Sex differences in risk factors for unsuccessful tuberculosis treatment outcomes in Eastern Europe from 2020 to 2022: a multi-country retrospective cohort study

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Summary

Background Addressing the disproportionate representation between sexes is essential for achieving universal health coverage. Studies on the association between sex and unsuccessful tuberculosis treatment outcomes have shown conflicting results. This study examines this association and analyses sex-stratified risk factors associated with unsuccessful outcomes.

Methods This retrospective, observational cohort study analysed prospectively collected data from six Eastern European countries from 2020 to 2022. Treatment outcomes were defined using World Health Organization criteria. Uni- and multivariable logistic regression models were used to assess the association between sex and unsuccessful outcomes ('treatment failure', 'lost to follow-up', 'died', or any of these). After propensity score matching females and males, the multivariable analysis was repeated. Risk factors were analysed separately for each sex and compared using interaction terms.

Findings Among females, 19·5% (n = 290/1490) (95% confidence interval [CI]: 18, 22) achieved an unsuccessful treatment outcome, compared with 30% (n = 1363/4553) (95% CI: 29, 31) among males. In the multivariable analyses, female sex was associated with 32% lower odds of any unsuccessful outcome (adjusted odds ratio [aOR] 0·68,

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95% CI: 0·58, 0·80), 36% lower odds of dying (aOR 0·64, 95% CI: 0·51, 0·80), and 37% lower odds of treatment failure (aOR 0·63, 95% CI: 0·47, 0·85). The association between sex and being 'lost to follow-up' was not significant. In the propensity score-matched cohort, sex was not associated with unsuccessful outcomes. Risk factors for unsuccessful outcomes were similar for females and males, except that in females aged >65 years, the odds of death were 2·2 times higher (95% CI: 1·1, 4·4).

Interpretation Male sex was associated with unsuccessful outcomes, including death and treatment failure, but adjusting for socio-demographic and clinical factors, and matching males to females, attenuated the association, suggesting that sex disparities in tuberculosis outcomes may be driven more by behavioural than biological factors. Longitudinal studies are needed to confirm these findings.

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Keywords: Tuberculosis; Treatment outcome; Sex; Healthcare; Socioeconomic factors; Gender and health

Research in context

Evidence before this study

A PubMed search on March 26, 2024, using keywords related to tuberculosis, sex, treatment outcomes, and risk factors, yielded 1887 results. After screening of titles and abstracts, 1464 studies were excluded as irrelevant, and 98 were excluded for not reporting relevant association measures or outcomes. Among the remaining 325 studies, 229 included sex as a variable and reported World Health Organization (WHO)-defined outcomes. Of these, 49% (n = 113/229) examined risk factors for the composite outcome of 'treatment failure', 'lost to follow-up', or 'died'. Nearly half (46%, n = 52/113) found male sex associated with unsuccessful outcomes, 5% (n = 6/113) found an association with female sex, and 49% (n = 55/113) found no significant association. Fourteen per cent (n = 32/229) of the studies examined sex as a risk factor for being 'lost to follow-up'; 75% (n = 24/32) found an association with male sex, 3% (1/32) with female sex, and 22% (n = 7/32) found no association. Eleven per cent (n = 25/229) examined sex as a risk factor for 'treatment failure'; with 44% (n = 11/25) finding an association with male sex and 56% (n = 14/25) finding no association with sex. Finally, 34% (n = 78/229) examined sex as a risk factor for 'died'; 35% (n = 27/78) found male sex to be significantly associated with mortality, 1% (n = 1/78) found female sex to be significantly associated, and 64% (n = 50/78) found no association. Only six studies reported risk factors for unsuccessful outcomes stratified by sex; however, none examined all three unsuccessful outcomes.

Added value of this study

This study examined risk factors for all three WHO-defined unsuccessful treatment outcomes for males and females combined and stratified by sex. Risk factors were generally similar between the sexes. However, our findings indicate that sex significantly modulates the association between being older than 65 years at diagnosis and the odds of death. Additionally, matching females and males on socio-demographic and clinical characteristics resulted in statistically insignificant associations between sex and unsuccessful outcomes.

Implications of all the available evidence

Matching females and males weakens the association between sex and unsuccessful outcomes, suggesting that sex disparities in tuberculosis outcomes may be driven more by behavioural than biological factors. Although risk factors are similar between the sexes, being older than 65 years at diagnosis seems to be a stronger predictor of unsuccessful outcomes in females than males. Longitudinal studies are needed to confirm these findings.

Introduction

Addressing disproportionate representation between sexes is essential for achieving universal health coverage, a key component of the World Health Organization's (WHO) Sustainable Development Goal 3.[1] This is especially important in tuberculosis epidemiology, where considerable sex disparities exist. Of the estimated 10·8 million individuals with tuberculosis in 2022, 55% were men, 33% were women, and approximately 12% were children.[2] Recent WHO data from 2021, focussing on 26 tuberculosis high-burden countries and reporting sex-stratified treatment outcomes, found slightly lower treatment success rates among males compared to females (88% vs 90%).[3] It

is well-known that males are much more likely than females to possess risk factors for tuberculosis and to be diagnosed with the disease.[4] Hence, implementing a sex-responsive approach to tuberculosis care is critical to both public health control and clinical management.

While numerous studies have examined risk factors for unsuccessful treatment outcomes, including sex, the observed association remains inconsistent. Most studies report that male sex is associated with unsuccessful outcomes[5,6] or find no association,[7,8] while some have found that female sex is associated with unsuccessful outcomes.[9,10] Additionally, unsuccessful treatment outcomes are typically evaluated as a composite measure, grouping 'failure', 'lost to follow-up' and 'died' together. However, these outcomes differ inherently, and the same risk factors may not necessarily apply to each. Lastly, risk factor analyses are rarely stratified by sex.

