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A cross-sectional study on the factors influencing drug resistance in clinical *Mycobacterium tuberculosis* in Hulunbuir, Inner Mongolia

Студија пресека фактора који утичу на резистенцију клиничких узорака *Mycobacterium tuberculosis* на лекове у Хулунбуиру, Унутрашња Монголија

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SUMMARY

Introduction/Objective This study aimed to enhance the understanding of drug-resistant tuberculosis (TB) by conducting a retrospective analysis of clinical data from patients with TB in Hulunbuir, Inner Mongolia, collected between 2015 and 2017.

Methods The study involved a retrospective analysis of clinical data from patients with TB. The data were used to determine the rankings of monodrug resistance, which included ethambutol, isoniazid, rifampicin (RIF) and streptomycin. Additionally, the study examined drug resistance rates in multidrug resistance (MDR) combinations, specifically isoniazid + RIF + streptomycin and isoniazid + RIF + ethambutol + streptomycin. A multivariate logistic regression analysis was performed to assess risk factors associated with drug resistance, including sex, hospitalisation status, age, and treatment history.

Results The findings revealed that the drug resistance rates for the MDR combinations were both 4.51%, the highest among the combinations analysed. Ethambutol, isoniazid, and RIF had the top three resistance rates among all isolates. Patients undergoing retreatment showed higher rates of monodrug resistance, MDR and polydrug resistance compared with those receiving initial treatment. Multivariate logistic regression analysis indicated that women were at a lower risk of developing drug resistance than men. Additionally, hospitalised patients were found to have a lower risk of drug resistance compared with outpatients. The study identified being aged between 20 and 40 years and undergoing retreatment as significant risk factors for developing drug-resistant TB.

Conclusion This study concluded that in the Hulunbuir region of Inner Mongolia, there was a notable presence of drug resistance among patients with TB, with specific demographic and treatment history factors contributing to this resistance. The findings underscore the importance of considering these factors in developing targeted treatment strategies and public health policies to combat drug-resistant TB.

Keywords: *Mycobacterium tuberculosis*; drug resistance; influence factor

САЖЕТАК

Увод/Циљ Ова студија је имала за циљ да побољша разумевање резистенције туберкулозе (ТБ) на лекове спровођењем ретроспективне анализе клиничких података пацијената са ТБ у Хулунбуиру, Унутрашња Монголија, прикупљених између 2015. и 2017.

Методе Студија је укључивала ретроспективну анализу клиничких података пацијената са ТБ. Подаци су коришћени за рангирање степена резистенције на један лек [укључујући резистенцију на етамбутол, изониазид, рифампицин (РИФ) и стрептомицин]. Студија је такође испитивала стопе вишеструке резистенције (МДР) на комбинације лекова, посебно изониазид + РИФ + стрептомицин и изониазид + РИФ + етамбутол + стрептомицин. Урађена је мултиваријантна логичка регресиона анализа да би се проценили фактори ризика повезани са резистенцијом на лекове, укључујући пол, статус хоспитализације, старост и претходна лечења.

Резултати Резултати су показали да су стопе резистенције на комбинације лекова, тј. МДР за обе била 4,51%, што је највећа стопа међу до сада анализираним комбинацијама. Етамбутол, изониазид и РИФ су имали најучесталије три стопе резистенције међу свим изолатима. Изолати од пацијенти који су били понављано лечени показали су веће стопе резистенције на један лек, МДР и резистенцију на више лекова у поређењу са онима који су примали терапију први пут. Мултиваријантна логичка регресиона анализа је показала да су жене у мањем ризику од развоја резистенције на лекове од мушкараца. Поред тога, утврђено је да хоспитализовани пацијенти имају мањи ризик од појаве резистенције на лекове у поређењу са амбулантним пацијентима. Студија је идентификовала старост између 20 и 40 година и поновну терапију као значајне факторе ризика за развој туберкулозе резистентне на лекове.

Закључак Ова студија је показала да је у региону Хулунбуир у Унутрашњој Монголији постојала приметна резистенција на лекове међу пацијентима са туберкулозом, а са специфичним демографским факторима и факторима претходног лечења који доприносе развоју резистенције. Налази наглашавају важност разматрања ових фактора у развоју циљаних стратегија лечења и јавно здравствене политике за борбу против ТБ резистентне на лекове.

