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Original Article

Risk Factors for Primary Pulmonary TB in Almaty Region, Kazakhstan: A Matched Case-Control Study

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Abstract

Background: This study examined the association between incident pulmonary tuberculosis (TB) and social and behavioral characteristics in Almaty Oblast, Kazakhstan from 2012 to 2013.

Methods: We used a matched case-control design to estimate the role of factors for acquiring pulmonary TB. Totally 324 individuals were recruited from Sep 2012 to Mar 2013. Participants included 110 TB index cases with newly detected pulmonary TB. Each case was matched with one household and one community control. A total of 107 household and 107 community controls were included to the study. Adjusted odds ratios measuring associations between TB and risk factors were calculated by using a conditional multiple logistic regression analysis.

Results: TB cases were more likely to be younger, recent smokers and have diabetes, when compared to household controls. Between TB cases and community controls, TB was significantly associated with age, non-married family status, living in a rented home, recent smoker, and having diabetes. Comparing TB cases with community controls, we found that foreign birth was marginally associated with incident TB case status.

Conclusion: Our findings confirm the role of modifiable risk factors for TB in Kazakhstan; highlighting the importance of developing interventions addressing social determinants and proximate risk factors for high TB burden regions.

Keywords: Tuberculosis, Risk factors, Kazakhstan

Introduction

Tuberculosis (TB) is a leading cause of global morbidity and mortality and remains an acute threat to global public health (1). While there has been a recent leveling off of the global TB burden of disease, the increase in TB cases after the dissolution of the Soviet Union has been well documented in the region (2). Multidrug-resistant TB (MDR-TB), a major public health problem that threatens progress made in TB control and care programs, has also been on the rise in Kazakhstan (3). While TB notification rates have declined in Kazakhstan in recent years (4), there is still a lack of understanding into the specific mechanisms that are driving TB transmission locally. The aim of this study is to understand incident TB case notification in Almaty Oblast, Kazakhstan from 2012-2013.

TB incidence and prevalence have stabilized in recent years in Kazakhstan with a reported incidence of 81.7 cases per 100,000 populations and a prevalence of 143.5 cases per 100,000 populations in 2010 (4). MDR-TB continues to rise with an incidence of 10.7 cases per 100,000 populations and prevalence of 62.5 cases per 100,000 populations in 2012 (3). The national TB program (NTP) oversees the surveillance and care of patients in Kazakhstan. The NTP provides diagnostic and treatment services to all legal residents of Kazakhstan at no cost through a network of microscopy laboratories, primary health care centers and district level TB clinics. Despite improvements in laboratory capacities to detect resistance to common anti-TB drugs, problems remain with diagnosis of incident TB cases (4). This process has limited the control and treatment efforts in Kazakhstan; TB and MDR-TB are not currently distinguishable in early treatment phases (5).

Globally, epidemiologic research has identified many known drivers of TB, such as modifiable socio-behavioral factors including confined living conditions such as imprisonment (6-12), migrant status (4, 13, 14), cigarette smoking (15-19), alcohol consumption (10, 20-24), and co-morbidity with HIV (3, 14, 25), diabetes (26-29), and some mental health illnesses (30). Given limitations in known risk factor documentation among official surveillance channels (85% of cases documented as having an unknown risk factor) (4), specific drivers of TB in Kazakhstan are still largely unknown.

The study objective is to explore the social and behavioral factors associated with incident TB in Almaty Oblast, Kazakhstan; findings from which may guide TB control and identification programming. We specifically investigated whether factors such as age, gender, socio-economic status, confined living conditions and increased burden of co-morbidity were associated with incident TB.

Materials and Methods

Sample

We used a matched case-control design to estimate the role of demographic, social, and behavioral factors on acquiring TB by comparing index cases with age-matched (10 yr) household and community controls. Presented here are baseline data from the six administrative regions of Almaty oblast (province) of Kazakhstan including Alakolskiy, Balkhashskiy, Enbekshikazakhskiy, Jambylskiy, Sarkandskiy regions and Kapchagay city from Sep 2012 to Mar 2013.