In summary, there is limited evidence on the different roles that risk factors play for females and males, as well as how sex may interact with these factors in influencing unsuccessful outcomes. In this study, we aimed to examine the overall association between sex and each unsuccessful treatment outcome ('failure', 'lost to follow-up', and 'died') in tuberculosis patients across six Eastern European countries. Secondly, we aimed to describe sex-stratified risk factors for these outcomes and to assess how sex may modulate their associations.

Methods

Study design, data collection, and participant eligibility

This study was an observational, retrospective cohort study of prospectively collected data from tuberculosis dispensaries in Georgia, Kazakhstan, Kyrgyzstan, Republic of Moldova, Romania, and Ukraine from January 2020 to December 2022. Data were stored in and extracted from the National Institute of Allergy and Infectious Diseases tuberculosis Portal (NIAID TB Portal), a multinational database containing comprehensive information on demographics, comorbidities, diagnostics, treatment, and treatment outcomes of bacteriologically confirmed tuberculosis patients.[11–14] The study included patients of all ages with bacteriologically confirmed tuberculosis and available treatment outcomes. Patients with unreported treatment outcomes were excluded. Only the first enrolment was included in cases where patients were registered more than once.

The study was reported following the guidelines provided by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Table 1 in Supplementary Material).[15]

Study setting

In 2021, the total number of new patients with tuberculosis ranged from 2100 in Georgia to 42,000 in Ukraine, whereas incidence rates ranged from 55 patients per 100,000 citizens in Romania to 112 in Ukraine.[2] Of the six countries, Kazakhstan, Kyrgyzstan, and Ukraine are included on the WHO's list of high tuberculosis burden countries due to high prevalences of HIV-associated tuberculosis and multidrug/rifampicin-resistant tuberculosis.[3] All study sites were included at various dates in early 2020 and 2021, and continued participation throughout the subsequent year. Based on the numbers reported in the 2024 WHO Global TB Report, roughly 156,000 incident tuberculosis cases were estimated across the six participating countries during the 2020–2021 period.[2] Thus, patients in the NIAID TB Portal represent only a subset of the total TB burden, with inclusion dependent on clinicians, patient participation, and local capacity.

Variables

The outcomes of interest were WHO-recommended mutually exclusive treatment outcomes (Table 2 in Supplementary Material).[16] An 'unsuccessful outcome' was defined as the composite of 'treatment failure', 'lost to follow-up', and 'died', while a 'successful outcome' comprised 'cure' and 'treatment completed'. Importantly, 'lost to follow-up' referred to patients whose treatments were interrupted for two consecutive months or more, not those who emigrated or transferred out; such cases were classified as not evaluated and excluded from the analyses. Biological sex was the main exposure variable, categorised as either male or female. Sex was also considered an effect modifier in the associations between other covariables and treatment outcomes.

The NIAID TB Portal database reports various socio-demographic and clinical covariables.[17] In line with a previous study, covariables utilised in this study included socio-demographic and clinical characteristics that are often associated with unsuccessful treatment outcomes (Table 1).[11] For regression analyses, all covariables were included as categorical variables, expressing the presence or absence of each characteristic.

Statistical methods

Socio-demographic and clinical characteristics were stratified by sex and presented as medians with interquartile ranges for continuous variables and as absolute numbers and proportions for categorical variables. Group comparisons were performed using Wilcoxon rank-sum test, Pearson's Chi-squared test, or Fisher's exact test, as applicable. False discovery rate corrections were applied to account for multiple testing. The number of patients with each successful and unsuccessful outcome was expressed in absolute and relative

Characteristics	Male (n = 4553, 75%)	Female (n = 1490, 25%)	p-value[a]	q-value[b]
Age at tuberculosis diagnosis in years, median (IQR)	45 (36, 53)	43 (30, 54)	<0·001	<0·001
Body mass index (kg/m^2), median (IQR)	20·2 (18·1, 22·0)	19·9 (17·6, 22·2)	0·009	0·012
Patient country, n (%)			<0·001	<0·001
Georgia	1046 (23)	401 (27)		
Kazakhstan	332 (7·3)	214 (14)		
Kyrgyzstan	22 (0·5)	16 (1·1)		
Moldova	148 (3·3)	36 (2·4)		
Romania	107 (2·4)	40 (2·7)		
Ukraine	2898 (64)	783 (53)		
Educational level, n (%)			<0·001	<0·001
College and higher education	772/3238 (24)	336/1011 (33)		
No education, basic or complete school	2466/3238 (76)	675/1011 (67)		
Employment group, n (%)			<0·001	<0·001
Employed, student, or homemaker	774/4495 (17)	342/1477 (23)		
Unemployed, disabled, or retired	3721/4495 (83)	1135/1477 (77)		
Social risk factors, n (%)				
A history of tuberculosis	1383/4550 (30)	299/1416 (20)	<0·001	<0·001
Alcohol misuse	1313/4350 (30)	180/1416 (13)	<0·001	<0·001
Drug abuse	293/4350 (6·7)	46/1416 (3·2)	<0·001	<0·001
Homelessness	143/4350 (3·3)	16/1416 (1·1)	<0·001	<0·001
Tobacco use[c]	2554/4350 (59)	393/1416 (28)	<0·001	<0·001
Previous incarceration	443/4350 (10)	8/1416 (0·6)	<0·001	<0·001
Comorbidities, n (%)				
Anaemia	627/4244 (15)	233/1401 (17)	0·093	0·11
Chronic hepatitis[d]	438/4244 (10)	84/1401 (6·0)	<0·001	<0·001
Diabetes mellitus	185/4244 (4·4)	91/1401 (6·5)	0·001	0·002
Living with HIV	543/4244 (13)	193/1401 (14)	0·3	0·4
Immunosuppression[e]	16/4244 (0·4)	5/1401 (0·4)	>0·9	>0·9
Psychiatric illness[f]	125/4244 (2·9)	19/1401 (1·4)	0·001	0·002
Renal insufficiency	44/4244 (1·0)	20/1401 (1·4)	0·2	0·3
Biochemical parameters, n (%)				
Elevated ESR[g]	1626/2536 (64)	360/708 (51)	<0·001	<0·001
Low total protein[h]	393/2804 (14)	124/780 (16)	0·2	0·2
Disease manifestation				
Pulmonary tuberculosis	4336 (95)	1374 (92)	<0·001	<0·001
Drug resistance pattern			<0·001	<0·001
Drug susceptible	1421 (31)	540 (36)		
MDR-tuberculosis	1307 (29)	375 (25)		
Pre-XDR-tuberculosis	835 (18)	229 (15)		
XDR-tuberculosis	463 (10)	136 (9·1)		
Other types of resistance[i]	527 (12)	210 (14)		
Multiple cavities	583/4281 (14)	139/1368 (10)	<0·001	0·001
Smear microscopy			<0·001	<0·001
Negative	1360/4544 (30)	570/1487 (38)		
Positive	3184/4544 (70)	917/1487 (62)		