Кључне речи: *Mycobacterium tuberculosis*; резистенција на лекове; фактори од значаја

INTRODUCTION

Tuberculosis (TB) is a disease primarily caused by *Mycobacterium tuberculosis* (Mtb) infection and poses a significant threat to public health [1]. Between 2016 and 2020, the World Health Organisation designated China as a high-burden country for TB, TB-HIV co-infection and multidrug-resistant TB (MDR-TB). The high burden of MDR-TB is a key factor hindering TB control [2]; it is difficult to treat, severely impacting patients' physical and mental health and livelihoods and endangering their lives.

In recent years, with the implementation of the National Tuberculosis Prevention and Control Program, some progress has been made in the prevention and control of drug-resistant TB in China. However, the epidemic of drug-resistant TB remains inadequately controlled in economically disadvantaged remote areas [3]. Recent reports indicate a significant upward trend in drug resistance rates, particularly towards rifampicin (RIF), multidrug-resistant strains and fluoroquinolones among TB patients in Inner Mongolia [4]. These regions face unique challenges due to their remoteness and economic disparities. This study aims to investigate the drug resistance status of TB and its associated influencing factors in the Hulunbuir area to guide individualized treatment plans for TB in this region. It also addresses a gap in the understanding of specific factors affecting drug resistance, which is essential for developing effective control measures.

METHODS

Study design and population

A cross-sectional study was conducted using convenience sampling of 688 patients with TB who were newly diagnosed or previously treated and who sought medical care at or were referred to or tracked in Hulunbuir Second People's Hospital in the Hulunbuir region between January 1, 2015 and December 31, 2017. A questionnaire survey was then undertaken to gather basic information, medical history and treatment history from the patients. The diagnostic criteria used in this study followed the Diagnostic Criteria for Pulmonary Tuberculosis formulated by the Tuberculosis Branch of the Chinese Medical Association [5]. The inclusion criteria were as follows: patients with (1) positive sputum culture identification for Mtb, including pulmonary TB and extrapulmonary TB, and (2) undergoing drug susceptibility testing (DST). The exclusion criteria were as follows: (1) patients undergoing treatment during the investigation period, (2) patients declining DST and (3) patients unwilling to participate in the survey. The

Ethics Committee of Baotou Medical College approved this study (ethics number: Baotou Medical College Ethics Committee approval [2023] No. 16). All participants signed informed consent forms before the examination.

Research methods

Sputum samples from all active patients with TB included in the study were cultured on a solid medium using Roche culture medium. Positive cultures were subsequently subjected to strain isolation, identification, and DST. The DST for TB was divided into two parts. First, sputum samples for culturing Mtb were collected, and then the drug susceptibility of Mtb was tested using kits. Strain identification was accomplished by qualified researchers using a gene chip method, which employed a DNA microarray chip to qualitatively detect samples from clinically suspected patients with TB *Mycobacterium* and non-TB *Mycobacterium*. The detailed procedures followed the Laboratory Testing Guidelines for Tuberculosis [6]. To ensure the accuracy and reliability of the gene chip method in strain identification, a series of quality assurance measures were implemented. These measures included the establishment of standardized operating procedures, the adoption of double-blind testing processes, the introduction of positive and negative controls, inter-laboratory comparisons, the development of quality control metrics, ongoing quality improvement plans, detailed record-keeping and adherence to ethical standards. Through these stringent quality control measures, the consistency and traceability of the experimental results were ensured, thereby enhancing the scientific validity and credibility of the research. The acidic Roche culture medium was manufactured by Hangzhou Innovation Biotechnology Co., Ltd. The DST kit and gene chip were purchased from Beijing Boao Biological Group Co., Ltd., and both were compliant with national standards.

Quality control

Patient questionnaires were completed by professional physicians to ensure the accuracy of the patients' medical history and treatment records. Smear examination, bacterial culture and DST were conducted in accordance with the Diagnostic Criteria for Pulmonary Tuberculosis and the Laboratory Testing Guidelines for Tuberculosis [5, 6].

