

Causes of death during tuberculosis treatment in Tomsk Oblast, Russia

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SUMMARY

SETTING: Tuberculosis (TB) incidence and mortality in Russia have risen dramatically over the past 15 years.

OBJECTIVE: To identify risk factors and causes of death among TB patients in Russia.

DESIGN: A retrospective study conducted to determine the risk factors and causes of death in patients receiving TB therapy in Tomsk, Siberia.

RESULTS: Of 1916 patients who initiated treatment between 1 January 2002 and 31 December 2003, 183 (9.6%) died during treatment, 38 (21%) in the first week of therapy. Twenty-five per cent of deaths were not di-

rectly attributable to TB. Risk factors for death included older age, previous treatment for TB, multidrug resistance and alcoholism.

CONCLUSIONS: The high death rate during TB treatment observed in this cohort likely reflects an increased risk of dying not only from TB, but also from comorbid conditions, such as alcoholism and cardiovascular disease. Overall, alcoholism and late presentation both contributed substantially to the mortality in this cohort.

KEY WORDS: tuberculosis; Russia; Tomsk, Siberia; mortality

TUBERCULOSIS (TB) incidence in the Russian Federation has risen over the past 15 years, from 34.2 per 100 000 population in 1991¹ to 115/100 000 in 2004.² Despite concerted national and regional efforts to improve TB services, TB mortality continues to rise,³ with estimates of 21 deaths per 100 000 population in 2004.² TB is now the leading infectious cause of death in Russia.⁴ TB mortality has been variously attributed to a dramatic rise in drug resistance,⁵ to an increase in substance use and homelessness,⁶⁻⁸ and to deteriorations in TB services.^{9,10} These factors reflect the socio-economic upheaval that occurred after the collapse of the Soviet Union,^{11,12} which has also contributed to a rise in mortality and a decline in life expectancy in the general Russian population during this period.¹³⁻¹⁵

In the present study, we sought to identify risk factors associated with dying during TB treatment and specific causes of death among patients receiving TB treatment in Tomsk Oblast, Russia.

METHODS

Setting and program description

The study was conducted in the Tomsk Oblast in western Siberia, where the incidence and mortality rates for

TB in 2003 were respectively 93.4 and 17.6/100 000.¹⁶ Rates of multidrug-resistant tuberculosis (MDR-TB) in Tomsk are among the highest reported worldwide; the proportion of MDR-TB among newly diagnosed patients rose from 6.5% in 1999¹⁷ to 13.1% by 2002.¹⁸ The Tomsk Oblast Tuberculosis Services (TOTBS) oversee the diagnosis and care of civilian adult TB patients in the oblast, using an approach based on World Health Organization (WHO) DOTS¹⁹ and DOTS-Plus guidelines.²⁰ Mandatory notification of cases and reporting of outcomes is required for all civilian TB patients in the oblast.

Study design

We conducted a retrospective record review to determine the proportion of TB patients who died during therapy, risk factors for dying and specific causes of death among TB patients in the Tomsk Oblast. We included patients in the study if they 1) were diagnosed with TB by the Central Physicians Committee using clinical, radiological and/or bacteriological criteria, and 2) initiated TB treatment between 1 January 2002 and 31 December 2003. We excluded those patients who were aged <18 years or were receiving care outside of the TOTBS. Human subject research approval was granted by the Institutional

Review Board of the Brigham and Women's Hospital in Boston, MA, USA.

We used the TOTBS registry to identify subjects and collect information on demographics, date of registration, treatment initiation date, sputum and culture data, drug susceptibility testing (DST) results, and date and status of treatment outcome. As this registry only characterized deaths as being due to TB or to other causes, we also reviewed three sources of data to determine specific causes of death; these included death certificates, autopsy reports and hospital medical charts.

