Factors associated with adult pulmonary TB treatment outcome: East Kazakhstan Region

Master of Public Health Integrating Experience Project Utilizing Professional Publication Framework

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Executive summary

Kazakhstan is in top 18 countries with the highest TB burden in European region [2, 9]. The tuberculosis burden for Kazakhstan is very high, annual years of healthy life lost per 100,000 people from tuberculosis in Kazakhstan has increased by 19.8% since 1990, an average of 0.9% a year. This research investigated factors associated with treatment outcome failure. The following factors has been examined: age, sex, residence, socio-economic status, year of admission, length of stay in the hospital, drug resistance, medical organization, hospital admission type. It has been found that following factors are associated with increased TB treatment outcome failure: being male by 17%; drug resistance by 206%; being emergency admitted to the hospital by 47%. Factors that are associated with decreased treatment outcome failure: being treated in Ust-Kamenogorsk TB center by 34%; being employed (as compared to being unemployed) by 36%; being student (as compared to being unemployed) by 65%; one additional day of stay by 1%. However, it should be admitted that obtained factors' association are generalizable for East-Kazakhstan region only due to study design limitations.

Key words: Tuberculosis, treatment outcome, drug resistance, East-Kazakhstan region.

Word count:180

1. INTRODUCTION

Effective tuberculosis (TB) control is largely dependent on successful treatment and diagnosis. 53 million lives have been saved between 2000 and 2016 by TB control strategies [1]. Albeit tremendous efforts, TB is the top infectious killer worldwide, and each year over 1 million deaths occur from TB [2]. It should be admitted that it is important to identify high risk groups and vulnerable population for TB [3-6]. Co-morbidities with TB may complicate the treatment and influence on poor outcome of the treatment, including treatment failure and death. Primarily, there is high association of TB with HIV and diabetes [7]. Early detection and appropriate treatment strategy may reduce transmission rate and better treatment outcome, including drug resistance [8].

Kazakhstan is in top 18 countries with the highest TB burden in European region [2, 9]. The tuberculosis burden for Kazakhstan is very high, annual years of healthy life lost per 100,000 people from tuberculosis in Kazakhstan has increased by 19.8% since 1990, an average of 0.9% a year. TB control in Kazakhstan is managed by Ministry of Health National TB Control program for 2014- 2020. The main partners of this program are: WHO, CDC, Global Fund to fight AIDS, TB and Malaria (GFATM), and the United States Agency for International Development (USAID) through Challenge TB, Project HOPE, TB CARE I, KNCV [9, 10]. TB treatment and diagnosis are free across the Kazakhstan [11]. Despite these advances in TB control efforts, treatment success rate in Kazakhstan of tuberculosis vary across the TB case types: new tuberculosis case treatment

success rate is 91%; previously treated TB case treatment success rate is 47%; and multi-drug resistance tuberculosis case treatment success is 76%. Moreover, it can be observed that country's success rates for treatment of TB are lower than WHO-recommended ≥85% cure rate.

From Ministry of Health order #994: "Instruction on the organization of medical care for tuberculosis", it can be observed that TB services are disproportionately distributed in favor of urban areas, potentially leaving a larger proportion of people from rural areas with poor access to TB care. Geographic barriers related to rural living influence access to TB care and clinical outcomes [12]. Additionally, individual risk factors of rural residents such as low educational attainment and income can influence care-seeking behaviors, resulting in treatment delays and poor treatment adherence [13]. Poor access to health care could also lead patients to seek less credible alternative care [14]. Though urban residence is a recognized risk factor for TB, especially in rapidly urbanizing communities due to poor living conditions, [12] the gap in TB services coverage between the rural and urban areas may have worsened inequalities to treatment access which can affect the treatment outcome. In addition to providing specialist services such as diagnosis of extra-pulmonary and smear-negative TB, several tertiary-level facilities in the country (which are largely urban-based) also provide primary care services, such as diagnosis and treatment of pulmonary TB. This imbalance may also further worsen rural-urban inequalities in TB care. Establishing the effect of

rural residence in the context of the country provides important policy-relevant information.