Relevant definitions

Newly diagnosed patients were defined as individuals who had never used anti-TB drugs or had used them for less than one month and had discontinued treatment for less than two months. Re-treatment patients, however, included those who underwent irregular anti-TB treatment for at least one month, as well as those who experienced treatment failure or relapse. The drug resistance classification was as follows: (1) any drug resistance: Mtb is resistant to a particular anti-TB drug, including but not limited to that specific drug; (2) mono-drug resistance: Mtb is resistant to a single first-line anti-TB drug; (3) MDR: Mtb is resistant to both isoniazid and RIF concurrently; and (4) poly-drug resistance: Mtb is resistant to two or more anti-TB drugs, excluding simultaneous resistance to both isoniazid and RIF.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics, Version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive and analytic statistics were employed to depict and examine drug resistance profiles and rates. Counts were described using proportions or percentages, and group differences were assessed using the χ^2 test. A logistic regression model was utilized to analyze the factors influencing drug resistance in patients with TB. The outcomes were visualized using GraphPad Prism 9.3. Two-tailed tests were performed, with a significance level of $\alpha = 0.05$.

This study was approved by the Ethics Committee of Baotou Medical College. The Ethics Committee approved the waiver of informed consent from parents/guardians of the minors, because the present study was a retrospective analysis of clinical data and all methods were performed in accordance with the ethical guidelines.

RESULTS

Basic information

Among the 688 patients with TB in this study, 393 were newly diagnosed, whereas 295 were re-treatment cases. The man-to-woman ratio among these patients was 2.8:1. Most patients were hospitalized due to pulmonary TB.

Drug resistance testing results

By examining the resistance results to four anti-TB drugs – isoniazid, RIF, ethambutol and streptomycin – this study identified a drug resistance rate of 44.04% among the 688 patients with TB isolates. Fifteen combinations of drug resistance were observed among these four drugs, with each combination exhibiting resistance. The ranking of monoresistance was as follows: ethambutol (8.14%), isoniazid (5.67%), RIF (5.52%), and streptomycin (1.45%). Among the combinations of multidrug resistance, the highest resistance rates were observed for isoniazid + RIF + streptomycin and isoniazid + RIF + ethambutol + streptomycin, each at 4.51% (see Table 1).

Drug resistance distribution among patients with tuberculosis

Among the 688 patients, 385 cases were drug-sensitive, 143 were mono-resistant, 61 were polyresistant and 99 were multidrug-resistant. At a significance level of $\alpha = 0.05$, a significant difference in the distribution of drug resistance was found between newly diagnosed and previously treated patients ($\chi^2 = 49.620$, $p < 0.001$). There were no significant differences in the composition ratios of the four drug resistance categories across sex, age groups, ethnicity, patient types, or diagnostic outcome groups (all p-values > 0.05) (see Table 2).

Analysis of factors influencing drug resistance in patients with tuberculosis

The multivariate analysis of the logistic regression model showed that women had a lower risk of developing drug resistance compared with men [odds ratio (OR) = 0.68, $p < 0.05$]. Patients aged 20–40 years had a higher risk of developing drug resistance than those aged 0–20 years (OR = 2.64, $p < 0.05$). Retreatment patients had a higher likelihood of developing drug resistance than initial treatment patients (OR = 2.34, $p < 0.05$). Hospitalized patients had a lower risk of developing drug resistance than outpatients (OR = 0.64, $p < 0.05$) (Figure 1).

DISCUSSION

The survey revealed that the prevalence of MDR-TB (14.39%) and overall drug resistance (44.04%) among patients in the Hulunbuir area of Inner Mongolia between 2015 and 2017 surpassed the rates reported in a drug resistance survey conducted among four provinces in northwest China between 2005 and 2011 (11.29% and 27.9%, respectively) and the national