Abbreviations: IQR, interquartile range; HIV, human immunodeficiency virus; ESR, erythrocyte sedimentation rate; MDR-tuberculosis, multidrug-resistant tuberculosis; pre-XDR-tuberculosis, pre-extensively drug-resistant tuberculosis; XDR-tuberculosis, extensively drug-resistant tuberculosis. [a]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. [b]False discovery rate correction for multiple testing. [c]Tobacco use was reported as ever having used tobacco. [d]Defined as a positive hepatitis B surface antigen test and/or a positive hepatitis C antibody test. [e]Includes patients treated with cytostatics, TNF-alpha inhibitors, and/or corticosteroids. [f]Most commonly included schizophrenia, anxiety, depression, and bipolar disorder, as diagnosed by psychiatrists at the study sites using ICD-10 diagnostic criteria. [g]Elevated erythrocyte sedimentation rates were defined as above 20 mm for females aged 0–50 years, above 30 mm for females aged 50 years or older, above 15 mm for males aged 0–50 years, and above 20 mm for males older than 50 years. [h]Low protein levels were defined as total serum protein below 62 g/L in adults and below 57 g/L for children and adolescents. [i]These included isoniazid mono resistance, rifampicin mono resistance, other types of mono resistance, and resistance to more than one non-first-line drug.

Table 1: **Sociodemographic and clinical characteristics of tuberculosis patients stratified by sex.**

numbers for the whole cohort, stratified by sex, and compared by calculating percentage point differences.

In our primary analysis, we examined the overall association between sex and unsuccessful outcomes, both individually and combined, using univariable and multivariable logistic regression models. The dependent variable was a binary outcome, with the composite successful outcome ('treatment completed' or 'cure') as the reference category and unsuccessful outcomes ('failure', 'lost to follow-up', 'death', or any of these) as the alternative. Covariables used for adjustment were selected a priori based on previously identified predictors of unsuccessful outcomes.[11] These included age, BMI, employment level, alcohol misuse, previous incarceration, living with HIV, low total protein, multiple cavities, history of tuberculosis, and drug resistance patterns. Results from univariable and multivariable regression models were presented as crude and adjusted odds ratios (cOR and aOR), respectively.

To account for missing data, we applied multiple imputations by chained equations (MICE) with 100 imputations and 10 iterations (R package *mice* v. 3·16·0).[18,19] Logistic regression was used to impute categorical variables, and predictive mean matching to impute continuous variables. The set of covariables included in the MICE models closely mirrored those used in the analytical models, with the addition of the outcome variable and a few auxiliary variables to improve the imputation process. A full list of covariables used in the imputation models is provided in Table 3 in Supplementary Material. Percentages of missing data and pairwise correlations were calculated for each imputed variable (Figures 2 and 3 in Supplementary Material). Convergence of the MICE algorithm was evaluated by visualising the means and standard deviations of each variable across iterations (Figures 4A–D in Supplementary Material).[20] Estimates from the imputed datasets were pooled using Rubin's rule and compared to complete-case analyses.[21]

We also conducted a propensity score analysis using optimal full matching (R package *MatchThem* v. 1·2·1) to estimate the causal effect of sex on treatment outcome, matching males to females based on several socio-demographic and clinical characteristics (Table 1).[22,23] Matching was performed after MICE, following the framework recommended by Pishgar et al.[24] All variables in Table 1 were considered clinically relevant and important to balance. Balance of the matched cohorts was visualised by plotting the standardised mean differences for the matched variables across all imputations, along with those in the unmatched population (Figures 1A–D in Supplementary Material). To guide the selection of a parsimonious set of covariables for the propensity score model, we used p-values to objectively prioritise variables showing the greatest imbalance between sexes. Optimal full matching involved computing subclass-specific weights to estimate a weighted effect of sex on treatment outcome.[23] While this approach retains all individuals in the matched population, the use of weights means that some individuals contribute less to the analysis, which may reduce the effective sample size (Table 4 in Supplementary Material).

In our secondary analysis, we examined sex-stratified risk factors for unsuccessful outcomes. As in the primary analysis, covariables used in the multivariable models were selected a priori as previously identified significant predictors of unsuccessful outcomes.[11] Models were fitted for males and females separately using the composite successful outcome ('treatment completed' or 'cure') as the reference category, and each of the unsuccessful outcomes ('failure', 'lost to follow-up', 'death', or any of these) as the alternative category, adjusting for covariables. Regression coefficients for the association between each variable and unsuccessful outcomes were presented separately as aORs for males and females. Finally, interaction terms between sex and each covariable were included in a pooled model to examine whether the strength of associations differed by sex. Interaction estimates >1 indicated a stronger association in females; estimates <1 indicated a stronger association in males.

Bias and sample size calculations

To mitigate potential bias due to sex imbalance and missing data, we used multiple imputation and propensity score matching as described above. As this was a retrospective study using all available data, no formal sample size calculation was performed.