Consistent with WHO recommendations (31), individuals were classified as TB cases if they were either: culture positive with positive smear examination confirmed by nucleic acid amplification testing, or had clinical and radiographic presentation consistent with TB and responded to treatment with anti-TB drugs. Index TB cases were defined as cases of pulmonary TB initially diagnosed within three months from data collection. Other eligibility criteria were universal across all study groups and include that participant: was at least 18 yr old at study screening; had a permanent address and been residing there for more than three months; had at least one other adult household member; had no plans to relocate in the next 12 months; spoke Russian or Kazakh fluently; did not have any severe psychiatric condition that could impede their ability to provide informed consent, assessed by research assistants during screening; and did not have an illness expected to be terminal within a year of screening, assessed by research assistants during screening. Both household and community control participants had no previous diagnosis of pulmonary TB. Community control participants were randomly selected from households located near the TB index case. The Kish method (32) was used to select a household or community contact participant if more than one eligible contact was available in a selected household.

All new TB cases (n=126) registered from Jun 2012 to Jan 2013 in these regions were pre-screened, 110 met the eligibility criteria and all agreed to participate. The response rate for community and household control was 97%, 107 controls from 110 identified ones agreed to participate in the study in both groups for a final sample of 324 participants.

Data collection

Socio-demographic, occupational, and behavioral information was collected from participants through a 60-min audio computer assisted self-interview (ACASI). We used DatStat, a software package providing audio and video presentation of standardized questionnaire and response options on a computer in both Kazakh and Russian. All interviews were conducted in private rooms, with a research assistant available to assist participants, as needed. The data were collected from Sep 2012 to Mar 2013.

Collected socio-demographic variables included age, gender, religion, profession, educational attainment, marital status, family composition, and variables on income, food security, and home ownership. Behavioral factors such as incarceration history, smoking history and status, alcohol consumption (both absolute and CAGE dependency scale) (33), physical activity and body mass index (BMI) were measured to explore associations and potential mechanisms of increased TB risk. Co-morbidity with hypothesized and known risk factors such as diabetes, HIV, hepatitis C virus (HCV), and common cancerous conditions were also assessed through interviews.

Data analysis

We analyzed the data using R version 3.0.1. We used univariate associations to describe the study population and assess variable level missingness. Religion had the highest variable level missingness (n=53, 16%), but was not imputed or used in further analysis as over 80% of the respondents recorded the same religion and no variation across populations was suggested. For categorical variables, we used frequencies and for continuous variables we explored mean, median, and standard deviation estimates. We calculated bivariate Mantel-Haenszel odds ratios (OR) to examine the associations between TB case status and control group status. Based on the results of the bivariate analysis, we conducted conditional logistic regressions to produce matched multivariable effect estimates. We analyzed three data sources for the final analysis, comparing index TB cases to their household matched control; and to their community control. Variables were considered for inclusion into the final multivariable model if the bivariate OR estimate was significant at a 0.10 level or had demonstrated epidemiological significance with incident TB case notification. Variables included in the final models were age, sex, birth country, education, current employment, housing, and marital status, and incarceration, smoking, alcohol abuse, diabetes and urinary tract or kidney disease history. The predictive accuracy of regression models was evaluated through classification tables.

Ethics

The institutional review boards of Columbia University and the Ethics Review Board of the Kazakh School of Public Health approved protocols of this study.

Results

A total of 324 participants were recruited to the study. Table 1 shows the baseline characteristics of the complete study population. The mean age of participants was 40 (standard deviation [SD] 13.58), slightly more female than male participants, predominantly Kazakh (by birth and ethnicity), and Muslim. Twelve (3.7%) participants were ever incarcerated, 100 (30.9%) had smoked tobacco in the past twelve months, and 298 (92.0%) have a low reported alcohol abuse score based on the CAGE alcohol dependency scale. A total of 13 (4.0%) participants had a previous diabetes diagnosis, 8 (2.5%) had a previous HCV diagnosis, 2 (0.8%) reported a positive HIV result, and 34 (10.5%) had a previous urinary tract or kidney disease diagnosis.

More than half of incident TB cases interviewed (56%) were male, household and community control groups were more likely to be female (66% and 52% respectively). Mean age of TB cases was 35 yr; household and community controls were 43 and 41 yr respectively. Most study participants were Kazakh (more than 75%), with Russians representing the next highest percentage in the sample (slightly more than 10%). The majority of respondents in all groups were Muslims (more than 80%). Around 60% of cases and approximately 80% of controls were married. One third of cases were never married.