Previous Kazakhstani studies examine factors associated with tuberculosis cases; however, there is lack of studies that examined factors associated with treatment outcome [17-19]. Results of the Terlibekova study shows, that the highest prevalence in TB cases and multidrug cases are in East-Kazakhstan region: 122 per 100,000 people, and 10.6 per 100,000 people respectively. Due to high TB-burden in Kazakhstan, we anticipate that treatment success rate may drop due to expected increase in multi-drug resistant tuberculosis cases. The aim of this study to examine factors associated with adult pulmonary TB treatment outcomes in East-Kazakhstan region. And, we hope that this study will present the first comprehensive description of possible factors associated with treatment outcome in East-Kazakhstan region based on Kazakhstani information system "Electronic register of inpatient care".

Discrete goals of the study

1. To examine factors associated with adult pulmonary Tb treatment outcome in East-Kazakhstan region;
2. To provide useful information for further interventions, research, and policies to decrease rates of Tb in East-Kazakhstan region.

2. METHODS

Study design and settings

The study utilized a cross sectional study design. In research, data from information system "Electronic register of inpatient form" was used. In Kazakhstan, this register was developed in 2013 [16]. All medical organizations must enter all the cases using unified form of fata entry type [16]. E-medical records are stored on SQL server at National Center of Public Health development [16]. Data access was permitted by NJSC "Social Medical Health Insurance Fund.

Subject selection information

All secondary patient records aged 18 and older from the national enhanced TB surveillance system from 2015 to 2017 in East Kazakhstan region was eligible for inclusion. TB cases include all patients whose diagnosis was confirmed.

Data entry and cleaning

Provided data was translated into English language in the Excel and then exported and analyzed in STATA 12.0 statistical package. Data entry lasted one month. Range and outlier check technique was used to clean the data.

Data Analysis

The study results were analyzed using STATA software [15]. Firstly, we conducted descriptive univariate analysis to illustrate relevant characteristics. Secondly, bivariate analysis was performed to identify statistically significant differences in factors and treatment outcome by performing Chi-square and Fisher's

exact tests for categorical variables, and Student t-test for continuous variables. Third, simple bivariate Poisson regression with robust equal variances to identify potentially significant ($p<0.25$) associations between factors and treatment outcome. Fourthly, the final multivariate Poisson regression with robust equal variances was used to calculate the adjusted prevalence risk ratios. This regression provides more reliable estimates than logistic regression in cross sectional studies with binary outcome analysis [20-21].

Variables

Provided data from electronic register of inpatients had following information: 1) organization, where patient is getting treatment; 2) age of patient; 3) gender of patient; 4) hospital admission type (planned/emergency); 5) length of stay at hospital; 6) year of admission; 7) residence (urban or rural); 8) drug resistance (yes or no); 9) complication wit surgery (yes/no); 10) socio-economic status (unemployed, disabled, employed, pensioner, student) ; 11) treatment outcome.

Treatment outcome variable had five categories: ‘treatment success’, ‘got better’, ‘no change’, ‘got worse’, and ‘death’. Treatment outcome categories such as ‘treatment success’ and ‘got better’ has been classified as successful treatment outcome. And, other categories were classified as unsuccessful treatment outcome.

Ethical considerations

Institutional Review Board of the Nazarbayev University School of Medicine approved the research. The research did not pose any significant risk to

the participants since secondary data did not include any identifiable information. The study focused only on information concerning TB treatment outcome.

3. RESULTS

Of the 3,198 patients, who were eligible to our study, 2,529 (79%) of all patients, 669 (21%) of the pulmonary TB patients, had successful and unsuccessful treatment outcomes respectively. Mean age and frequency of complication with surgery between two treatment groups was not different, p-value was equal to 0.6714 and 0.558 respectively (Table 1). The mean age for successful treatment outcome was equal to 42.64±14.67, and in unsuccessful treatment outcome 42.90±14.47. Other frequencies of risk factors' such as: sex; residence; socio-economic status; year of admission; length of stay; drug resistance; medical organization, where patient has been treated; hospital admission was statistically different between two treatment groups outcomes, p-values were less than 0.1 (Table 1).

