Clinical Microbiology and Infection 30 (2024) 360–367

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Treatment outcomes and risk factors for an unsuccessful outcome among patients with highly drug-resistant tuberculosis in Ukraine

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ARTICLE INFO

Article history:
Received 23 October 2023
Received in revised form
28 November 2023
Accepted 2 December 2023
Available online 6 December 2023

Editor: E. Bottieau

ABSTRACT

Objectives: To describe demographics, clinical features, and treatment outcomes of patients with highly drug-resistant tuberculosis (TB) in Ukraine, and to evaluate risk factors for an unsuccessful outcome.

Methods: Data from patients with multi-, pre-extensively, or extensively drug-resistant TB were collected prospectively from TB dispensaries in 15 out of 24 Ukrainian oblasts (regions) from 2020 to 2021. Treatment outcomes were evaluated using WHO definitions. Risk factors for an unsuccessful outcome were identified using a multivariable logistic regression model.

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https://doi.org/10.1016/j.cmi.2023.12.001

Keywords:
BPaL
COVID-19
Drug-resistant tuberculosis
Extensively drug-resistant tuberculosis
Multidrug-resistant tuberculosis
Pre-extensively drug-resistant tuberculosis
Risk factors
Treatment outcomes

Results: Among 1748 patients, the overall proportion of successful outcomes was 58% (95% confidence interval [95% CI] 56–60) ($n = 1015/1748$), ranging from 65% (95% CI: 62–69) ($n = 531/814$) for multidrug-resistant TB to 54% (95% CI: 49–58) ($n = 301/563$) for pre-extensively drug-resistant TB and 49% (95% CI: 44–55) ($n = 183/371$) for extensively drug-resistant TB. Results were similar across oblasts, with few exceptions. The strongest risk factors for an unsuccessful outcome were extensively drug-resistant TB (adjusted OR [aOR] 3.23; 95% CI: 1.88–5.53), total serum protein below 62 g/L in adults and below 57 g/L for children and adolescents (aOR 2.79; 95% CI: 1.93–4.04), psychiatric illness (aOR 2.79; 95% CI: 1.46–5.33), age at TB diagnosis >65 years (aOR 2.50; 95% CI: 1.42–4.42), and alcohol misuse (aOR 2.48; 95% CI: 1.89–3.26).

Discussion: The overall proportion of successful outcomes among Ukrainians treated for highly drug-resistant TB was 58%, notably better compared with previous years, but still low for extensively drug-resistant TB. Risk factors for unsuccessful outcomes highlight that addressing socioeconomic factors in TB management is crucial. Efforts in maintaining TB dispensaries during and following the ongoing war are highly warranted. **Ole Skouvig Pedersen, Clin Microbiol Infect 2024;30:360**

Introduction

In Eastern Europe, the prevalence of highly drug-resistant tuberculosis (TB) among new and retreated patients with TB is alarmingly high [1,2]. In 2021, Ukraine had the second-highest number of incident cases of rifampicin-resistant/multidrug-resistant TB (RR/MDR-TB) in the WHO European Region [3]. In 2019, Ukraine had third highest number of patients with confirmed extensively drug-resistant TB (XDR-TB) worldwide [3]. Previously, only smaller regional studies have assessed treatment outcomes of Ukrainian patients with highly drug-resistant TB, all demonstrating low rates of success [2,4–6]. The high TB incidences and low success rates in Ukraine underscore the urgency of implementing novel treatment regimens, such as the highly promising short-course all-oral bedaquiline, pretomanid, and linezolid (BPaL) regimen [7]. Encouragingly, in November 2021, Ukraine became the first country in the world to commence research on the operational use of BPaL in clinical settings [8].

Using data from several Ukrainian regions, we aimed to describe demographics, clinical features, and treatment outcomes of patients with highly drug-resistant TB in the period leading up to the war and before the implementation of BPaL, and to evaluate risk factors for an unsuccessful outcome.

