Original Article

Prevalence of primary anti-tuberculosis drug resistance at the tertiary center in Saudi Arabia and associated risk factors

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ABSTRACT

الأهداف: تقدير معدل انتشار السل أحادي المقاومة (MR–TB) والسل المقاوم للأدوية المتعددة (MDR–TB) وتقييم عوامل الخطر المرتبطة بالمقاومة (DR–TB).

المنهجية: أجريت دراسة وصفية بأثر رجعي للسجلات الطبية لمرضى السل في مستشفى الملك فهد للقوات المسلحة بجدة، المملكة العربية السعودية. تمت مراجعة سجلات المرضى الذين تم إخطارهم بين عامي 2000م و 2018م. اشتملت الدراسة على الحالات التي كانت إيجابية الزرع لأنواع السل الرئوي. بالإضافة الى معلومات المرضى كالعمر، والجنس، وتاريخ التدخين، وأمراض الكلى، وأمراض الكبد، ومستوى بيليروبين بالدم، ومرض السكري ،وفيروس نقص المناعة البشري (الايدز).

النتائج: تم إشراك 901 حالة في الدراسة، من بينها (21.4%) 193 حالة لم يستجيبوا للعلاج. بالنسبة لنمط المقاومة للأدوية، فمن بين 21.4% من السل المقاوم للأدوية، كان هناك 91.7% من السل أحادي المقاوم للأدوية و8.3% من السل المقاوم للأدوية المتعددة. وقد كانت مقاومة دواء بيرازيناميد أعلى معدل انتشار بنسبة 33.4%، بينما كانت مقاومة دواء إيثامبوتول أقل انتشاراً (7.1%). بالنسبة لعوامل خطر الإصابة بالسل المقاوم للأدوية، أظهر العمر فقط ارتباطًا، ذا دلالة إحصائية (p>0.01)، علاقة ضعيفه سلبية (r=–0.145) بمقاومة الأدوية المضادة للسل.

الخلاصة: تعتبر معدلات السل المقاوم للأدوية المبلغ عنها في الدراسة أعلى مقارنة بالمعدلات الوطنية المبلغ عنها مؤخرًا. وفقًا للنتائج، فإن الشباب فقط هم أكثر عرضة لخطر الإصابة بالسل المقاوم للأدوية. علاوة على ذلك، قد تلعب الطفرة الجينية دورًا في مقاومة الأدوية بين حالاتنا تحديدًا لمقاومة أحادي بيرازيناميد.

Objectives: To estimate the prevalence mono-resistant tuberculosis (MR-TB) and multidrug resistant TB (MDR-TB), and evaluate the risk factors associated with the drug-resistant tuberculosis (DR-TB).

Methods: A descriptive, retrospective study was applied, utilizing the TB patients' medical records at King Fahd Armed Forces Hospital (KFAFH), Jeddah, Saudi Arabia. The records of patients notified between 2000 and 2018 were reviewed and culture positive cases for *Mycobacterium tuberculosis* species were included. Moreover, the risk factors included were age, gender, smoking history, renal disease, liver disease, hyperbilirubinemia, diabetes mellitus, and human immunodeficiency virus (HIV).

Results: Nine hundred and one cases in entirety were involved in the research, out of which 193 had drug-resistant tuberculosis (DR-TB) (21.4%). Out of the 21.4% DR-TB, 91.7% were MR-TB and 8.3% were MDR-TB. The highest MR prevalence was for pyrazinamide at 33.4%, while the lowest resistance was for ethambutol at 7.1%. For the risk factors of drug-resistant TB, only age depicted a statistically significant (p<0.01) but weak negative (r= -0.145) correlation with anti-TB drug resistance.

Conclusion: Rates of DR-TB reported in the study are considered higher compared to the recently reported national and international rates. According to the results, only younger people are at risk of developing DR-TB. Moreover, genetic mutation may play a role in drug resistance among our cases specifically for pyrazinamide monoresistance.

Keywords: prevalence, primary, anti-tuberculosis, drug, resistant, risk factors.