Table 1. Characteristics of individuals receiving standard initial tuberculosis treatment, comparing patients with successful treatment to patients with unsuccessful treatment.

Variable	Type	Successful treatment outcome, n (%), n = 2529	Unsuccessful treatment outcome, n (%), n = 669	p-value
Mean Age (years)		42.64±14.67	42.90±14.47	0.6714*
Sex	Female	787 (31.12%)	158 (23.62%)	<0.001
	Male	1742 (68.88%)	511 (76.38%)	
Residence	Urban	1033 (59.15%)	421 (63.52%)	0.076

	Rural	1496 (40.85%)	248 (37.07%)	
Socio-economic status	Unemployed	1536 (60.73%)	476 (71.15%)	<0.001
	Disabled	119 (4.71%)	65 (9.72%)	
	Employed	630 (24.91%)	81 (12.11%)	
	Pensioners	202 (7.99%)	44 (6.57%)	
	Students	43 (1.66%)	3 (0.44%)	
Year	2015	849 (33.57%)	248 (37.07%)	<0.001
	2016	843 (33.33%)	267 (39.91%)	
	2017	837 (33.10%)	154 (23.02%)	
Length of stay (in days)		159.56±112.85	93.20±118.59	<0.001
Drug resistance	Yes	1298 (48.67%)	492 (73.54%)	<0.001
	No	1231 (51.32%)	177 (26.46%)	
Medical organization	Semey	1204 (47.61%)	367 (54.86%)	0.001
	Ust'-Kamenogorsk	1325 (52.39%)	302 (45.14%)	
Hospital admission type	Emergency	852 (33.69%)	305 (45.59%)	<0.001
	Planned	1677(66.31%)	364 (54.41%)	
Complication with surgery	Yes	7 (0.28%)	1 (0.15%)	0.558*
	No	2522 (99.72%)	668 2(99.85%)	

In a Poisson regression analysis with robust equal variances (Table 2.), patients who had drug resistance for TB were at higher risk of a unsuccessful treatment outcome (RR = 3.06±0.23, p-value≤0.01). Also, patients, who were emergency admitted to the hospital had a higher likelihood of treatment failure compared to those who were admitted to the hospital in planned manner (RR = 1.47±0.09, p-value≤0.01). Male patients have a higher risk of treatment failure in comparison to female patients (RR=1.17±0.09, p-value = 0.042). One additional stay at the hospital decrease the likelihood of treatment failure by 1% (RR = 0.99±0.001, p-value≤0.01). From the model, it could be observed that residence type does not influence on treatment failure, p-value= 0.219. Socio-economic status as being unemployed, disabled or pensioner

have approximately the same association with treatment outcome, while person's who are employed or a student have less chances of treatment failure in comparison with people who are unemployed (RR=0.64±0.07, p-value<0.01; RR=0.35±0.19, p-value=0.05, respectively). The most interesting observation is that patients that were admitted in 2017 decrease likelihood of treatment failure in comparison with other years (RR=0.57±0.05, p-value<0.01). Additionally, persons treated in Ust'-Kamenogorsk TB center associated with decrease of likelihood of treatment failure in comparison to those who were treated in Semey TB center (RR=0.66±0.04, p-value<0.01)

Table 2. Risk factors for unsuccessful treatment outcome: Poisson regression with robust equal variances

Variable	**Status**	**Prevalence RR**	**p-value**
Sex	**Female**	1	
	Male	1.17±0.09	0.042
Residence	**Rural**	1	
	Urban	0.92±0.06	0.219
Socio-economic status	**Unemployed**	1	
	Disabled	1.23±0.11	0.24
	Employed	0.64±0.07	<0.01
	Pensioners	1.00±0.13	0.99
	Students	0.35±0.19	0.05
Year	**2015**	1	
	2016	0.99±0.07	0.98
	2017	0.57±0.05	<0.01
Length of stay	**1 day increment**	0.99±0.001	<0.01
Drug resistance	**No**	1	<0.01
	Yes	3.06±0.23	
Medical organization	**Semey**	1	
	Ust'-Kamenogorsk	0.66±0.04	<0.01

Hospital admission type	**Planned**	1	<0.01
	Emergency	1.47±0.09	

4. DISCUSSION

According to CDC, some people are affected by TB more than others. The occurrence of TB at greater levels among certain population groups is often referred as a health disparity [22]. Difference may occur by gender, race or ethnicity, income, comorbid medical conditions, residency, geographic location, etc. Our research results may help to achieve equity by addressing disparities.