baseline survey (39.12% drug resistance rate) [7, 8]. These findings indicate a potentially higher drug resistance rate among patients with TB in the Hulunbuir area compared with other regions. The survey ranked the drug resistance rates of various anti-TB drugs as follows: isoniazid (24.13%), RIF (23.98%), streptomycin (23.84%) and ethambutol (11.48%). These rankings closely corresponded to the reported drug resistance rates of acid-fast bacilli-positive samples in the Inner Mongolia region, as reported by Feng et al. [4]. The high resistance rate for streptomycin is notable, as TB treatment guidelines recommend its limited use. However, current guidelines that advocate for reduced use of streptomycin may unintentionally withhold a potentially lifesaving, inexpensive, and readily available drug from certain patients with drug-resistant TB. Isoniazid and RIF are the most commonly used first-line oral anti-TB drugs, characterized by their strong bactericidal effects, antimicrobial activity, and low toxicity [9]. The appearance and progression of the resistant strain of Mtb depends largely on the genetic mutant selection. The *Mycobacterium* population takes advantage of the arising mutants under selective pressure and ensures its survival by choosing antibiotic resistance as the predominant trait. This study's OR analysis emphasizes the heightened risk of drug-resistant TB in patients aged 20–40 years and those undergoing retreatment, informing tailored clinical strategies. These findings provide actionable insights for healthcare providers to enhance treatment adherence and outcomes in these high-risk groups.

The virulence of *Mycobacterium,* genetic factors of the host, HIV infection, and incomplete treatment of patients all contribute to the outbreak of drug-resistant TB [10]. Studies have revealed that risk factors for drug-resistant TB include monotherapy resulting from intermittent treatment, actual monotherapy due to irrational combination therapy and insufficient drug concentration leading to ineffective treatment [11]. Therefore, in the diagnosis and treatment of patients with TB, it is crucial to prioritize strict adherence to drug use principles and the rational utilization of anti-TB drugs, particularly first-line medications.

In this survey, the proportions of mono-drug resistance, MDR and poly-drug resistance among newly diagnosed patients were 21.37%, 6.87% and 7.12%, respectively, indicating possible transmission of drug resistance in the community [12]. Phenotypic DST is considered the gold standard for DST in China. However, TB laboratory tests in primary hospitals mainly consist of time-consuming methods, such as modified acid-fast staining and acid-fast culture [13, 14]. Current clinical practice relies on early anti-TB treatment principles that are essentially similar to those for MDR-TB. However, these treatment regimens lack phenotypic DST results for other drugs. Consequently, when resistance to these drugs arises, it significantly impacts

treatment efficacy and prognosis. Additionally, the analysis reveals that drug-resistant TB patients in the Hulunbuir area are distributed differently between newly diagnosed and retreatment patients. Several studies have demonstrated that drug resistance patterns vary between newly diagnosed and previously treated patients, potentially due to differences in drug exposure history and patient compliance [15]. Therefore, it is crucial to consider the characteristics of these patient populations in the clinical diagnosis and treatment process and choose appropriate individualized treatment plans based on specific situations, emphasizing the importance of drug guidance to enhance compliance.

Multivariate logistic regression analysis revealed several independent risk factors for drug-resistant TB, consistent with previous research findings [16]. Patients aged 20–40 years had a 2.64 times higher risk of drug resistance compared with those aged 0–20 years. This may be attributed to higher levels of life stress, social activities and mobility among young and middle-aged patients, resulting in lower treatment compliance. Another reason is the relatively poor physical fitness to resist TB infection, which leads to prolonged disease [17]. This method was used for data collection in this study because of the high feasibility and validity of convenience sampling. However, selection bias, resulting from the use of convenience sampling, is a possible reason for this result. The risk of drug resistance is also higher in previously treated patients with pulmonary TB compared with newly diagnosed patients, potentially due to factors such as insufficient professional knowledge, improper medication, self-discontinuation of treatment or treatment failure in the initial stages [18]. Additionally, outpatients undergoing follow-up have a higher risk of drug resistance compared with hospitalized patients. This may be due to the non-adherence of patients to their six-month therapy and/or a lack of physicians in therapy management. Another cause may be that some patients who require hospitalization exhibit a weaker willingness to partake in it, leading to poor compliance among outpatients. This emphasizes the importance of improving patient cooperation during outpatient follow-up.

Among newly diagnosed patients, being male, aged 20–40 years, and receiving outpatient follow-up were identified as risk factors for drug resistance. In the re-treatment group, risk factors included being male, aged 20–40 years, and having a history of a previous treatment failure or relapse. These findings highlight the importance of tailoring interventions and management strategies based on the patient's treatment history and specific risk factors.