We assigned primary and contributing causes of death based on WHO definitions (Table 1), and further categorized deaths into five mutually exclusive groups: TB-related, alcohol-related, cardiovascular, external causes and all other causes. We defined TB-related causes as death due to TB of any organ or side effects of anti-tuberculosis drugs. We classified the following conditions as alcohol-related: alcoholism, alcohol-related liver disease, cirrhosis, diseases of the pancreas, alcoholic hepatitis, steatosis, mental and behavior disorders due to alcohol use, unintentional alcohol poisoning, and unintentional ethanol substitute poisoning.²² Cardiovascular included only cardiovascular causes of death, such as acute myocardial infarction, congestive heart failure and conditions such as hypertension and arteriosclerosis. External causes of death included falls, hypothermia, fire-related deaths, unintentional drowning, suicide, homicide, injury of undetermined intent, and unintentional poisoning with a non-ethanol substitute. We classified conditions not listed in the above categories as 'other.'

A bilingual physician translated reports from Russian to English. Two physicians then coded primary causes and contributing causes, using death certificate data as the primary source and referring to autopsy and medical records when the diagnosis was unclear. A third physician resolved the 29 discrepancies that occurred; this accounted for 4.2% of all causes. In a second analysis, we re-categorized deaths into five groups so that we could compare cause-specific rates with those reported for all Russia.

Table 1 Definitions for causes of death and contributing conditions

Term	Data source
Primary cause of death: disease or condition directly leading to death. This does not include the mode of dying, such as heart failure or respiratory failure ²¹	Death certificate
Contributing condition: all other diseases or conditions believed to have unfavorably influenced the course of the morbid process and thus contributed to the fatal outcome but which were not related to the disease or condition directly causing death	Death certificate, autopsy reports, and medical chart

Data analysis

Proportions were compared using the χ^2 test or, for expected cell values of <5 , Fisher's exact test. Means and medians were compared by Student's *t*-test and the Wilcoxon rank-sum test, respectively. Kaplan-Meier survival analyses were used to estimate the time from the initiation of TB therapy to death. For patients who did not reach the end point of death, the data were censored at the end of TB therapy. The log-rank test was used to compare survival times between strata. The Cox proportional hazards model was used for multivariable analysis. Variables associated with mortality in previous studies or in our clinical experience were included in the initial model. We combined indicators of disease severity—presence of cavitory lesions, baseline smear-positive and/or culture-positive status—to create a single severity variable. As we considered that disease severity might be an intermediate in the causal pathway from risk factors to death, we compared models with and without the severity variable. Variables were removed from the model by a backward selection procedure if the value of alpha was >0.05 . Confounders causing $\geq 10\%$ change in another predictor were left in the model.

Cause-specific death rates were compared with those reported for Russia by indirect standardization. We calculated annualized death rates by cause in our cohort by dividing the number of deaths by person-years at risk calculated from the time of treatment initiation until death or end of treatment. The expected number of deaths in the study cohort was calculated by multiplying person-years at risk by the national death rates in 2000 for the same 5-year age and sex categories. Standardized mortality rates were calculated by dividing the observed number of deaths by the expected number. Exact 95% confidence intervals (CIs) and *P* values were calculated by using the Poisson distribution. Statistical analyses were performed using Statistical Analysis Software and STATA Software (SAS Institute, Cary, NC, USA).

RESULTS

Between 1 January 2002 and 31 December 2003, 1916 patients initiated TB treatment in the TOTBS. The baseline characteristics of these patients are shown in Table 2; 1656 (86.4%) were newly diagnosed and 260 (13.6%) had been treated previously for TB. The median age was 42 years (range 18–88) and 1326 (69.2%) were male. Seven patients (0.4%) were human immunodeficiency virus (HIV) positive and 550 (28.7%) were alcoholic. Of the 856 for whom baseline DST results were available, 152 (17.8%) had MDR-TB.

