and CFP-10), with positive and negative controls.[11] Positive test results were defined as exceeding a threshold of 0.35 international units per milliliter (IU/mL) for interferon measurements and a 25 % increase compared with the negative control tube. A negative test result was defined as an interferon measurement in the MTB antigen tube ≤0.35 IU/mL or <25 % of the interferon measured in the negative control.[11]

Statistical analyses

Continuous variables were expressed as means and standard deviations (SDs), whereas categorical variables were expressed as frequencies and percentages. Variables were classified and compared using Fisher's exact test for categorical variables and the Student's *t*-test for continuous variables with normal distributions. The Wilcoxon rank-sum test was used to compare non-normally distributed continuous variables. Multivariate logistic regression was performed using a forward stepwise selection method. Variables were selected for inclusion based on statistical significance ($p < 0.05$) in univariate analyses. The forward stepwise method added variables iteratively to the model, retaining only those that significantly improved the model fit.

Results

In total, 1026 individuals underwent the QFT-GIT test during the study period. Among these individuals, 773 participants met the inclusion criteria, where 291 (37 %) and 482 (62 %) participants had positive and negative QFT-GIT results, respectively.

Table 1 shows the demographic and clinical characteristics of participants with positive and negative QFT-GIT results. A significant difference was observed in the mean age between the positive group (mean = 39 years, SD = 13) and negative group (mean = 34 years, SD = 11) ($p < 0.001$). The cohort comprised 49 % females and 51 % males, and females were less likely to have positive test results than males ($p = 0.006$). Furthermore, most participants (59 %) were Saudi nationals and they had a notably lower rate in the positive group (43 %) compared with non-Saudi citizens (68 %) ($p < 0.001$).

Table 1: Demographic and clinical characteristics of participants with positive and negative QuantiFERON®-TB Gold In-Tube (QFT-GIT) test results.

Variable	All 773 N (%)	Positive QFT-GIT N (%) 291 (37.6)	Negative QFT-GIT N (%) 482 (62.4)	*p*-value
Age				
Mean	36.44 (12)	39 (13)	34 (11)	0.001
Median	34 (27−42)	36 (29−47)	32 (26−39)	0.001
15−40	543 (70)	176 (60)	367 (76)	0.001
41−60	185 (24)	91 (31)	94 (20)	0.000
>60	45 (6)	24 (9)	21 (4)	0.005
Female	379 (49)	124 (43)	255 (53)	0.006
Male	394 (51)	167 (57)	227 (47)	0.006
Saudi	454 (59)	124 (43)	330 (68)	0.000
Non-Saudi	319 (41)	167 (57)	152 (32)	0.000
Healthcare workers	647 (84)	226 (35)	421 (65)	0.001
Non-healthcare workers	126 (16)	65 (52)	61 (48)	0.001
Family contact	19 (2)	17 (6)	2 (0.4)	0.000
Work contact	87 (11)	24 (8)	63 (13)	0.041
Smoker	41 (5)	16 (6)	25 (5)	0.869
CKD	9 (1)	7 (78)	2 (22)	0.031
CKD on dialysis	6 (1)	3 (50)	3 (50)	0.678
Reactive airways	21 (3)	13 (62)	8 (38)	0.023
Complicated diabetes mellitus	18 (2)	14 (78)	4 (22)	0.001
Uncomplicated diabetes mellitus	33 (4)	15 (45)	18 (55)	0.362
Connective tissue disorders	17 (2.20)	12 (71)	5 (29)	0.009
Abnormal chest X-ray	38 (10)	21 (7)	17 (4)	0.026
Abnormal chest CT scan	33 (4)	20 (7)	13 (3)	0.009
Steroid treatment	40 (5)	22 (8)	18 (4)	0.028
Chemotherapy treatment	6 (0.7)	4 (1)	2 (0.4)	0.205
TNF treatment	11 (1)	8 (2)	3 (0.6)	0.024

CT, computed tomography; TNF, tumor necrosis factor; CKD, chronic kidney disease.

Multivariate logistic regression identified several significant risk factors associated with LTBI. Greater age was associated with higher odds of LTBI (odds ratio (OR) = 1.03; 95 % confidence interval (CI): 1.02−1.04; $p < 0.001$), and males had a greater likelihood of testing positive compared with females (OR = 1.51; 95 % CI: 1.13−2.03; $p = 0.006$). Among comorbidities, complicated diabetes mellitus (OR = 6.04; 95 % CI: 1.97−18.53; $p = 0.002$) and connective tissue disorders (OR = 4.10; 95 % CI: 1.43−11.77; $p = 0.009$) were strongly associated with LTBI. Non-Saudi patients had significantly higher odds of LTBI

Table 2: Univariate analysis of risk factors for patients with positive QuantiFERON®-TB Gold In-Tube test results.