Table 1: TB cases, household, and community control participants in Almaty Region, Kazakhstan, 2012-2013

Variables	All respondents n (%)	TB cases n (%)	Household controls n (%)	Community controls n (%)
	324	110	107	107
Socio-demographic				
Age, yr, mean [SD]	39.59 [13.58]	34.75 [13.66]	42.97 [12.73]	41.19 [13.00]
Sex				
Female	175 (54.0)	48 (43.6)	71 (66.4)	56 (52.3)
Male	149 (46.0)	62 (56.4)	36 (33.6)	51 (47.7)
BMI, kg/m^2, median [range]	22.78 [14.53-42.31]	20.99 [15.62-33.30]	23.73 [16.60-35.63]	22.78 [14.53-42.31]
Ethnicity				
Kazakh	254 (78.4)	89 (80.9)	81 (75.7)	84 (78.5)
Russian	38 (11.7)	11 (10.0)	13 (12.1)	14 (13.1)
Other	32 (9.9)	10 (9.1)	13 (12.1)	9 (8.4)
Kazakhstan born	269 (83.0)	87 (79.1)	88 (82.2)	94 (87.9)
Religion				
Muslim	271 (83.6)	94 (85.5)	87 (81.3)	90 (84.1)
Christian	39 (12.0)	12 (10.9)	12 (11.2)	15 (14.0)
Agnostic	14 (4.3)	4 (3.6)	8 (7.5)	2 (1.9)
Completed education				
Less than high school	28 (8.6)	9 (8.2)	8 (7.5)	11 (10.3)
High school [a]	146 (45.1)	54 (49.1)	45 (42.1)	47 (43.9)
Vocational education	104 (32.1)	33 (30.0)	37 (34.6)	34 (31.8)
Some higher education [b]	46 (14.2)	14 (12.7)	17 (15.9)	15 (14.0)
Current professional status [c]				
Employee	137 (42.3)	41 (37.6)	52 (49.0)	44 (41.2)
Pensioner	70 (21.6)	15 (13.8)	25 (23.6)	30 (28.0)
Business owner	19 (5.9)	5 (4.6)	6 (5.7)	8 (7.5)
Student	15 (4.6)	11 (10.1)	2 (1.9)	2 (1.9)
Unemployed, able to work	61 (21.6)	29 (26.6)	14 (13.2)	18 (16.8)
Unemployed, disable	20 (6.2)	8 (7.3)	7 (6.8)	5 (4.7)
Monthly income, in USD, mean [SD]	179 [188]	157 [203]	194 [182]	187 [178]
Currently rent home	44 (13.6)	20 (18.2)	15 (14.0)	9 (8.4)
Marital status				
Single, never married	51 (15.7)	36 (32.7)	3 (2.8)	12 (11.2)
Married	234 (72.2)	63 (57.3)	87 (81.3)	84 (78.5)
Previously married [d]	39 (12.0)	11 (10.0)	17 (15.8)	11 (10.3)
Have children	261 (80.6)	70 (63.6)	98 (91.6)	93 (86.9)
Behavioral				
Ever incarcerated	12 (3.7)	3 (2.7)	3 (2.8)	6 (5.6)
Recently smoked tobacco [e]	100 (30.9)	41 (37.3)	26 (24.3)	33 (30.8)
Alcohol abuse [f]				
0-1	298 (92.0)	103 (93.6)	101 (94.4)	94 (87.9)
>2	26 (8.0)	7 (6.4)	6 (5.6)	13 (12.1)
Physical activity, days [g]				
0	75 (23.1)	34 (30.9)	26 (24.3)	15 (14.0)
1-3	41 (12.7)	20 (18.2)	9 (8.4)	12 (11.2)
4-7	208 (64.2)	56 (50.9)	72 (67.3)	80 (74.8)
Co-morbidity				
Diabetes diagnosis [h]	13 (4.0)	11 (10.0)	1 (0.9)	1 (0.9)
HCV diagnosis [h]	8 (2.5)	4 (3.6)	0 (0.0)	4 (3.7)
Recent HIV+ result [i]	2 (0.8)	2 (2.1)	0 (0.0)	0 (0.0)
Urinary tract or kidney disease diagnosis [h]	34 (10.5)	7 (6.4)	13 (12.1)	14 (13.1)