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Tuberculosis (TB) is an infectious disease primarily caused by the *Mycobacterium tuberculosis* species that spread through aerosols. Globally, it is the ninth main cause of mortality, and the foremost cause of mortality resulting from a single contagious affliction, even exceeding HIV.[1,2] In spite of the accomplishment of prevention and control strategies, it is one of the foremost causes of mortality in Saudi Arabia.[3,4] Recently, it has been ranked 11th among causes of death in Saudi Arabia, with approximately 65,000 cases reported in the Kingdom between 1991 and 2010.[5] One of the main contributors to TB-related deaths is drug resistance. In 2013, the World Health Organization (WHO) announced that multidrug-resistant TB (MDR-TB), distinct as *Mycobacterium tuberculosis*, is resistant to both isoniazid and rifampicin, 2 of the most formidable anti-TB drugs.[6] In addition, the world is witnessing the emergence of a wide range drug-resistant strains of TB (XDR-TB), which are categorized as resistant to both isoniazid and rifampicin, in addition to one fluroquinolone drug, and one of the second-line injectable drugs (kanamycin, amikacin, and capreomycin).[7,8] The treatment of MDR-TB requires a long course of expensive and toxic drugs.[9] Moreover, despite being an enormous financial load, drug-resistant TB is associated with poor outcomes, having a mortality rate close to 90% if accompanied by HIV.[10-13] According to the literature, the treatment of drug resistant TB (DR-TB) has a considerably lower success rate, reaching 52% for MDR-TB and 28% for XDR-TB, compared to 82% for drug-susceptible TB.[14] The reported causes for drug-resistant strains in *Mycobacterium tuberculosis* are poor adherence to TB medications, inappropriate utilization of anti-TB drugs, spontaneous chromosomal mutations, and treatment failure.[15-17] In addition, experts have suggested that inadequate healthcare systems, insufficient political commitment, unsound drug policies, poor disease management, and long-standing neglect in research have facilitated the global rise of DR-TB.[18,19] In Saudi Arabia, the MDR-TB rates are reported to be between 1% and 5%.[20] A national study published in 2013 by Al-Hajoj et al[21] reported a total MDR-TB rate of 4%. In a recent local study, Al Ammari et al found that the rate of MDR-TB is 4.4%, while the rates of mono-resistance (MR) are 3.8% for ethambutol, 5.4% for pyrazinamide, 10.2% for isoniazid, 11% for streptomycin, and 5.9% for rifampicin. This study found that women, younger age groups and those with a history of TB had a higher rate of MDR.[14] Multidrug-resistant TB has become a significant issue worldwide due to its community-based and cost-effective consequences.[22] Jeddah, being a tourist and business hub, has the potential to escalate communicable infections. Close contact between people for a long duration elevates the danger of the escalation of respiratory infections.

Our study aims to assess the rates of MR and MDR in Jeddah in Saudi Arabia. We were also deeply interested in the interrelation between the demographic status, clinical attributes, and the grades of resistance in the studied population.

Methods. This cross-sectional study was conducted by retrospectively collecting data from the medical records of TB patients between 2000 and 2018 in King Fahd Armed Forces Hospital (KFAFH), a tertiary hospital and JCI accredited organization with a capacity of 540 beds in Jeddah, Saudi Arabia. Ethical approval was obtained from the Ethical and Research Committee (REC-248) at KFAFH, Jeddah, Saudi Arabia.

A total of 901 patients were included in this study as they showed a positive culture for mycobacteria TB and completed the regimen of anti-tuberculosis medication. Those who did not complete the regimen of anti-tuberculosis medication were excluded from this study. Furthermore, the exclusion criteria were applied to patients who showed positive culture of mycobacteria TB.

For mycobacteria diagnosis, clinical samples are screened by performing an acid-fast bacilli smear and culturing in the Bactec MGIT 960 liquid system (Becton, Dickinson, New Jersey, USA), which contains 7 mL of modified Middlebrook 7H9 broth base. The MGITTM OADC enrichment and PANTA antibiotic mixture (Becton, Dickinson, New Jersey, United states), are also used for mycobacteria cultivation.[23] With the exception of blood and urine samples, all types of clinical samples can be used for primary isolation in the MGIT tube. The sputum sample was the most common type of sample received during this period for *Mycobacterium tuberculosis* diagnosis, as shown in **Figure 1**.

This study defined drug resistance as resistance to at least one of the following: isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. MDR-TB was defined as being resistant to at least isoniazid and rifampicin. The variables used include age, gender, smoking history, renal disease, liver disease, hyperbilirubinemia, diabetes mellitus, and HIV. All

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age groups were included. Serum creatinine was taken as a marker of impaired renal function. According to the national kidney foundation, a creatinine level greater than 1.4 mg/dL for men and 1.2 mg/dL for women was an early sign of renal disease. If the level of serum creatinine was higher than the above level, then creatinine clearance was estimated by glomerular filtration rate.[24] Serum aminotransferases, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin were taken as biochemical markers for liver injury. The sensitivity and specificity of serum aminotransferases, particularly serum ALT, for differentiating liver disease from non-liver disease depended on the cut-off values chosen to define an abnormal test. The cut off value for serum ALT for men is 33 units/L and women 25 units/L. In children, the cut off value for ALT for boys is 38 and girls 32 units/L.[25] The serum AST cut off value for men is 40 and women 32 units/L. Total bilirubin was used to assess hyperbilirubinemia with a cut off value of 1.0 mg/dl.