Ethics approval

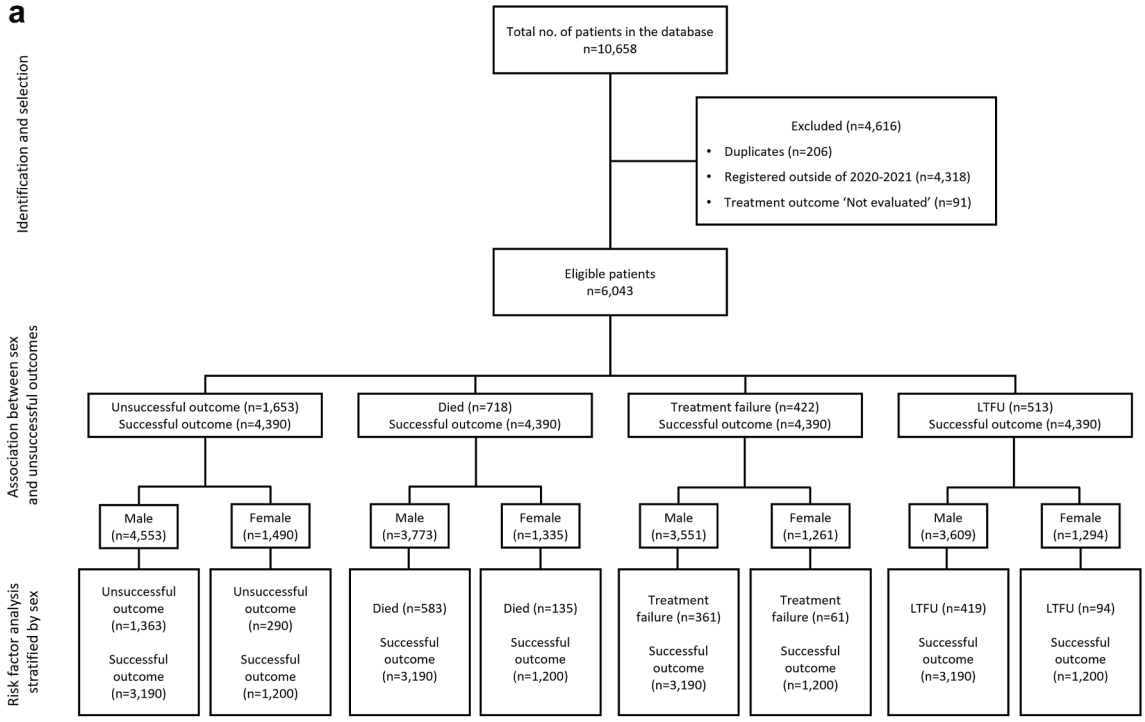
Ethical approvals for this study were obtained from the relevant national or institutional ethics committees in all participating countries: Ukraine (Protocol #1, February 5, 2020), Romania (Protocol #1346, February 6, 2015), Georgia (Protocol #796/01–14, March 9, 2015), Kazakhstan (Protocol #5723-1-12247/16-9, December 7, 2017), Moldova (Protocol #2, February 2, 2024), and Kyrgyzstan (Protocol #6, December 21, 2018).

Role of the funding source

The funder for the publication fee had no role in study design, data collection, data analysis, interpretation, or writing of the report.

Results

A total of 6134 patients were identified, of whom 91 (1·5%) were excluded due to missing outcomes, resulting in a cohort of 6043 patients (Fig. 1a). The overall proportion of unsuccessful outcomes across all six countries was 27% (n = 1653/6043, 95% confidence interval [CI]: 26, 28) (Fig. 1b). For females, the overall



b Summary

Outcome, n (%)	Total (n=6,043, 100%)	Female (n=1,490, 25%)	Male (n=4,553, 75%)	Percentage point difference (95%CI)[1]
Successful	4,390 (72·6)	1,200 (80·5)	3,190 (70·1)	10·4 (8·0, 13·0)
Treatment completed	1,061 (17·6)	331 (22·2)	730 (16·0)	6·2 (3·8, 8·6)
Cured	3,329 (55)	869 (58·3)	2,460 (54·0)	4·3 (1·4, 7·2)
Unsuccessful	1,653 (27·4)	290 (19·5)	1,363 (29·9)	-10·4 (-13·0, -8·0)
Treatment failure	422 (7·0)	61 (4·1)	361 (7·9)	-3·8 (-5·2, -2·5)
Lost to follow-up	513 (8·5)	94 (6·3)	419 (9·2)	-2·9 (-4·4, -1·4)
Died	718 (12)	135 (9·1)	583 (13)	-3·7 (-5·5, -1·9)

Abbreviations: CI, confidence interval.
[1]Two sample test for equality of proportions.

Fig. 1: Flowchart of patient inclusion (panel a) and summary of treatment outcomes by sex with percentage point differences (panel b).

proportion was 19·5% (95% CI: 18, 22), while for males it was 30% (95% CI: 29, 31), with notable country-specific variations (Figure 5 in Supplementary Material). Ukraine contributed the largest number of patients (n = 3681, 61%), while Kyrgyzstan contributed the fewest (n = 38, 0·6%) (Table 1). Most patients were male (n = 4553, 75%), and several baseline characteristics differed between female and male patients.

In the primary analysis that examined the overall association between sex and unsuccessful outcomes, female sex was associated with 32% lower odds of any unsuccessful outcome, adjusting for covariables (adjusted odds ratio [aOR] 0·68, 95% CI: 0·58, 0·80), 36% lower odds of dying (aOR 0·64, 95% CI: 0·51, 0·80), and 37% lower odds of treatment failure (aOR 0·63, 95% CI: 0·47, 0·85) (Fig. 2). The association between sex and being 'lost to follow-up' was not statistically significant in the multivariable model. In the propensity score-matched population, none of the associations remained statistically significant. Regression coefficients were comparable across the adjusted analysis with complete cases, multiple imputations, and multiple imputations with propensity score matching (Tables 5A–D in Supplementary Material). Regardless of sex, the strongest predictor of unsuccessful treatment outcomes was extensively drug-resistant tuberculosis (XDR-tuberculosis) (aOR 2·74, 95% CI: 2·18, 3·46); for death, it was pre-XDR-tuberculosis (aOR 4·57, 95% CI: 3·34, 6·21); for treatment failure, it was alcohol misuse (aOR 2·73, 95% CI: 2·16, 3.45); and for loss to follow-up, it was XDR-tuberculosis (aOR 4·07, 95% CI: 2·86, 5·79). Several other variables were also significant predictors of unsuccessful treatment outcomes (Tables 5A–D in Supplementary Material).