BMI; body mass index, HCV; hepatitis C virus, SD; standard deviation, USD; United States Dollar conversion of Kazakh tenge $1USD = 154 tenge, HIV; human immunodeficiency virus/[a] High school includes completed education through grade 11/[b] Started higher education, university or college/[c] Primary professional status for the past twelve months, total n for sample = 322; cases = 109, household controls = 106, community controls = 107/[d] Category includes divorced, separated, and widowed/[e] Past twelve months/[f] Based on the CAGE scale with a maximum score of 4/[g] Days within the past seven days/[h] Ever diagnosed with disease/[i] Result of most recent HIV test, total n for sample = 253; cases = 96, household controls = 75, community controls = 82

Bivariate results are summarized in Table 2. TB status has demonstrated significant associations with age, BMI, marital status, and diabetes mellitus co-morbidity while comparing TB cases with both household and community controls. Smoking in past twelve months and being unemployed has been positively associated with TB in the TB cases – household controls comparison. Living in a rented home has been found as an unadjusted risk factor in the TB cases – community controls comparison. Table 3 presents the final two multivariable models.

Table 2: Factors associated with TB case status in Almaty Region, Kazakhstan

Variable	TB cases vs household controls OR (95%CI)	*P* value	TB cases vs community controls OR (95%CI)	*P* value
Socio-demographic				
Age				
18-24 yr	7.91 (2.15-29.08)	0.002[e]	3.05 (1.03-9.02)	0.044[e]
25-34 yr	3.31 (1.07-10.26)	0.038[e]	1.86 (0.73-4.75)	0.196
35-44 yr	1.21 (0.39-3.77)	0.747	0.65 (0.23-1.86)	0.424
45-54 yr	1.05 (0.28-3.89)	0.940	1.01 (0.34-3.01)	0.991
>55 yr	Ref		Ref	
Sex				
Male	1.93 (1.21-3.07)	0.006[e]	1.47 (0.82-2.64)	0.192
Female	Ref		Ref	
BMI, kg/m^2	0.77 (0.69-0.86)	<0.001[e]	0.87 (0.81-0.93)	<0.001[e]
Birth country				
Born outside Kazakhstan	2.0 (0.60-6.64)	0.258	2.11 (0.96-4.67)	0.065
Born inside Kazakhstan	Ref		Ref	
Education				
Some higher education	0.75 (0.32-1.78)	0.514	0.90 (0.37-2.21)	0.819
Less than higher education	Ref		Ref	
Current employment status [a]				
Employed	0.58 (0.34-1.0)	0.050[e]	0.77 (0.45-1.32)	0.347
Unemployed	Ref		Ref	
Current housing status				
Rent home	2.33 (0.60-9.02)	0.220	2.37 (1.04-5.43)	0.040[e]
Own home	Ref		Ref	
Marital status				
Single, never married	4.57 (2.02-10.36)	<0.001[e]	2.44 (1.36-4.36)	<0.001[e]
Ever married	Ref		Ref	
Behavioral				
Incarceration				
Ever incarcerated	1.0 (0.2-4.95)	1.000	0.33 (0.07-1.65)	0.178
Never incarcerated	Ref		Ref	
Recent tobacco smoking [b]				
Smoked	1.82 (1.01-3.29)	0.047[e]	1.32 (0.73-2.39)	0.367
Did not smoke	Ref		Ref	
Alcohol abuse [c]				
Ever abused	1.0 (0.32-3.10)	1.000	0.30 (0.08-1.09)	0.067
Never abused	Ref		Ref	
Co-morbidity				
Diabetes diagnosis [d]				
Yes	11.0 (1.42-85.2)	0.022[e]	10.8 (1.38-85.2)	0.028[e]
No	Ref		Ref	
Urinary tract or kidney disease diagnosis [d]				
Yes	0.33 (0.11-1.03)	0.057	0.38 (0.14-1.08)	0.069
No	Ref		Ref	

TB; TB, OR; odds ratio, CI; confidence interval, HIV; human immunodeficiency virus
[a] Primary employment status within the past 12 months/[b] Past twelve months/[c] CAGE score ≥ 2/[d] Ever diagnosed with disease
[e] Statistically significant at a $p < 0.05$ level