Methods

Study design and data collection

A register-based cohort study of prospectively collected data from the largest central TB dispensaries in Ukraine. Data were stored in a NIAID TB portal database that contains information about patient demographics, including risk factors for TB, clinical, and microbiological data. Patient records were continuously submitted and reviewed by doctors and radiologists from the participating TB hospitals. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [9] (Supplementary Material 1).

Study setting

The TB dispensaries represented 15 of 24 different Ukrainian oblasts (regions): Chernivetska, Donetska, Dnipropetrovska, Ivano-Frankivska, Khersonska, Kharkivska, Kyiv city, Mykolaivska, Sumska, Ternopilska, Vinnytska, Volynska, Zakarpatska, Zhytomyrska, and Zaporizka. Study sites were included at different periods in early 2020 and then participated for 1 year each. In 2021, the estimated total TB incidence was 31 000 in Ukraine, with 11 000 cases of RR/MDR-TB, corresponding to a rate of 71 per 100 000 citizens per year, and approximately 20% HIV coinfected [3]. With such extensive regional coverage in a TB high-incidence country, the study size was expected to be more than sufficient.

Population

Patients of all ages with bacteriologically confirmed MDR-, pre-XDR-, or XDR-TB were included consecutively at each individual study site. Patients were excluded if pheno- or genotypic drug resistance patterns were not available, or if treatment outcomes were not evaluated, including patients still on treatment.

Definitions of outcomes

Drug resistance was classified using WHO's 2006 criteria (Table 1) because only few patients fulfilled the criteria established in 2021 [10–12,16]. According to national recommendations, WHO recommended treatment outcomes were used (Table 1) [10–12,16]. Patients in palliative care were considered 'treatment failure'. Patients were followed at least until one of the outcomes were achieved.

Definitions of other variables

Psychiatric illnesses were diagnosed by a psychiatrist at the individual study sites according to International Classification of Diseases 10th revision. The most prevalent illness was schizophrenia, but the definition also included other psychiatric diagnoses (anxiety, depression, bipolar disorder, among others). A cavity was considered as such if it was visible on a chest radiograph, tomography, or computed tomography (>1 cm). Age at TB diagnosis and body mass index (BMI) were dichotomized using a cut-off value of 65 years and 18.5 kg/m^2, respectively. Total serum protein level and erythrocyte sedimentation rate were included in the study because these were consistently measured in all study sites and are known to be associated with TB disease and severity [13,14]. Protein levels were considered low if below 62 g/L in adults and below 57 g/L for children and adolescents (<18 years). Erythrocyte sedimentation rate was considered elevated if above 20 mm for females between 0 and 50 years and above 30 mm for females older than 50 years. For

Table 1
Definitions of drug resistance and treatment outcomes

	Definition
Resistance patterns[a]	
Multidrug-resistant tuberculosis (TB)	Tuberculosis caused by *Mycobacterium tuberculosis* strains with resistance to rifampicin and isoniazid
Extensively drug-resistant TB	Multidrug-resistant TB with additional resistance to any fluoroquinolone and at least one second-line injectable drug (amikacin, kanamycin, capreomycin)
Pre-extensively drug-resistant TB	Multidrug-resistant TB with additional resistance to either any fluoroquinolone or at least one second-line injectable drug, but not both[b]
Treatment outcomes[c]	
Successful	The sum of 'cured' and 'treatment completed'
Unsuccessful	The sum of 'lost to follow-up', 'treatment failure', and 'died'

[a] Using 2006 definitions from the WHO [10,11].
[b] Until 2021, pre-extensively drug-resistant tuberculosis was not officially defined by the WHO; however, the used definition has been used widely in clinical practices and research [16].
[c] Defined as recommended by the WHO [12].

males older than 50 years, above 20 mm was considered elevated, and above 15 mm for younger males.