In the secondary analysis that examined sex-stratified risk factors for unsuccessful outcomes, several risk factors were identified for females and males (Figure 6 in Supplementary Material). For females, the strongest risk factors for the composite unsuccessful outcome were XDR-tuberculosis (aOR 3·4, 95% CI: 2·0, 5·8) and low total protein (aOR 2·9, 95% CI: 1·9, 4·5). For males, the strongest risk factors were

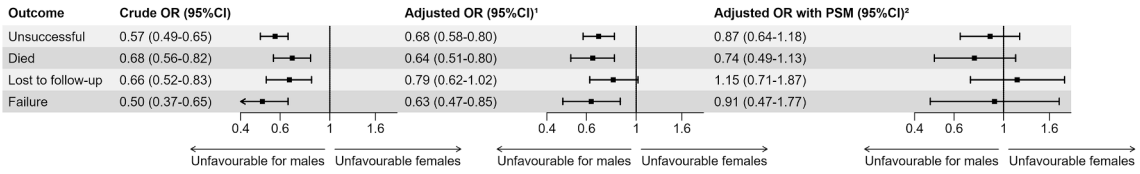


Fig. 2: Association between sex and unsuccessful treatment outcomes with male sex as the reference category: Crude, adjusted, and propensity score-matched odds ratios. Abbreviations: OR, odds ratio; CI, confidence interval; PSM, propensity score matching. [1]Based on multivariable logistic regression adjusted for a priori selected variables: age, body mass index, employment group, alcohol misuse, previous incarceration, HIV status, total protein level, having multiple cavities, history of tuberculosis, and tuberculosis resistance pattern. [2]Females patients were matched with male patients using optimal full matching based on variables that differed significantly between males and females: body mass index, tuberculosis resistance pattern, age, diagnosis year, patient country, employment group, educational level, smear positivity, history of tuberculosis, tuberculosis disease manifestation, chronic hepatitis, diabetes mellitus, psychiatric illness, erythrocyte sedimentation rate, smoking status, alcohol misuse, drug abuse, homelessness, previous incarceration. Following propensity score matching, the multivariable regression was adjusted for the same a priori selected variables as mentioned above.

XDR-tuberculosis (aOR 2·6, 95% CI: 2·0, 3·4) and alcohol misuse (aOR 2·4, 95% CI: 2·1, 2·8). For 'treatment failure', the strongest risk factors were a history of tuberculosis (aOR 2·6, 95% CI: 2·0, 3·3 and aOR 2·5, 95% CI: 1·3, 4·6) and alcohol misuse (aOR 2·6, 95% CI: 2·0, 3·4 and aOR 3·4, 95% CI: 1·7, 6·9) for both sexes. For 'lost to follow-up', the strongest risk factors for both females and males were XDR-tuberculosis (aOR 3·5, 95% CI: 2·3, 5·2 and aOR 6·1, 95% CI: 3·0, 12·7) and pre-XDR-tuberculosis (aOR 3·0, 95% CI: 2·1, 4·3 and aOR 2·6, 95% CI: 1·2, 5·4). For the outcome 'died', the strongest risk factors for females were age >65 years at diagnosis (aOR 6.0, 95% CI: 3·3, 10·9) and pre-XDR-tuberculosis (aOR 7·1, 95% CI: 3·5, 14·5), while for males, the strongest risk factors were XDR-tuberculosis (aOR 4·4 95% CI: 2·9, 6·5) and pre-XDR-tuberculosis (aOR 4·2, 95% CI: 3·0, 5·9). Regression coefficients were similar for complete case and for all cases with multiple imputations (Tables 6A–H in Supplementary Material).

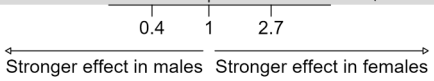
The association between higher age and 'died' was significantly modulated by sex (Fig. 3). The odds of dying when aged >65 years at diagnosis were 2·2 times higher for females compared with males (95% CI: 1·1, 4·4). For the association between multiple cavities and 'died', sex appeared to modulate the effect, with females having 1·8 times higher odds of dying compared to males when cavities were present (95% CI: 1·0, 3·3), although the interaction was not statistically significant. The interaction terms between sex and the remaining analysed risk factors were not statistically significant. The main effects are available in Tables 7A–E in Supplementary Material.

Discussion

In this retrospective analysis of prospectively collected data from 6043 tuberculosis patients from across Georgia, Kazakhstan, Kyrgyzstan, Moldova, Romania, and Ukraine in 2020–2022, we examined risk factors for unsuccessful treatment outcomes (both combined and individually) stratified by sex. Overall, the proportion of unsuccessful outcomes was significantly lower among female patients (19·5%) than male patients (30%). In unadjusted analyses, female sex was associated with lower odds of all types of unsuccessful treatment outcomes. However, after adjusting for socio-demographic and clinical characteristics, the association between sex and the likelihood of being 'lost to follow-up' was no longer statistically significant. In the propensity score-matched cohort, female sex was not associated with any unsuccessful outcome. Risk factors for unsuccessful outcomes were similar across both sexes, except for patients aged >65 years at diagnosis, where the odds of death were twice as high for female patients compared with male patients.