Model 1 has incident TB cases compared to household controls; and model 2 has incident TB cases compared to community controls. We excluded BMI from the models as weight loss is considered both a symptom and potential risk factor for TB diagnosis (34). Model 1 (TB cases and household controls) results show that TB cases were more likely to be younger (adjusted odds ratio [aOR]=11.36, 95% confidence interval [CI]=1.67-77.49 for 18-24; aOR=7.41, 95%CI=1.29-42.52 for 25-34; aOR=1.99, 95%CI=0.35-11.47 for 35-44; aOR=1.5, 95%CI=0.23-9.6 for 45-54 yr old), smoked in past 12 months (aOR=3.27, 95%CI=1.10-9.68) and had diabetes (aOR=48.59, 95%CI=3.05-773.01).

Table 3: Multivariable factor associations with TB case status in Almaty Region, Kazakhstan

Variable	Model 1 AOR[a] (95%CI)	Model 1 *P* value	Model 2 AOR[a] (95%CI)	Model 2 *P* value
Age				
18-24 yr	11.36 (1.67-77.49)	0.013[f]	5.13 (1.01-26.18)	0.049[f]
25-34 yr	7.41 (1.29-42.52)	0.025[f]	2.77 (0.64-12.01)	0.172
35-44 yr	1.99 (0.35-11.47)	0.440	0.54 (0.1-2.89)	0.471
45-54 yr	1.5 (0.23-9.66)	0.672	2.39 (0.46-12.6)	0.303
>55 yr	Ref		Ref	
Sex				
Male	1.24 (0.54-2.84)	0.610	0.87 (0.3-2.49)	0.789
Female	Ref		Ref	
Birth country				
Born outside Kazakhstan	5.1 (0.72-35.98)	0.102	2.85 (0.9-9.0)	0.074
Born inside Kazakhstan	Ref		Ref	
Education				
Some higher education	1.08 (0.31-3.76)	0.898	0.92 (0.23-3.69)	0.909
Less than higher education	Ref		Ref	
Current employment status [b]				
Employed	0.75 (0.32-1.77)	0.514	0.75 (0.33-1.68)	0.480
Unemployed	Ref		Ref	
Current housing status				
Rent home	0.93 (0.14-6.15)	0.942	5.15 (1.39-19.05)	0.014[f]
Own home	Ref		Ref	
Marital status				
Single, never married	3.49 (0.99-12.23)	0.051	3.21 (1.28-8.05)	0.013[f]
Ever married	Ref		Ref	
Incarceration				
Ever incarcerated	0.63 (0.06-6.54)	0.697	0.66 (0.08-5.24)	0.693
Never incarcerated	Ref		Ref	
Recent tobacco smoking [c]				
Smoked	3.27 (1.1-9.68)	0.032[f]	4.07 (1.16-14.32)	0.029[f]
Did not smoke	Ref		Ref	
Alcohol abuse [d]				
Ever abused	0.66 (0.1-4.3)	0.668	0.16 (0.02-1.16)	0.069
Never abused	Ref		Ref	
Diabetes diagnosis [e]				
Yes	48.59 (3.05-773.01)	0.006[f]	23.43 (1.86-295.49)	0.015[f]
No	Ref		Ref	
Urinary tract or kidney disease diagnosis [e]				
Yes	1.39 (0.29-6.59)	0.676	0.29 (0.06-1.38)	0.120
No	Ref		Ref	

Model 1 compares TB cases to household controls; model 2 compares TB cases to community controls /TB; TB, AOR; adjusted odds ratio, CI; confidence interval, HIV; human immunodeficiency virus/ [a] Adjusted for all other covariates in model/ [b] Primarily employed within the past 12 months as compared to unemployed in the past 12 months /[c] Past twelve months/ [d] CAGE score ≥ 2 /[e] Ever diagnosed with disease /[f] Statistically significant at a $p < 0.05$ level

Model 2 (TB cases and community controls) found that TB is significantly associated with age (18-24 as compared to 55 plus, aOR=5.13, 95%CI=1.01-26.18), non-married family status (aOR=3.21, 95%CI=1.28-8.05), living in rented house or apartment (aOR=5.15, 95%CI=1.39-19.05), smoking in past 12 months (aOR=4.07, 95%CI=1.16-14.32), and having diabetes (OR=23.43, 95%CI=1.86-295.49). The first and second models correctly predict 84.4% and 82.2% respectively, of participants' TB status.