Patients were treated for a median of 241 days (range 0–912); 183 deaths occurred during treatment. Among those who died, the median time to death after the initiation of TB treatment was 49 days

Table 2 Cohort characteristics among TB patients in Tomsk, Russia ($n = 1916$)

Characteristics	Died of TB ($n = 38$) n (%)	Died of non-TB ($n = 45$) n (%)	Survived ($n = 1733$) n (%)	Total ($n = 1916$) n
Age by quartiles, years				
18–29	12 (2.52)	1 (0.21)	463 (97.27)	476
30–41	27 (5.71)	5 (1.06)	441 (93.23)	473
42–50	32 (6.46)	14 (2.83)	449 (90.71)	495
51–88	67 (14.19)	25 (5.30)	380 (80.51)	472
Sex				
Male	106 (7.99)	37 (2.79)	1183 (89.22)	1326
Female	32 (5.42)	8 (1.36)	550 (93.22)	590
TB history				
Newly diagnosed TB	90 (5.43)	37 (2.23)	1529 (92.33)	1656
Relapse starting retreatment	48 (18.46)	8 (3.08)	204 (78.46)	260
TB regimen*				
Category I	88 (6.01)	37 (2.53)	1340 (91.47)	1465
Category II+ or II–	41 (19.90)	5 (2.43)	160 (77.67)	206
Category III	0	0	3 (100.00)	3
Individual	9 (3.72)	3 (1.24)	230 (95.04)	242
Baseline smear status				
Smear-positive	109 (11.86)	34 (3.70)	776 (84.44)	919
Smear-negative	29 (2.91)	11 (1.10)	957 (95.99)	997
Baseline culture status				
Culture-positive	112 (8.38)	41 (3.07)	1184 (88.56)	1337
Culture-negative	26 (4.49)	4 (0.69)	549 (94.82)	579
Baseline cavity status				
Cavity present	127 (11.42)	32 (2.88)	953 (85.70)	1112
Cavity absent	11 (1.37)	13 (1.62)	780 (97.01)	804
Other characteristics				
Baseline MDR-TB [†]	22 (14.47)	5 (3.29)	125 (82.24)	152
Diabetes	6 (13.64)	2 (4.55)	36 (81.82)	44
Alcoholism	83 (15.09)	17 (3.09)	450 (81.82)	550
Narcotic use	1 (1.82)	0	54 (98.18)	55
HIV-positive	0	0	7 (100)	7
History of prior incarceration	7 (6.54)	3 (2.80)	97 (90.65)	107

* Category I: treatment for new TB case, smear-positive or extensive disease.

Category II+: regimen for patient with recurrent smear-positive TB.

Category II–: regimen for patient with recurrent smear-negative TB.

Category III: treatment for new TB patient, smear-negative and more limited disease than Category I.

Individual: treatment with second-line drugs or for extended treatment duration.

[†] Baseline MDR-TB: resistance to isoniazid and rifampin documented prior to treatment start date. Drug sensitivity results were available for 856 patients.

TB = tuberculosis; MDR-TB = multidrug-resistant tuberculosis; HIV = human immunodeficiency virus.

(range 0–667). Eight patients died on the day of starting therapy, 38 patients within one week, and 78 within 3 months; 138 (75.4%) reportedly died from TB, while 45 (24.6%) died from other causes.

More detailed information regarding causes of death was available for 174 patients. Death certificates were located for all patients. Of the 174 deaths, 130 (74.7%) were due to TB, 11 (6.3%) to cardiovascular disease, 6 (3.4%) to alcohol-related causes, and 4 (2.3%) to cancer. Among the deaths attributed to TB, only one was due to adverse effects of anti-tuberculosis drugs; all the remaining TB deaths were due to direct sequelae. No deaths were attributed to HIV. As shown in Table 3, the proportion of deaths directly attributable to TB was higher in the first 3 months of therapy than thereafter (84.1% vs. 61.2%, $P = 0.0006$). At least one contributing condition was reported in 87 of the 174 patients, with alcoholism and cardiovascular conditions being the most frequent

(32.2% and 28.7%, respectively). Table 4 compares the cause-specific death rates observed in this cohort with published mortality rates for all Russia in 2000;²³ death rates from vascular disease and 'other'

Table 3 Primary causes of death in early vs. late mortality groups in patients who died during TB treatment within 12 months ($n = 174$)

Cause of death	Early ($n = 107$) n (%)	Late ($n = 67$) n (%)	P value*
TB	90 (84.1)	41 (61.2)	0.0006
Non-TB			
Alcohol	2 (1.9)	4 (6.0)	0.15
External	1 (0.9)	4 (6.0)	0.053
Cardiovascular	7 (6.5)	4 (6.0)	0.88
Other medical conditions	7 (6.5)	14 (20.9)	0.008

* P value for each category calculated by comparing that category vs. other categories combined.