This research investigated factors associated with treatment outcome failure. The following factors has been examined: age, sex, residence, socio-economic status, year of admission, length of stay in the hospital, drug resistance, medical organization, hospital admission type. It has been found that following factors are associated with increased TB treatment outcome failure: being male by 17%; drug resistance by 206%; being emergency admitted to the hospital by 47%. Factors that are associated with decreased treatment outcome failure: being treated in Ust-Kamenogorsk TB center by 34%; being employed (as compared to being unemployed) by 36%; being student (as compared to being unemployed) by 65%; one additional day of stay by 1%. However, it should be admitted that obtained factors' association are generalizable for East-Kazakhstan region only due to study design limitations.

Age in our model does not have an influence on treatment outcome. However, WHO report represent that tuberculosis affects mostly people aged 25-34 among both sexes

[22]. It may imply that even though tuberculosis affects certain age group, age by itself does not have an association with treatment outcome.

A disproportionate number of TB cases occur among high-risk populations, including people experiencing homelessness [23]. Our research results showed that treatment failure predominantly at higher risk among such socio-economic statuses as being unemployed, pensioner or disabled. From the secondary data that was provided, there was no information about whether patient is homeless or not. Therefore, they might be also in high-risk populations that may have higher risk of treatment outcome failure.

Geographic barriers related to rural living influence access to TB care and clinical outcomes [12]. Poor access to health care could also lead patients to seek less credible alternative care [14]. Though urban residence is a recognized risk factor for TB, especially in rapidly urbanizing communities due to poor living conditions, [12] the gap in TB services coverage between the rural and urban areas may have worsened inequalities to treatment access which can affect the treatment outcome. Even though, our research shows that rural or urban residency in East-Kazakhstan region does not have an association with treatment outcome. However, there is an association between medical organization, where patient has been treated and treatment outcome. This is an interesting factor that is associated with treatment outcome because, in fact, both organizations follow the same clinical protocols approved by Republican center of health development.

There is no information on how year of admission to the hospital influence on treatment outcome. Our results showed that admission at 2017 in comparison to 2015 decrease the likelihood of treatment failure. But definite explanation to this observation can not be made.

5. Strength of the study

Previous Kazakhstani studies investigated factors associate with TB cases that are alcohol use, diabetes, drug use, being incarcerated within past 2 years, being migrant, non-regular uptake of anti-tuberculosis medication, socio-economic status, being prison system staff member, being recent mother, being tuberculosis health care staff member, and HIV status [17-19]. However, there was no any studies in Kazakhstan that investigated factors associated with treatment outcome. It is a first comprehensive study in Kazakhstan to measure the factors associated with treatment result using multivariate analysis and first study in the regions of Kazakhstan with a big sample size.

6. Limitations of the study

Analytical cross-sectional study design is limited in its ability to draw valid conclusions about any association or possible causality because the presence of risk factors and outcomes are measured simultaneously. From this study design we cannot draw any causation patterns, it should always be confirmed by more rigorous studies. The collection of information about risk factors is provided by different organization staff members running the data entry issues. Moreover, it should be admitted that results of this study are generalizable only for East-Kazakhstan region.

7. RECOMMENDATIONS

The study findings suggest the following steps and recommendations that could help to decrease unsuccessful pulmonary tuberculosis treatment outcome among adult population in East-Kazakhstan region:

- To develop strategies to better treatment outcome for following high-risk groups: male population; people with socio-economic status as being unemployed, disabled, and being pensioner; people who has emergency admission; patients with drug resistance.
- To conduct research to identify the reason for the differences between hospitals;
- Further research is required for factors associated with multi-drug resistant TB treatment outcomes;
- To develop strategies for listed high-risk groups applied to modern treatment regimens or clinical procedure.

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