Discussion

Modifiable socio-behavioral risk factors and non-communicable co-morbid states are associated with incident TB case status. Consistent with current literature (35) our multivariable model showed strong positive associations with young age, single marital status, and living in a rented house or apartment. Comparing to household and community controls, incident TB cases are younger (less than 35 yr old), tend to be single and live separately in a rented house or apartment with roommates or friends. These factors are both reflective of demographics and socio-economic status (SES). We assessed living conditions as a proxy for income and SES as both concepts are relatively difficult to measure. In another study ownership of the house by the TB case's family was a constant predicator of the TB case's SES (35).

Smoking in the past 12 months was found as an independent risk factor for TB. We assessed smoking in the past 12 months as opposed to current smoking to avoid the effect of reduced smoking because of the TB disease status. Other studies have also confirmed the association of smoking as a risk factor for TB morbidity and have even gone further to show that it leads to a more severe progression of TB (15, 18) We found that a history of diabetes was a risk factor for TB in this population. This finding is consistent with reports from other studies linking type 2 diabetes mellitus with TB (26-28). Data shows that type 2 diabetes mellitus not only increases the risk of treatment failure and death among TB patients but also increases relapse (26). Past migration, as measured by country of birth, had a marginally significant association with TB in the case-community control comparison. Foreign-born individuals from high TB burden countries retain higher risks of disease as compared to their household and community controls born in the host country (13). This could be the result of an exogenous re-infection or endogenous reactivation of original latent infection (35). Because Kazakhstan is a country with high TB burden, immigration could also be linked with TB through deteriorating living conditions. To explore living conditions in this dataset we looked at BMI as a proxy for adequate nutrient consumption. BMI was significantly associated with TB in a bivariate analysis but excluded from the final multivariable model based on concerns around temporality in a cross-sectional study. Associations between BMI and TB have been shown in a few studies (34).

This study has a number of strengths. It explored and estimated multifaceted drivers of TB in the Kazakhstan's first population-based case-control study. The inclusion of all incident cases within the geographic region during the study period was another strength. Some limitations of our study include: data was cross-sectional, which precluded us from establishing temporality between factors and incident TB diagnosis; recall bias could play a role as the survey is based on self-report of key factors; and as baseline data for a larger longitudinal study, TB incident cases without stable living condition or an eligible household member without TB were excluded from the study, potentially missing the most vulnerable incident cases in the region. We have no reason to believe that these limitations would result in systematic error.

Effective interventions are needed to stem the TB epidemic and target high-risk populations. There are available interventions addressing social determinants and risk factors for TB globally. Innovative integrated community and household socioeconomic interventions include food and cash transfers, microcredit, microenterprise, vocational training, community mobilization, education, and psychosocial support (36). Such interventions provided in economically deprived areas of Kazakhstan can address the social and economic causes of vulnerability and could increase uptake of TB prevention and services. In Kazakhstan, interventions such as food and money transfers, transportation vouchers, hygienic packages, and accommodation have been made available for some TB patients. Legal and psychosocial support is currently provided. As an effort to address other risk factors, tobacco control interventions, screenings for TB among persons with diabetes and migrants are routinely implemented in Kazakhstan. However, availability and coverage of these services have been unequal and inadequate. The preventive therapy with isoniazid is offered only to children and HIV-positive individuals (1).

Conclusion

This case-control study, for the first time in Kazakhstan, confirmed roles of major risk factors for TB: young age, single marital status, living in rented apartment, smoking, diabetes and migration. These findings have important TB prevention and control implications for the NTP. In addition to medical technologies focused on stopping TB transmission, it is important to develop and strengthen existing interventions addressing social determinants and proximate risk factors for TB. Mapping key population groups with high risk of TB and offering preventive chemotherapy to selected groups at higher risk of converting from latent infection to active disease, including diabetes patients and migrants, can be included into the NTP. Health system strengthening and collaboration with other public health and social programs, such as tobacco and diabetes control as well as migration policies should be part of the national TB prevention and control strategies.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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