TB = tuberculosis.

Table 4 SMRs for Tomsk TB cohort for causes other than TB compared with those for the general population of the Russian Federation in 2000*

Cause of death	Observed deaths	Expected deaths	SMR	95%CI
Cancer	4	2.96	1.35	0.72–2.32
Vascular disease	4	2.29	1.75	1.45–2.09
External causes	5	6.58	0.76	0.47–1.14
Other	14	1.19	11.79	10.85–12.79

* From Peto et al.²³

SMR = standardized mortality ratio; TB = tuberculosis; CI = confidence interval.

causes were significantly higher in our cohort of TB patients compared to people in similar age and sex categories who were residing in Russia in the same period. Of note, the category 'other' included liver cirrhosis and alcohol poisoning, which accounted for five deaths in our cohort.

The factors present at the initiation of TB therapy that were predictors of death in univariate analysis included age, male sex, retreatment, smear positivity, culture positivity, cavitary disease, MDR-TB, diabetes and alcoholism. Prior incarceration, HIV positivity and narcotic use were not risk factors for death in this analysis. In the multivariate model, age, baseline MDR-TB, alcoholism and previous treatment for TB remained independent risk factors for death (Table 5). This finding did not change when we controlled for severity. The Figure shows the survival patterns for cohort members stratified by factors associated with death in the multivariable analysis.

DISCUSSION

In this study of TB patients in Tomsk Oblast, Russia, overall mortality during TB treatment was 9.6%, consistent with mortality rates previously reported from this area and from other Russian Oblasts.^{2,8,24} Risk factors for death were consistent with those reported in other TB cohorts and included older age,

MDR-TB, alcoholism and previous TB treatment.^{25–30} Despite the high death rate, 25% of these deaths were not directly due to TB, but resulted from cardiovascular disease, alcohol use and cancer. In other TB cohorts worldwide, the proportion of deaths caused directly by TB has ranged from 10.5% to 85.6%.^{27,30–35} Interestingly, death rates among those undergoing treatment for TB are often higher in industrialized than developing countries.² This trend may reflect the fact that, in low-incidence settings, TB is most common among highly vulnerable individuals, who are older, sick with other comorbidities, and/or marginalized from health services, as opposed to young, otherwise healthy individuals who develop TB in resource-poor settings due to high rates of ongoing transmission.

Although MDR-TB was associated with death in this study, the hazard ratio was less than those reported in other cohorts.^{25,26} As all patients in Tomsk undergo routine DST and receive individualized therapy based on drug resistance profiles, excess deaths among patients with MDR-TB are unlikely to be the consequence of delayed diagnosis of drug resistance or inadequate therapy, but rather reflect poorer outcomes for patients on second-line therapy.

The DOTS strategy endorsed by the WHO emphasizes the need for active surveillance and monitoring, including the reporting of treatment outcomes to a central registry. These treatment outcomes are then used to assess the efficacy of TB programs. In this study, we found that even when we adjusted for age and sex, death rates due to cardiovascular disease, alcoholism and cancer were significantly greater than the already high rates experienced in the general Russian population during the same period. These findings suggest that Russian patients with TB may have underlying vulnerabilities that put them at high risk for poor outcomes and may require more intensive interventions than are usually provided through traditional TB treatment programs. The finding that a substantial proportion of deaths among TB patients may be due to other causes also suggests that using deaths

Table 5 Factors associated with survival (*n* = 1916)