Variable	Odds ratio	95 % confidence interval	*p*-value
Age (years)	1.03	(1.02−1.04)	0.000
15−40	−	−	−
40−60	2.012	(1.44−2.83)	0.000
>60	2.38	(1.29−4.40)	0.005
Female	0.66	(0.49−0.89)	0.006
Male	1.51	(1.13−2.03)	0.006
Saudi	0.34	(0.25−0.46)	0.000
Non-Saudi	3.86	(1.80−8.27)	0.000
Healthcare workers	0.50	(0.34−0.74)	0.000
Non-healthcare workers	1.98	(1.35−2.92)	0.000
Family contact	14.89	(3.41−64.93)	0.001
Work contact	0.60	(0.36−0.98)	0.041
Smoker	1.06	(0.56−2.03)	0.851
Abnormal chest X-ray	2.13	(1.10−4.10)	0.024
Abnormal chest CT scan	2.66	(1.30−5.44)	0.007
Steroid treatment	2.11	(1.11−4.00)	0.023
TNF treatment	4.51	(1.19−17.15)	0.027
Chemotherapy treatment	3.34	(0.61−18.38)	0.165
Received immunotherapy	1.67	(0.62−4.51)	0.308
CKD	5.92	(1.22−28.67)	0.027
CKD on dialysis	1.66	(0.33−8.30)	0.535
Reactive airways	2.77	(1.13−6.77)	0.025
Complicated diabetes mellitus	6.04	(1.97−18.53)	0.002
Uncomplicated diabetes mellitus	1.40	(0.69−2.82)	0.346
Connective tissue disorders	4.10	(1.43−11.77)	0.009
Neoplastic conditions	3.36	(0.83−13.54)	0.088

TNF, tumor necrosis factor; CKD, chronic kidney disease; DM, diabetes mellitus; CT, computed tomography.

Table 3: Factors associated with a positive QuantiFERON®-TB Gold In-Tube (QFT-GIT) test according to adjusted logistic regression analysis.

Positive QFT-GIT	Adjusted OR	95 % confidence interval	*p*-value
Age	1.02	1.00−1.03	0.009
Male	1.50	1.10−2.06	0.011
Saudi national	0.34	0.25−0.47	0.001
Complicated diabetes mellitus	6.18	1.88−20.29	0.003
Connective tissue disorders	4.41	1.47−13.26	0.008

compared with Saudi nationals (OR = 3.86; 95 % CI: 1.80−8.27; $p < 0.001$). These findings are summarized in Table 2.

Table 3 shows the results obtained by multivariate logistic regression analysis. Among the different countries of origin, participants from KSA had a lower risk of a positive QFT-GIT test compared with other nationalities, where the adjusted OR (aOR) was 0.34 (95 % CI, 0.25−0.47). By contrast, participants from the Philippines, Pakistan, and Bangladesh had higher aORs of 4.14 (95 % CI, 2.75−6.25), 3.86 (95 % CI, 1.80−8.27), and 3.81 (95 % CI, 1.16−12.49), respectively. Greater age was significantly associated with increased odds of a positive QFT-GIT test (aOR = 1.02; 95 % CI, 1.00−1.03), where each additional year correlated with a 2 % increase in odds of positivity. In addition, males had a greater likelihood of a positive test result than females (aOR = 1.5; 95 % CI, 1.10−2.06). Patients diagnosed with complicated diabetes mellitus had a significantly increased likelihood of testing positive (aOR = 6.18; 95 % CI, 1.88−20.29). Similarly, individuals with connective tissue disease had increased odds of testing positive (aOR = 4.41; 95 % CI, 1.47−13.26).

Discussion

This study identified several factors associated with LTBI in patients in Al-Madinah, KSA. In particular, age, sex, nationality, and specific medical conditions (especially complicated diabetes) were significantly associated with LTBI.

Individuals with LTBI were older than those without, as also found in previous studies.[12−15] Similarly, according to a large study conducted in China, the OR for a positive IGRA increased from 2.95 to 20.92 as age increased from 20 to 70 years, respectively.[13] This association can be attributed to the intricate interplay between age-related alterations in the immune system, prolonged exposure to *M. tuberculosis*, and underlying health conditions that may increase the susceptibility to LTBI in older individuals.[12−14]

In this study, we identified specific epidemiological factors that contributed to LTBI in Al-Madinah, KSA, a region with unique demographic and migratory characteristics. Previous studies addressed global LTBI risk factors but our findings provide region-specific data that highlight vulnerable populations, such as patients with diabetes, connective tissue disorders, and non-Saudi residents. These findings align with evidence suggesting that chronic diseases and migration patterns increase LTBI risk, particularly in regions with high international travel and exposure risks.[12,16] These data are essential for implementing targeted screening programs and preventive strategies to limit the progression to active TB and reduce the LTBI reservoir in Al-Madinah.