Statistical analysis was performed using the Statistical Package for Social Sciences software, version 24.0 (Armonk, NY: IBM Corp.). All factors affecting the treatment responses were included in our analyses (namely, age, gender, nationality, smoking history, renal failure, liver failure, hyperbilirubinemia, diabetes mellitus, and HIV). Multivariate logistical regression analyses were applied to predict the possible risk factors and Spearman correlation analysis was used to validate the statistical significance of the different factors. Variables with $p<0.05$ in the multivariate analysis were considered to be statistically significant.

Results. There were 901 participants. More than half of them (55.8%) were males and the remainder were female (44.2%). The vast majority (96.1%) were Saudi, and the largest proportion (29.3%) was in the age group of 21-40 years followed by 27.1% in the age group of 61-80 years. The data is presented in **Table 1**.

Overall, more than three quarters (78.6%) of the patients were sensitive to anti-tuberculosis drugs, which was noted to decrease throughout the follow-up period: being 90.5% from 2000 to 2002 and peaking at 79.6% in the years from 2012-2014. Furthermore, 21.4% of cases were resistant to anti-TB drugs, and the resistance rate increased during the follow-up period from 9.5% to 33.7% in the periods of 2000-2002 and 2009-2011, respectively, as shown in **Table 2**.

It was found that out of the 21.4% resistant patients, 91.7% were mono-resistant TB and 8.3% were multi drug-resistant TB. The results reveal that during the follow-up years, the prevalence of mono-resistant TB decrease ranged from 85.7% to 100% from 2000 to 2014, and in the last follow-up period (2015-2018), it became 67.7%. In contrast, MDR-TB was highly prevalent in the last year (2015-2018) reaching 32.3% even though its rate dramatically decreased or was even absent (zero) after the first follow up years in which it was 14.3%. The data is shown in **Table 2**.

Table 3 shows the prevalence of resistance to each of the primary anti-tuberculosis drugs. The highest resistance prevalence was for pyrazinamide at 33.4%, followed by isoniazid at 26.7%, and streptomycin at 20.6%, while the lowest reported resistance was for ethambutol at 7.1%. Regarding the multivariate logistical regression analyses, none of the possible risk

Table 1 - Comparison of tuberculosis patients according to various parameters.

Parameters	2000 - 2002	2003 - 2005	2006 - 2008	2009 - 2011	2012 - 2014	2015 - 2018	Total n (%)
Age (years)							
0-20	0	5	16	14	11	15	**61 (6.8)**
21-40	28	42	55	58	37	44	**264 (29.3)**
41-60	41	50	45	39	18	22	**215 (23.9)**
61-80	42	62	57	42	21	20	**244 (27.1)**
>80	37	30	21	13	6	10	**117 (13.0)**
Total	148	189	194	166	93	111	**901 (100)**
Gender							
Female	61	92	96	81	29	39	**398 (44.2)**
Male	87	97	98	85	64	72	**503 (55.8)**
Total	148	189	194	166	93	111	**901 (100)**
Nationality							
Non-Saudi	7	5	8	7	3	5	**35 (3.9)**
Saudi	141	184	186	159	90	106	**866 (96.1)**
Total	148	189	194	166	93	111	**901 (100)**

Table 2 - Drugs sensitive/resistant tuberculosis with resistant pattern.

Drugs sensitive/ resistant	2000 - 2002	2003 - 2005	2006 - 2008	2009 - 2011	2012 - 2014	2015 - 2018	Total n (%)
Drug susceptibility							
Sensitive	134 (90.5)	162 (85.7)	148 (76.3)	110 (66.3)	74 (79.6)	80 (72.1)	**708 (78.6)**
Resistant	14 (9.5)	27 (14.3)	46 (23.7)	56 (33.7)	19 (20.4)	31 (27.9)	**193 (21.4)**
Total	148	189	194	166	93	111	**901 (100)**
Resistant pattern							
Mono-resistant	12 (85.7)	27 (100)	43 (93.5)	55 (98.2)	19 (100)	21 (67.7)	**177 (91.7)**
Multi-resistant	2 (14.3)	0	3 (6.5)	1 (1.8)	0	10 (32.3)	**16 (8.3)**
Total	14	27	46	56	19	31	**193 (100)**