The lower overall proportions of unsuccessful outcomes among female patients in our cohort align with the existing literature that reports worse outcomes for male tuberculosis patients. Two main hypotheses have been proposed to explain these sex differences. The first hypothesis suggests that biological factors, such as sex hormones and genetic differences, may increase male susceptibility to tuberculosis. The second hypothesis attributes the discrepancy to non-biological factors influenced by sex, including smoking, occupational exposure, and health-care-seeking behaviours.[25] Our findings support the second hypothesis, as socio-demographic risk factors, such as low educational level, unemployment, tobacco usage, substance abuse, homelessness, and previous incarceration, were more prevalent among male patients. These patient-related factors could contribute to health disparities and differences in healthcare-seeking behaviour. Moreover, our multivariable regression analyses, both with and without propensity score matching, revealed that the association between sex and unsuccessful outcomes weakened after adjusting for these potential confounders. This suggests that the higher rate of unsuccessful outcomes among male patients in our cohort is likely due to indirect effects rather than a direct influence of sex on treatment outcomes. A recent mediation

Risk factor	Outcome	Female vs. Male aOR (95%CI)	P-value for interaction
Age > 65 years	Unsuccessful	1.4 (0.8-2.3)	0.23
	Died	2.2 (1.1-4.4)	0.03
	LTFU	0.4 (0.2-1.2)	0.09
	Failure	1.8 (0.7-4.8)	0.21
Alcohol misuse	Unsuccessful	1.1 (0.7-1.6)	0.73
	Died	1.0 (0.6-1.7)	0.97
	LTFU	1.2 (0.6-2.2)	0.59
	Failure	1.3 (0.6-2.7)	0.48
A history of TB	Unsuccessful	1.0 (0.7-1.4)	0.98
	Died	0.9 (0.5-1.6)	0.73
	LTFU	1.4 (0.8-2.4)	0.28
	Failure	0.9 (0.5-1.8)	0.80
BMI < 18.5 kg/m2	Unsuccessful	1.0 (0.7-1.5)	0.81
	Died	1.0 (0.6-1.7)	0.89
	LTFU	1.0 (0.5-1.7)	0.87
	Failure	1.5 (0.8-2.9)	0.21
Living with HIV	Unsuccessful	1.2 (0.8-1.8)	0.43
	Died	1.2 (0.7-2.2)	0.47
	LTFU	0.8 (0.4-1.6)	0.57
	Failure	1.4 (0.6-3.2)	0.39
Low total protein	Unsuccessful	1.2 (0.8-2.0)	0.34
	Died	1.5 (0.8-2.6)	0.18
	LTFU	1.5 (0.7-3.0)	0.27
	Failure	0.7 (0.3-1.7)	0.49
Multiple cavities	Unsuccessful	1.3 (0.8-2.1)	0.22
	Died	1.8 (1.0-3.3)	0.06
	LTFU	1.3 (0.6-2.8)	0.50
	Failure	0.7 (0.3-1.9)	0.49
Previous incarceration	Unsuccessful	2.3 (0.5-11.3)	0.29
	LTFU	2.3 (0.3-16.2)	0.39
	Failure	3.5 (0.3-38.2)	0.30
	Unsuccessful	1.3 (0.4-3.7)	0.67
Psychiatric illness	Died	2.1 (0.5-7.8)	0.29
	Failure	3.9 (0.8-20.0)	0.10
	Unsuccessful	1.2 (0.7-1.9)	0.48
Unemployed	Died	1.2 (0.6-2.5)	0.65
	LTFU	1.0 (0.5-2.0)	0.95
	Failure	1.7 (0.6-4.7)	0.31
Other types of resistance[1]	Unsuccessful	1.1 (0.7-2.0)	0.64
	Died	1.2 (0.5-2.9)	0.65
	LTFU	1.1 (0.5-2.7)	0.79
	Failure	0.9 (0.3-2.8)	0.87
MDR-TB[1]	Unsuccessful	1.3 (0.8-2.1)	0.27
	Died	1.8 (0.9-3.9)	0.11
	LTFU	0.8 (0.4-1.8)	0.65
	Failure	1.0 (0.4-2.4)	0.99
Pre-XDR-TB[1]	Unsuccessful	1.2 (0.7-2.0)	0.54
	Died	1.7 (0.8-3.8)	0.18
	LTFU	0.8 (0.3-1.8)	0.58
	Failure	0.8 (0.3-2.1)	0.66
XDR-TB[1]	Unsuccessful	1.3 (0.7-2.3)	0.36
	Died	0.8 (0.3-2.3)	0.74
	LTFU	1.7 (0.7-3.8)	0.24
	Failure	1.1 (0.4-2.8)	0.90



analysis found that the link between male sex and unsuccessful outcomes was mediated by behavioural factors, particularly treatment adherence, rather than biological differences.[6] Nevertheless, regarding the use of propensity score matching in our study, it is important to note that the methodology itself could also influence the weaker association observed in our propensity score-matched cohort, as some researchers have argued that combining this method with multiple imputations may lead to excessively wide confidence intervals for the effect estimate.[26]

By examining sex differences in risk factors for unsuccessful outcomes, we found that sex significantly modified the association between older age and mortality. Specifically, females over 65 years had significantly higher odds of dying compared to males. While previous studies on tuberculosis have shown that females typically present with a lower mycobacterial burden and are less likely to experience composite unsuccessful outcomes, our findings show that certain groups, particularly older females, may require increased attention in diagnostics or treatment.[27] One possible explanation for the elevated mortality risk in older females may be biological differences in the naturally occurring immunosenescence. Interestingly, a recent study in Nature Communications highlighted pronounced sex differences in immune ageing, with differences accelerating after the age of 65.[28] Older females exhibited enhanced adaptive immune activity, including more active B- and T-cell responses, while males demonstrated heightened innate and pro-inflammatory activity alongside reduced adaptive responses.[28] This difference might contribute to the increased mortality in females over 65 years, as their comparatively lower innate activity could impair their ability to contain new infections. Conversely, an enhanced adaptive immunity in females over 65 years could also lead to increased immunopathology in tuberculosis. However, these hypotheses are purely speculative and require further investigation. Finally, it is important to note that although we observed female sex being a statistically significant modifier of the association between being older than 65 years and having the outcome 'died', the significance could be a result of multiple testing.