Similar to the present study, two Chinese studies also found that male patients had a greater likelihood of LTBI than females.[12,17] Various factors, including occupational exposure, cultural and behavioral patterns, healthcare-seeking behaviors, hormonal influences, healthcare occupations, and potential variations in the immune response, may contribute to this sex disparity. However, a study in Panama that assessed LTBI rates among household contacts of patients with TB found no sex-associated difference between IGRA-positive and IGRA-negative patients.[14]

The association between country of origin and LTBI highlights broader epidemiological patterns. Individuals born in KSA had a lower LTBI rate (OR = 0.34; 95 % CI, 0.25−0.46), whereas non-Saudi nationals from TB-prevalent regions, such as the Philippines and Indian subcontinent, had higher odds of developing LTBI. Similarly, a study conducted in Bisha, KSA, found a seven-fold increase in positive TST among healthcare workers from other countries compared with Saudi nationals.[18] Another study in KSA found that non-Saudi nationality was associated with a significantly higher risk of LTBI among laboratory personnel (OR = 21.67; 95 % CI, 6.69−73.94; $p < 0.0001$).[19] This higher rate of LTBI among non-Saudis may explain

their higher incidence of TB disease because the Saudi national TB report from 2018 stated that non-Saudis had approximately twice the incidence rate of TB disease compared with Saudis.[20]

Several studies demonstrated that patients with complicated diabetes mellitus had a higher risk of LTBI than those with controlled diabetes mellitus.[16,21] A recent systemic review and meta-analysis based on 20 studies demonstrated a significant association between diabetes mellitus and LTBI (OR = 1.55; 95 % CI, 1.30−1.84).[21] Possible explanations for this association include impaired monocyte and lymphocyte function due to hyperglycemia and reduced T-cell function in patients with diabetes.[21,22]

Similarly, individuals diagnosed with connective tissue diseases were more likely to have LTBI in the present study (aOR = 4.41; 95 % CI, 1.47−13.26; $p = 0.008$). The increased susceptibility to TB infection among these patients may have been due to the complex interaction between their compromised immune systems and the widespread use of immunosuppressive treatments, including steroids.[23] According to a large systematic review and meta-analysis based on 35 studies, the prevalence of TB was 3.59 % (95 % CI, 2.57−5.02 %) per 100 person-years in patients with systemic lupus erythematosus.[21] Higher rates of LTBI and TB have been reported in patients with different connective tissue disorders.[24−26] These findings highlight the importance of implementing diligent surveillance and customized preventive measures for managing the risk of TB in this specific group of patients.

The present study is one of the first and largest studies of LTBI conducted in Al-Madinah, KSA. Our results highlight the potential need for multicenter studies in the Al-Madinah region, considering its status as a holy city that attracts millions of visitors from around the world each year. The impact of this influx on the epidemiology of LTBI in this city warrants further investigation.

The findings obtained in this study have significant implications for the clinical management of LTBI in Al-Madinah. Identifying high-risk populations, such as patients with diabetes, connective tissue disorders, and non-Saudi residents, highlights the importance of targeted screening and prevention programs. For instance, integrating routine LTBI screening in clinical workflows for individuals with these risk factors could enhance early detection and treatment, reducing the risk of progression to active TB.

Furthermore, our results demonstrate the need for tailored public health interventions, particularly in this region with high international travel and a diverse population. Future research should evaluate the effectiveness of implementing these types of targeted strategies, as well as their potential for reducing the TB burden at both local and global levels.

This study had the following limitations. First, our findings were limited by the availability and accuracy of recorded data because this was a retrospective study based on medical records. Potential misclassifications or missing data could have influenced the observed associations. Second, reliance on medical records restricted the ability to collect additional variables of interest, such as socioeconomic status, detailed occupational history, or other behavioral factors that might have contributed to the risk of LTBI. Finally, the cross-sectional nature of the data did not permit causal inference between risk factors and LTBI, limiting the interpretation to associations only. Despite these limitations, our findings provide valuable insights into the epidemiology of LTBI in Al-Madinah.

Conclusion

The findings obtained in this study contribute substantially to understanding the different factors that influence the epidemiology of LTBI. Age, sex, nationality, diabetes mellitus, and connective diseases were identified as crucial factors that increased the susceptibility to LTBI. These results highlight the need for individualized screening, identification, and management. Identifying and addressing these factors is essential for advancing clinical knowledge and effectively refining public health strategies to combat TB infection.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethical approval

The requirement for informed consent was waived because this was an observational retrospective study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board at King Abdullah International Research Center, National Guard Health Affairs, Jeddah, KSA (IRB number: NRM22M/009/05).

Author contributions

Conceptualization, Z.G.; Data curation, L.A., H.K.J., S.A.A., M.W.D., and B.H.A.; Formal analysis, Z.G. and A.A.; Investigation, S.A.A. and B.H.A.; Supervision, Z.G. and A.A.; Writing − original draft, L.A., S.A.A., M.W.D., and S.N.; Writing − review & editing, A.A. All authors read and agreed to the final version of the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Data availability statement

The original data obtained in this study are included in the article and further inquiries can be directed to the corresponding author.

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