Table 3 - Prevalence of primary mono-drug resistant tuberculosis

Mono-drug resistant	2000 - 2002	2003 - 2005	2006 - 2008	2009 - 2011	2012 - 2014	2015 - 2018	Total n (%)
Ethambutol	5	3	3	3	1	6	**21 (7.1)**
Isoniazid	6	3	21	25	8	16	**79 (26.7)**
Pyrazinamide	0	4	27	32	16	20	**99 (33.4)**
Rifampicin	3	15	4	3	0	11	**36 (12.2)**
Streptomycin	4	5	18	18	0	16	**61 (20.6)**
Total	18	30	73	81	25	69	**296 (100)**

factors have shown a statistically significant association, except for HIV patients. Statistically, it appears that MTB drug resistance is more strongly correlated with non-HIV patients. However, in this study, we only found one positive case of HIV. Importantly, Saudi Arabia remains a low HIV prevalence country with approximately 1.5/100,000 cases yearly.[26] The data is shown in **Table 4**.

The Pearson correlation coefficient was calculated to assess the risk factors for drug resistance (overall resistance), and the results are shown in **Table 5**. For the correlation of tested factors with patients who showed both mono-resistance and multi-resistance to TB treatment, there was a statistically significant *p*-value ($p<0.01$) weak negative (r= -0.145) association between age and anti-TB drug resistance. For the other assessed factors (gender, CREAT, ALT, AST, TBIL, and diabetes), the association is weakly negative (r= -0.001, r= -0.024, r= -0.025, r= -0.062, r= -0.009, and r= -0.011, respectively), but statistically non-significant since all $p>0.05$. However, smoking showed a weakly positive borderline-significant association with drug resistance (r= 0.054, $p=0.053$). For the individual Spearman's correlation of multi-resistance and mono-resistance, it was found that all the assessed factors showed a weak association, either positive or negative, with non-significant statistical correlation ($p>0.05$).

Discussion. This study found that the rate of MDR-TB is significantly high at 8.3%, which is almost double that of the Al Ammari study.[14] The prevalence of any drug-resistant TB in our study was 21.4%, which is higher than the recently published German study (12.7%)[2] but is much lower than Iranian study (41.6%).[27] Monoresistance accounted for more than 90% of any DR-TB, which is parallel to the results of Glasauer's study.[2]

This study observed that the rate of DR-TB increased over time. This is opposite to Oman's study,[28] which revealed that the rate of drug-resistant TB decreased in follow up time. The rate of mono-resistant TB peaked in 2009 while MDR-TB peaked in 2016. This issue could be explained by expansion in rapid molecular testing and the availability of the GeneXpert system which was implemented in our hospital in 2007. A study conducted in Saudi Arabia over a period of 15 years showed that isoniazid has the highest mono-resistance followed by ethambutol, while in our study ethambutol has the lowest rate of monoresistance; however, the resistant rate for ethambutol is approximately the same at 7.5% and 7.1% respectively.[29]

According to the WHO's 2016 report, the global rate of MDR-TB is 4.1% and it caused approximately 240,000 deaths. According to our data, the MDR-TB rate has doubled and is now 8.3%.[30] A systemic review carried out in Europe in 2006 showed that previous

Table 4 - Possible risk factors associated with mono-drug, multi-drug resistant tuberculosis.

Variables	Mono-resistant	Multi-resistant	Odds ratio	95% confidence interval	*P*-value
Smoking					
Yes	26	3	1.305	0.39-4.3	0.663
No	151	13	0.95	0.85-1.11	
Gender					
Female	77	8	1.5	0.69-1.93	0.616
Male	100	8	0.89	0.53-1.47	
Nationality					
Saudi	164	16	1.1	1.05-1.15	0.262
Non-Saudi	13	0			
Creatinine					
Normal	83	3	0.96	0.93-1.01	0.421
High	18	0			
Alanine aminotransferase					
Normal	124	5	0.96	0.93-0.99	
High	26	0			
AST					
Normal	51	1	0.98	0.94-1.02	0.643
High	11	0			
Total bilirubin					
Normal	111	3	0.4	0.13-1.25	0.157
High	21	2	1.4	0.7-.9	
Diabetes mellitus					
Normal	91	3	0.65	0.21-1.99	0.488
High	32	2	1.23	0.6-2.5	
HIV					
Negative	177	15	12.8	7.87-20.8	0.001
Positive	0	1	0.078	0.05-0.13	

*p-value is considered significant for <0.05. AST: aspartate aminotransferase, HIV: human immune deficiency virus

Table 5 - Correlation of tested factors with patients showed resistance to TB treatment either (multi and/or mono) compared to non-resistant patients.