When compared to international data, our results are particularly striking. A global analysis by the World Health Organization (2023) reported a lower global average for drug-resistant TB, indicating that Inner Mongolia, and particularly the Hulunbuir region, may be a hotspot for

drug resistance. The high resistance to first-line drugs such as isoniazid and rifampicin, observed in our study, echoes the findings of Shabani et al. [9], who noted the increasing prevalence of resistance to these cornerstone anti-TB medications. In contrast to our findings, a study by Magotra et al. [13] reported lower resistance rates but noted the importance of personalized treatment strategies, which is also a key takeaway from our study. The need for tailored interventions is further emphasized by the high resistance rates to ethambutol, isoniazid, and rifampicin, which are consistent with the patterns reported by Feng et al. [15] in their study on drug sensitivity in Xi'an, China.

This study in Hulunbuir, Inner Mongolia, uniquely revealed high rates of drug resistance to ethambutol, isoniazid and RIF among patients with TB, emphasizing the need for tailored treatment strategies in the region. Additionally, it identified social support and physical function as critical factors influencing resistance patterns, underscoring the importance of a holistic approach to combat drug-resistant TB. This study's findings prominently indicate that healthcare providers urgently need to adopt personalized treatment strategies that take into account the specific patterns of drug resistance observed in the region. This may include revised guidelines for the initial and ongoing treatment of TB, with a focus on more effective drug regimens and stricter monitoring of patient adherence. From a public health perspective, the findings highlight the importance of strengthening surveillance systems to monitor drug resistance trends and inform policy decisions. There is a clear need for targeted public health campaigns to raise awareness about the dangers of drug-resistant TB and the importance of completing the full course of medication.

The limitations of this study are as follows: (1) the analysis of the course of pulmonary TB, treatment methods and the results of relevant laboratory tests is lacking, necessitating further research; (2) the molecular correlation could be further studied, and the evaluation index of patients should be improved; and (3) due to the use of pre-existing data, retrospective studies may not obtain certain specific information as it may not have been fully documented in past records.

CONCLUSION

The drug resistance spectrum exhibited diversity and complexity, with variations in the distribution of drug resistance between newly diagnosed and previously treated patients. Specifically, for men, particularly those aged 20–40 years, and patients under outpatient follow-up, it

is crucial to strengthen health education, improve healthcare insurance systems, and enhance patient management models to improve compliance.

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Availability of data and materials: The data supporting this study are available from the corresponding author upon reasonable request.

Conflict of interest: None declared.

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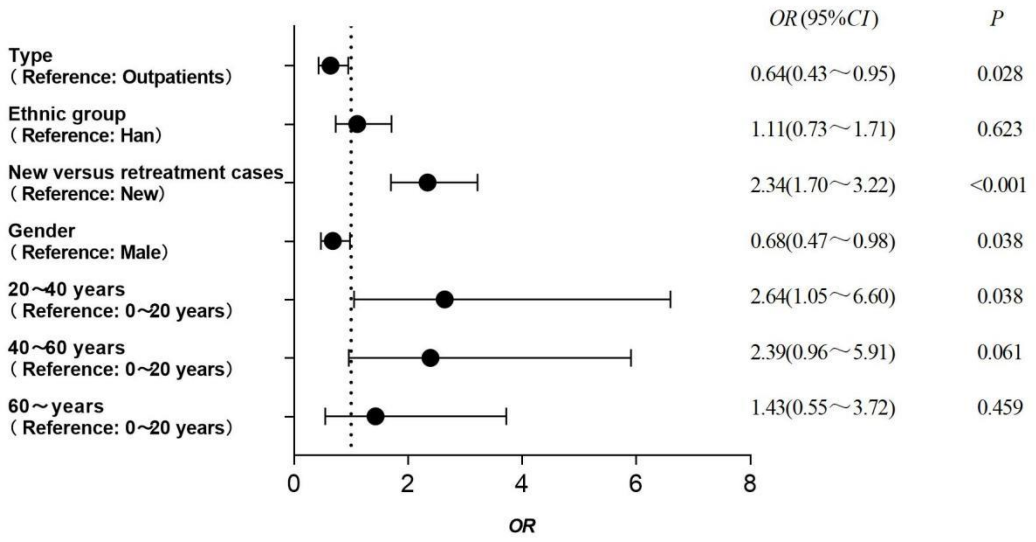