This study has limitations. Despite using multivariable regression and propensity score matching, the retrospective design carries an inherent risk of selection bias. The NIAID TB Portal is not fully representative and includes only a subset of the tuberculosis patients in the participating countries. Because patients were prospectively included by treating clinicians, sampling bias is possible. This may be augmented if individuals with poorer outcomes were less likely to seek care, or if one sex was more or less likely to be diagnosed or included in the dataset. While propensity score matching was applied to increase the comparability between female and male patients, this method may have led to excessively wide confidence intervals, potentially diluting any true effects. Moreover, residual confounding is a concern, as unmeasured confounders may still influence the relationship between sex and treatment outcomes. Notably, information on factors that could differentially affect the risk of unsuccessful outcomes between males and females, such as symptom duration before healthcare contact or treatment adherence, was not available. Furthermore, while the covariables used to match female and male patients were clinically relevant and important to balance, they were partly selected based on observed imbalances in this specific sample, potentially introducing sample-specific bias. Additionally, although the overall number of patients was high, the sex-stratified risk factor analysis resulted in some cohorts, particularly those with female patients, having relatively few patients with the analysed outcomes, which may affect the validity of regression coefficients. There are also limitations to the application of MICE. For most imputed variables, missing data was below ten per cent. Still, for low total protein, erythrocyte sedimentation rate, education group, and BMI, missing data were close to 50%, potentially affecting the validity of the imputations. Furthermore, correlations were observed between some variables, particularly social risk factors, country, and resistance patterns. Nevertheless, regression coefficients based on MICE were generally comparable to those based on complete case analysis. Finally, direct biological markers, such as hormonal or genetic profiles, which could have provided more insight into sex-related differences in outcomes, were not available. Hence, our results were limited to socio-demographic and behavioural factors, and we could not explore potential biological mechanisms. Regarding representativeness, only biological sex was recorded in the database, limiting our ability to examine how these factors may influence outcomes and reducing the generalisability of our findings to minority populations.

This study also has strengths. The study is multinational and includes a large sample size of patients with tuberculosis, increasing external validity. Data were collected prospectively and are publicly available,

Fig. 3: Interaction effects between sex and risk factors on unfavourable tuberculosis treatment outcomes. aOR > 1 indicates a stronger association in females compared to males; aOR < 1 indicates a stronger association in males. Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; LTFU, lost to follow-up; TB, tuberculosis; BMI, body mass index; HIV, human immunodeficiency virus; MDR-TB, multi-drug-resistant tuberculosis; pre-XDR-TB, pre-extensively drug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis. [1]Compared to drug-susceptible tuberculosis.

ensuring transparency. Comprehensive statistical approaches were applied to examine the effect of sex on treatment outcomes. Additionally, we analysed risk factors for all three WHO-defined unsuccessful outcomes, unlike most published risk factor studies, providing a more detailed examination.

Our findings suggest that sex disparities in tuberculosis outcomes may be driven more by behavioural factors rather than biological ones. This highlights the clinical importance of considering patient sex when identifying individuals at higher risk of unsuccessful outcomes. To validate these findings, longitudinal studies, particularly those exploring biological mechanisms, are needed. At the policy-making level, our results emphasise the need for tuberculosis programmes to adopt a more individualised, patient-centred approach that considers the unique risk factors and treatment needs of different populations. Addressing these disparities can contribute to reducing disproportionate representation between sexes in tuberculosis care.

Contributors

Ole Skouvig Pedersen: Conceptualisation, Methodology, Formal Analysis, Data Curation, Data Visualisation, Writing - Original Draft, Writing - Review & Editing, Visualisation; **Tetiana Butova**: Investigation, Writing - Review & Editing; **Valerii Miasoiedov**: Investigation, Writing - Review & Editing; **Yurii Feshchenko**: Investigation, Writing - Review & Editing; **Mykhailo Kuzhko**: Investigation, Writing - Review & Editing; **Stefan Niemann**: Investigation, Writing - Review & Editing; **Alex Rosenthal**: Investigation, Writing - Review & Editing; **Alina Grinev**: Investigation, Writing - Review & Editing; **Gabriel Rosenfeld**: Investigation, Writing - Review & Editing; **Michael Drew Hoppes**: Investigation, Writing - Review & Editing; **Julia Kilmnick**: Investigation, Writing - Review & Editing; **Valeriu Crudu**: Investigation, Writing - Review & Editing; **Nelly Ciobanu**: Investigation, Writing - Review & Editing; **Alexandru Codreanu**: Investigation, Writing - Review & Editing; **Bekzat Toxanbayeva**: Investigation, Writing - Review & Editing; **Lyailya Chingissova**: Investigation, Writing - Review & Editing; **Kateryna Yurko**: Investigation, Writing - Review & Editing; **Valerii Kucheriavchenko**: Investigation, Writing - Review & Editing; **Vitalii Vekshyn**: Investigation, Writing - Review & Editing; **Sergo Vashakidze**: Investigation, Writing - Review & Editing; **Natalia Shubladze**: Investigation, Writing - Review & Editing; **Zaza Avaliani**: Investigation, Writing - Review & Editing; **Abdullaat Kadyrov**: Investigation, Writing - Review & Editing; **Gulmira Kalmambetova**: Investigation, Writing - Review & Editing; **Merbubu Sydykova**: Investigation, Writing - Review & Editing; **Eugenia Ghita**: Investigation, Writing - Review & Editing; **Victor Ionel Grecu**: Investigation, Writing - Review & Editing; **Alina Marinela Miulescu**: Investigation, Writing - Review & Editing; **Christian Morberg Wejse**: Supervision, Writing - Review & Editing; **Andreas Fløe**: Supervision, Writing - Review & Editing; **Victor Naestholt Dahl**: Conceptualisation, Methodology, Writing - Original Draft, Writing - Review & Editing, Supervision, Project Administration; **Dmytro Butov**: Investigation, Resources, Writing - Review & Editing, Funding Acquisition, Project Administration.