Variables	Age	Gender	Creatinine	ALT	AST	Total bilirubin	Diabetes mellitus	SMOK	HIV
Spearman's rho resistance (mono & multi)									
Correlation coefficient	-0.145**	-0.001	-0.024	-0.025	-0.062	-0.009	-0.011	0.054	0.064
Sig. (2-tailed)	0.000	0.483	0.272	0.241	0.117	0.398	0.383	0.053	0.055
N	901	901	647	805	370	752	713	901	901
Correlation of tested factors with patients showed multi-resistance to TB treatment compared to mono-resistant patients.									
Spearman's rho multi-resistance									
Correlation coefficient	0.020	0.036	-0.079	-0.082	-0.058	0.121	0.061	-0.031	0.24**
Sig. (2-tailed)	0.780	0.618	0.426	0.311	0.649	0.159	0.492	0.665	0.001
N	193	193	104	155	63	137	128	193	193
Correlation of tested factors with patients showed Mono-resistance to TB treatment compared to Multi-resistant patients.									
Spearman's rho mono-resistance									
Correlation coefficient	-0.020	-0.036	0.079	0.082	0.058	-0.121	-0.061	0.031	-0.24**
Sig. (2-tailed)	0.780	0.618	0.426	0.311	0.649	0.159	0.492	0.665	0.001
N	193	193	104	155	63	137	128	193	193

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). ALT: alanine aminotransferase, AST: aspartate aminotransferase, HIV: human immune deficiency virus, SMOK: smoking

treatment with anti-TB drugs is the strongest factor for developing MDR-TB.[18,31] In addition, improper dose or the presence of a low concentration of anti-TB drugs in the serum may facilitate drug resistance and delay the eradication of the TB pathogen.[32]

Among the risk factors included, there was a significant association between the younger age group and resistance to anti-TB drugs, this association was observed in other previous published studies.[2,15] A recently published Chinese study showed that males have a higher rate of drug resistance than females, which supports our findings regarding mono-resistant cases (odd ratio [OR] 0.89; 95% CI 0.53-1.47).[33] Gender has no significant risk of MDR-TB in our study. However, Gaifer et al[28] reported that females have a statistical association with DR-TB. Regarding other possible risk factors, our results showed a positive association between smoking and DR-TB. However, this association is weak and a borderline significant. This finding is within the same context as the previous systemic review[34] and meta-analysis study.[35] There is a lack of research on the association between renal and liver failure with DR-TB. In this study, we did not find a significant correlation between renal or liver failure with the rate of DR-TB. A recently published systemic review and meta-analysis showed that diabetes mellitus has no significant impact on rifampicin mono-resistant or MDR-TB.[36] This result is compatible with our findings that there is a weak and non-statistically significant association between diabetes mellitus and DR/MDR TB.

The previous literature states that HIV patients infected with TB have an increased mortality rate.[12,13,37] Moreover, a cross sectional study showed that HIV does not appear to be a risk factor for MDR-TB.[36] Saudi Arabia is a low HIV prevalence country, and it has a low HIV/TB co-infection rate.[26] Only one case of MDR-TB experienced HIV co-infection. Consequently, it is difficult to evaluate the association between HIV and DR-TB.

Study limitations. Though we provided sufficient evidence to support our conclusions, it is a single-center study that only includes patients of Arab ethnicity. Due to the nature of the study, namely, retrospective, we were unable to analyze the modifiable factors such as patient compliance, which may have a role in developing anti-TB resistant. Besides, additional information of other MDR-TB patients was not accessible and genetic mutation study, which may lead to a high rate of MDR-TB.

There are certain points that make our study different from the existing literature. First, we used a large sample compared to other studies. Second, TB drug-resistance increased during the follow-up period. In addition, there is no association between DR-TB and gender. However, further studies are needed to identify the mechanism of drug resistance in TB patients.

In conclusion, pyrazinamide has the highest resistance prevalence. In addition, no risk factors appear to have a strong significant association with DR-TB, either MR or MDR. Accordingly, we believe that there are underlying genetic mutations, which could cause patients infected with TB to develop drug resistance. A recently published study that supports our hypothesis shows that among 318 clinical isolates smear-positive TB, the prevalence of the pncA mutation in isolates resistant to first-line anti-TB drugs was significantly higher than drug-susceptible isolates.[38] Even with the limitations present in this study, our results determined the overall MR and MDR-TB rate over the follow-up period and the factors associated with such resistance in Saudi Arabia which might help policymakers to address the rising concern of DR-TB in Saudi Arabia.

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