Cohort characteristics	Univariate HR (95%CI)	<i>P</i> value	Multivariable HR (95%CI)	<i>P</i> value
Age	1.05 (1.04–1.06)	<0.0001	1.05 (1.04–1.06)	<0.0001
Male	1.61 (1.13–2.28)	0.0080	1.24 (0.87–1.78)	0.23
TB retreatment	2.72 (1.98–3.74)	0.0027	1.77 (1.25–2.50)	0.0012
Smear-positive	3.88 (2.73–5.51)	<0.0001	NA	
Culture-positive	2.06 (1.39–3.05)	0.0003	NA	
Cavity present	4.79 (3.11–7.35)	<0.0001	NA	
Multidrug resistance	2.32 (1.44–3.75)	0.0006	2.01 (1.22–3.32)	0.0060
Prior incarceration	1.00 (0.53–1.89)	1.000	NI	
Diabetes	1.82 (0.89–3.70)	0.010	1.43 (0.69–2.96)	0.34
HIV-positive	1.00 (0.00–3.07)	0.97	NI	
Alcoholism	3.17 (2.37–4.25)	<0.0001	2.69 (2.0–3.62)	<0.0001
Narcotic use	0.17 (0.024–1.24)	0.081	NI	

HR = hazard ratio; CI = confidence interval; TB = tuberculosis; NA = not applicable; NI = not included (in multivariable model); HIV = human immunodeficiency virus.

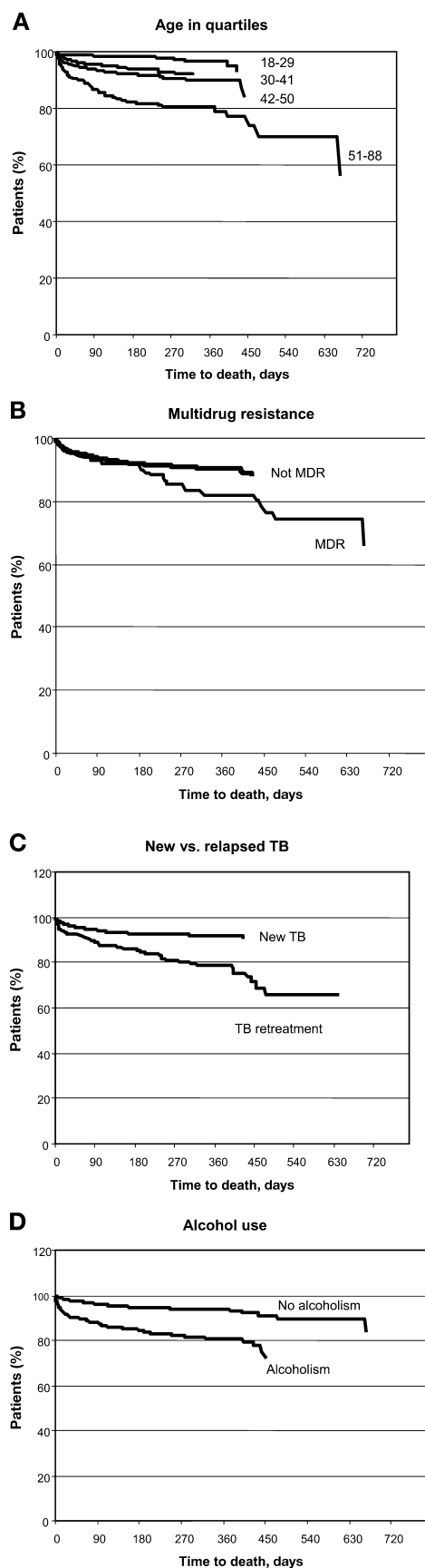


Figure Kaplan-Meier estimates of the proportion of TB patients surviving after the initiation of therapy. **A.** Age quartile. **B.** Drug resistance status. **C.** Retreatment status. **D.** Alcohol status. MDR = multidrug-resistant; TB = tuberculosis.

during TB treatment as an indicator of TB program performance may be misleading, as such deaths may not be preventable even with improvements in the TB services.