Data sharing statement

Data is publicly available (https://datasharing.tbportals.niaid.nih.gov/#/home), and all coding is available upon reasonable request.

Declaration of interests

CMW reports being a co-inventor on a pending patent application related to diagnosing tuberculosis in saliva (PCT/EP2023/080683; TECH-2022-631-459) (outside the scope of this work); serves as chairperson of the Danish Society for Migrant Health (since 2023) and as Chair of ESGITM (ESCMID Study Group for Infections in Migrants and Travellers) (outside of the scope of this work). This had no influence on the design, analysis, interpretation, or reporting of the current study. All other authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2025.101354.

References

1 Achrekar A, Akselrod S, Clark H, et al. Delivering health for all: the critical role of gender-responsive health systems. *Lancet Glob Health*. 2024;12(5):e733–e734.
2 *Global Tuberculosis Report 2024*. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.
3 *Global Tuberculosis Report 2023*. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.
4 Sex matters for tuberculosis control. *Lancet Infect Dis*. 2002;2(6):317.
5 Bogale L, Tsegaye T, Abdulkadir M, Akalu TY. Unfavorable treatment outcome and its predictors among patients with multidrug-resistance tuberculosis in Southern Ethiopia in 2014 to 2019: a multi-center retrospective follow-up study. *Infect Drug Resist*. 2021;14:1343–1355.
6 Barathi A, Krishnamoorthy Y, Sinha P, et al. Effect of treatment adherence on the association between sex and unfavourable treatment outcomes among tuberculosis patients in Puducherry, India: a mediation analysis. *J Public Health (Oxf)*. 2023;45(2):304–311.
7 Massud A, Khan AH, Syed Sulaiman SA, et al. Unsuccessful treatment outcome and associated risk factors. A prospective study of DR-TB patients from a high burden country, Pakistan. *PLoS One*. 2023;18(8):e0287966.
8 Ngah VD, Rangoanana M, Fwemba I, et al. Evaluating determinants of treatment outcomes among tuberculosis patients in the mining district of Butha Buthe, Lesotho. *IJID Reg*. 2023;6:62–67.
9 Matulyte E, Davidaviciene E, Kancauskiene Z, et al. The sociodemographic, clinical characteristics and outcomes of tuberculosis among HIV infected adults in Lithuania: a thirteen-year analysis. *PLoS One*. 2023;18(3):e0282046.
10 Simieneh A, Gashaneh S, Dereje R. Nutritional status and treatment outcomes of tuberculosis in Mizan Tepi University Teaching Hospital, a five -year retrospective study. *PLoS One*. 2024;19(2):e0298244.
11 Pedersen OS, Butova T, Kapustnyk V, et al. Treatment outcomes and risk factors for an unsuccessful outcome among patients with highly drug-resistant tuberculosis in Ukraine. *Clin Microbiol Infect*. 2024;30(3):360–367.
12 Dahl VN, Butova T, Rosenthal A, et al. Drug-resistant tuberculosis, Georgia, Kazakhstan, Kyrgyzstan, Moldova, and Ukraine, 2017-2022. *Emerg Infect Dis*. 2024;30(4):831–833.
13 Skouvig Pedersen O, Butova T, Borovok N, et al. Chest X-ray alone is insufficient for predicting drug-resistant pulmonary tuberculosis. *Clin Microbiol Infect*. 2024;30(8):1075–1077.
14 Rosenthal A, Gabrielian A, Engle E, et al. The TB Portals: an open-access, web-based platform for global drug-resistant-tuberculosis data sharing and analysis. *J Clin Microbiol*. 2017;55(11):3267–3282.
15 von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806–808.
16 *Definitions and reporting Framework for Tuberculosis – 2013 Revision (updated December 2014 and January 2020)*. World Health Organization; 2020. Available at: https://iris.who.int/bitstream/handle/10665/79199/9789241505345_eng.pdf.

17 NIAID TB Portals data dictionary (n.d.). Available at: https://data.tbportals.niaid.nih.gov/dictionary.
18 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30(4):377–399.
19 Austin PC, White IR, Lee DS, van Buuren S. Missing data in clinical research: a tutorial on multiple imputation. *Can J Cardiol*. 2021;37(9):1322–1331.
20 Woods AD, Gerasimova D, Van Dusen B, et al. Best practices for addressing missing data through multiple imputation. *Infant Child Dev*. 2024;33(1):e2407.
21 Schafer JL, Kang J. Average causal effects from nonrandomized studies: a practical guide and simulated example. *Psychol Methods*. 2008;13(4):279–313.
22 Austin PC, Stuart EA. Estimating the effect of treatment on binary outcomes using full matching on the propensity score. *Stat Methods Med Res*. 2017;26(6):2505–2525.
23 Greifer N. Matching methods. MatchIt vignette. R package version 4.5.2. Available at: https://cran.r-project.org/web/packages/MatchIt/vignettes/matching-methods.html; 2025.
24 Pishgar F, Greifer N, Leyrat C, Stuart E. MatchThem: matching and weighting after multiple imputation. *R J*. 2020;13(2):292–305.
25 Dabitao D, Bishai WR. Sex and gender differences in tuberculosis pathogenesis and treatment outcomes. Sex and Gender Differences in Infection and Treatments for Infectious Diseases. *Curr Top Microbiol Immunol*. 2023;441:139–183.
26 Ségalas C, Leyrat C, Carpenter JR, Williamson E. Propensity score matching after multiple imputation when a confounder has missing data. *Stat Med*. 2023;42(7):1082–1095.
27 Deshmukh S, Sane M, Gaikwad S, et al. Sex differences in TB clinical presentation, drug exposure, and treatment outcomes in India. *Chest*. 2023;163(4):778–789.
28 Márquez EJ, Chung CH, Marches R, et al. Sexual-dimorphism in human immune system aging. *Nat Commun*. 2020;11(1):751.