Figure 1. Multivariate analysis of a tuberculosis patient in a logistic regression model

Table 1. Drug resistance frequencies of various drug combinations in treatment-resistant patients with tuberculosis

Combinations	n	Drug resistance rate (95% CI)	Composition ratio % (n/303)
Any drug resistance	—	—	—
H	166	24.13 (20.93–27.33)	—
R	165	23.98 (20.79–27.17)	—
E	79	11.48 (9.10–13.86)	—
S	164	23.84 (20.65–27.02)	—
Mono-drug resistance	143	20.78 (17.75–23.82)	47.19 (143/303)
H	39	5.67 (3.94–7.40)	12.87 (39/303)
R	38	5.52 (3.82–7.23)	12.54 (38/303)
E	56	8.14 (6.10–10.18)	18.48 (56/303)
S	10	1.45 (0.56–2.35)	3.30 (10/303)
Multi-drug resistance	99	14.39 (11.77–17.01)	32.67 (99/303)
H+R	26	3.78 (2.35–5.2)	8.58 (26/303)
H+R+E	11	1.60 (0.66–2.54)	3.63 (11/303)
H+R+S	31	4.51 (2.96–6.06)	10.23 (31/303)
H+R+E+S	31	4.51 (2.96–6.06)	10.23 (31/303)
Poly-drug resistance	61	8.87 (6.74–10.99)	20.13 (61/303)
H+E	2	0.29 (0.11–0.69)	0.66 (2/303)
H+S	23	3.34 (2.00–4.69)	7.59 (23/303)
H+E+S	3	0.44 (0.06–0.93)	0.99 (3/303)
R+E	13	1.89 (0.87–2.91)	4.29 (13/303)
R+S	11	1.60 (0.66–2.54)	3.63 (11/303)
R+E+S	4	0.58 (0.01–1.15)	1.32 (4/303)
E+S	5	0.73 (0.09–1.36)	1.65 (5/303)
Total	303	44.04 (40.33–47.75)	100 (303/303)

H – isoniazid; R – rifampicin; E – ethambutol; S – streptomycin; "—" indicates no corresponding value

Table 2. Analysis of the distribution of drug resistance among patients with different characteristics

Characteristics	Drug resistance type				χ^2	p
	Sensitivity (%)	Mono-drug resistance (%)	Poly-drug resistance (%)	Multi-drug resistance (%)		
Sex						
Male	269 (53.06)	111 (21.89)	49 (9.66)	78 (15.38)	7.049	0.070
Female	116 (64.09)	33 (18.23)	11 (6.08)	21 (11.6)		
Age（years）						
0–19	22 (75.86)	4 (13.79)	2 (6.9)	1 (3.45)	15.010	0.091
20–39	110 (52.38)	45 (21.43)	20 (9.52)	35 (16.67)		
40–59	165 (52.05)	73 (23.03)	29 (9.15)	50 (15.77)		
60–older	88 (66.67)	22 (16.67)	9 (6.82)	13 (9.85)		
Ethnic group						
Han	326 (56.50)	120 (20.8)	52 (9.01)	79 (13.69)	1.775	0.620
Mongolian	59 (53.15)	24 (21.62)	8 (7.21)	20 (18.02)		
New versus retreatment cases						
new	254 (64.63)	84 (21.37)	27 (6.87)	28 (7.12)	49.620	< 0.001
retreatment	131 (44.41)	60 (20.34)	33 (11.19)	71 (24.07)		
Type						
Outpatients	68 (50.37)	31 (22.96)	17 (12.59)	19 (14.07)	4.168	0.244
Inpatients	317 (57.32)	113 (20.43)	43 (7.78)	80 (14.47)		
Diagnosis						
Pulmonary tuberculosis	380 (55.96)	141 (20.77)	60 (8.84)	98 (14.43)	—	0.788
Extrapulmonary tuberculosis	5 (55.56)	3 (33.33)	0 (0)	1 (11.11)		

"—" represents the use of the Fisher exact probability method to calculate precise probabilities without calculating the χ^2 value