One limitation of this study is that we classified the causes of deaths based on death certificate data rather than autopsy reports, which are often considered the gold standard for cause of death data. However, because only 26% of our cohort had autopsy reports, the data collected from autopsies were neither complete nor necessarily representative of the causes of death among those who died. Furthermore, we chose to use death certificates as the primary data source because they represent information that is used to generate official mortality statistics in Russia.

Despite this limitation, we draw several conclusions from our results. First, patients who died from TB tended to do so early in the course of treatment, with 21% dying within the first week of therapy. Such patients are likely diagnosed and started on treatment late in the course of their disease. These data suggest that active surveillance and case finding could reduce mortality among TB patients by leading to earlier detection and treatment.

Second, alcoholism was not only associated with an increased risk of death but also contributed heavily, either directly or indirectly, to the mortality of this cohort. Given the high prevalence of alcohol disorders among TB patients in Russia and its contribution to poor outcome, establishing a systematic approach to screening and treating alcohol use disorders among TB patients may be a useful addition to routine TB care and lead to improved treatment outcomes.

Finally, in this cohort of Russian TB patients, the high death rate during treatment likely reflects an increased risk of poor outcome not only from TB but also from comorbid conditions, such as alcoholism and cardiovascular disease. Because TB disproportionately affects the marginalized and poor, it is likely that these same underlying socio-economic factors place them at increased risk for dying of other diseases.

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R É S U M É

CONTEXTE : L'incidence et la mortalité par tuberculose (TB) ont augmenté de façon dramatique en Russie au cours des 15 dernières années.

OBJECTIF : Identifier les facteurs de risque et les causes de décès chez les patients tuberculeux en Russie.

SCHÉMA : Nous avons mené une étude rétrospective pour déterminer les facteurs de risque et les causes de décès chez les patients sous traitement antituberculeux à Tomsk, en Sibérie.

RÉSULTATS : Sur les 1.916 patients qui avaient commencé leur traitement entre le 1^{er} janvier 2002 et le 31 décembre 2003, 183 (9,6%) sont décédés pendant le traitement. Parmi ceux-ci, 38 (21%) sont décédés pendant la première semaine de traitement. Le décès n'a pas été directement attribuable à la TB dans 25% des cas. Les facteurs de risque de décès ont comporté un âge avancé, un traitement antérieur pour la TB, une multirésistance ainsi que l'alcoolisme.

CONCLUSIONS : Le taux élevé de décès observé dans cette cohorte au cours du traitement de la TB reflète probablement un risque accru de décès, non seulement par TB mais aussi par des affections associées comme

l'alcoolisme et les maladies cardiovasculaires. Au total, l'alcoolisme et un recours tardif aux soins ont contribué tous deux de manière substantielle à la mortalité dans cette cohorte.

RESUMEN

MARCO DE REFERENCIA : La incidencia y la mortalidad por tuberculosis (TB) han aumentado en forma alarmante en la Federación de Rusia durante los últimos 15 años.

OBJETIVO : Determinar los factores de riesgo y las causas de muerte en los pacientes con TB en la Federación de Rusia.

DISEÑO : Se llevó a cabo un estudio retrospectivo a fin de determinar los factores de riesgo y las causas de muerte de pacientes en curso de tratamiento antituberculoso en Tomsk, Siberia.

RESULTADOS : De los 1926 pacientes que iniciaron tratamiento entre el 1º enero de 2002 y el 31 de diciembre de 2003, 183 (9,6%) fallecieron durante el tratamiento. De

estos, 38 (21%) murieron durante la primera semana de tratamiento. El 25% de las defunciones fue atribuible directamente a la TB. Entre los factores de riesgo de muerte se encontraron : edad avanzada, antecedente de tratamiento antituberculoso, multidrogorresistencia y alcoholismo.

CONCLUSIÓN : La alta tasa de mortalidad durante el tratamiento antituberculoso observada en esta cohorte traduce probablemente un aumento del riesgo de muerte, no solo por TB, sino también por trastornos concomitantes como el alcoholismo y la enfermedad cardiovascular. Globalmente, el alcoholismo y la consulta tardía contribuyeron en forma considerable a la mortalidad en la población del estudio.