Statistical analyses

Data were analysed in R version 4.2.3. For comparisons, we grouped patients into MDR-non-XDR-TB and XDR-TB. Unadjusted ORs were calculated to estimate the association between potential risk factors and an unsuccessful outcome without controlling for covariates. The risk factors were pre-defined variables that made clinical sense. A multivariable logistic regression model was used to calculate adjusted ORs (aOR), modelling the log-odds of the binary dependent variable (unsuccessful or successful outcome) as a linear function of several covariates. The covariates included in the adjusted model were selected based on an *a priori* decision to include independent variables associated with unsuccessful outcomes in the unadjusted model at p value $\leq$ 0.2 [5,15]. Fluroquinolones were precluded from the adjusted model to avoid multicollinearity. To account for missing values, we performed a complete case analysis, excluding patients with missing data. To evaluate the impact of the complete case analysis compared with the adjustment itself, we also calculated unadjusted estimates using all cases with complete data in each respective variable. A sensitivity analysis was performed where missing data were

Table 2
Demographics of patients with drug-resistant TB in Ukraine

	MDR-non-XDR-TB, $n = 1377$	XDR-TB, $n = 371$
Age at TB diagnosis in years, median (IQR)	42 (15.0)	43 (16.0)
Male, *n* (%)	1080/1377 (78)	292/371 (79)
BMI[a] (kg/m^2) median (IQR)	20.0 (4.2)	19.8 (4.1)
Employment, *n* (%)		
Employed, student, or homemaker	281/1364 (21)	52/366 (14)
Unemployed, disabled, or retired	1083/1364 (79)	314/366 (86)
Educational level, *n* (%)		
College and higher education	348/1156 (30)	99/334 (30)
No education, basic or complete school	808/1156 (70)	235/334 (70)
Homelessness, *n* (%)	71/1377 (5.2)	19/371 (5.1)
Tobacco usage, *n* (%)	1029/1377 (75)	276/371 (74)
Alcohol misuse, *n* (%)	611/1377 (44)	167/371 (45)
Drug abuse, *n* (%)	173/1377 (13)	58/371 (16)
Previous incarceration, *n* (%)	183/1377 (13)	56/371 (15)
Known MDR-TB contact, *n* (%)	40/1377 (2.9)	17/371 (4.6)

BMI, body mass index; IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.
[a] Missing data for 10 patients with MDR-/non-XDR-TB and 4 patients with XDR-TB.

Table 3
Clinical characteristics of patients with drug-resistant TB in Ukraine

	MDR non-XDR, $n = 1377$	XDR, $n = 371$
Comorbidities, *n* (%)		
HIV positive	295/1377 (21)	80/371 (22)
HBV positive	42/1377 (3.1)	10/371 (2.7)
HCV positive	172/1377 (12)	63/371 (17)
Anaemia	329/1377 (24)	98/371 (26)
COVID-19	55/1377 (4.0)	13/371 (3.5)
Diabetes mellitus	53/1377 (3.8)	21/371 (5.7)
Renal insufficiency	27/1377 (2.0)	9/371 (2.4)
Psychiatric illness[a]	51/1377 (3.7)	21/371 (5.7)
Immunosuppression[b]	10/1377 (0.7)	2/371 (0.5)
Biochemical parameters, *n* (%)		
Low total protein[c]	196/1294 (15)	64/343 (19)
Elevated ESR[d]	728/1185 (61)	208/313 (66)
TB manifestation, *n* (%)		
Pulmonary TB	1299/1377 (94)	351/371 (95)
Pulmonary and/ or extrapulmonary TB	78/1377 (5.7)	20/371 (5.4)
Smear positive	989/1374 (72)	279/371 (75)
Cavitation	570/1335 (43)	150/356 (42)
Multiple cavities	190/1335 (14)	57/356 (16)
TB treatment		
Retreatment, *n* (%)	555/1377 (40)	216/371 (58)
Duration[e] (d) median (IQR)	274 (298)	324 (379)
BPaL[f], *n* (%)	11/1312 (0.8)	13/319 (4.1)
Group A drug[g], *n* (%)	1285/1312 (98)	316/319 (99)
Injectable, *n* (%)	221/1312 (17)	49/319 (15)
Drug resistance, *n* (%)		
Injectable(s)	277/1164 (24)	371/371 (100)
Fluroquinolone(s)	286/1177 (24)	371/371 (100)
Bedaquiline	3/867 (0.3)	5/224 (2.2)
Delamanid	20/823 (2.4)	8/223 (3.6)
Linezolid	12/1040 (1.2)	26/310 (8.4)

ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR: interquartile range; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.
[a] Psychiatric illnesses were diagnosed by a psychiatrist at the individual study sites according to ICD-10 diagnostic codes. The most prevalent illness was schizophrenia, but the definition also included other psychiatric diagnoses (anxiety, depression, bipolar disorder, among others).
[b] Defined as treatment with either cytostatics, TNF-alpha inhibitors, and/or corticosteroids.
[c] Protein levels were considered low if below 62 g/L in adults and below 57 g/L for children and adolescents (<18 years).
[d] Erythrocyte sedimentation rate was considered elevated if above 20 mm for females between 0 and 50 years and above 30 mm for females older than 50 years. For males older than 50 years, above 20 mm was considered elevated, and above 15 mm for younger males.
[e] Data missing for 12 patients with MDR non-XDR-TB and for 19 patients with XDR-TB.
[f] Delamanid and pretomanid were equally considered part of a BPaL regimen.
[g] Group A drugs according to WHO: Bedaquiline, linezolid, levofloxacin, moxifloxacin [10].

addressed using the multiple imputation by chained equations method (R package *mice* v. 3.16.0).

Ethical considerations

The study was approved by the Ethics Committee of the Kharkiv National Medical University, Kharkiv, Ukraine (5 February 2020, no. 1).

Results

Patient demographics

In total, 814 (46.6%) patients with MDR-TB, 563 (32.2%) with pre-XDR-TB, and 371 (21.2%) with XDR-TB were included (Supplementary Material 2).

Most patients were male ($n = 1372$, 78.5%) (Table 2), the median age at TB diagnosis was 42 years (interquartile range [IQR] 35–50), and the median BMI was 19.9 kg/m^2 (IQR 17.9–22.1). Study sites in Zaporizka (13.7%), Kharkivska (11.6%), Donetska (10.4%), Sumska (9.0%), and Kyiv city (8.8%) accounted for the most patients.

Clinical characteristics

Hepatitis C coinfection (17.0% vs. 12.5%), retreatment (58.2% vs. 40.3%), and use of BPaL (4.1% vs. 0.8%) were more common among patients with XDR-TB compared with MDR-non-XDR-TB (Table 3) [10]. Among patients with isolates examined, 0.7%, 2.7%, and 2.8% had bedaquiline, delamanid, and linezolid resistance, respectively, with more patients with XDR-TB having bedaquiline (2.2% vs. 0.3%) and linezolid resistance (8.4% vs. 1.2%) compared with patients with MDR-non-XDR-TB.

Treatment outcomes and risk factors

The overall proportion of patients who achieved a successful outcome was 58% (95% CI: 56–60) ($n = 1015/1748$), ranging from 65% (95% CI: 62–69) ($n = 531/814$) for MDR-TB to 54% (95% CI: 49–58) ($n = 301/563$) for pre-XDR-TB and 49% (95% CI: 44–55) ($n = 183/371$) for XDR-TB (Fig. 1) [10–12,16]. Outcomes were similar across most oblasts but varied for some regions. Notably, Vinnytsia ($n = 3/18$, 17%) and Kyiv city ($n = 121/154$, 79%) had lower and higher treatment successes, respectively (Fig. 2). People living with HIV had a lower treatment success ($n = 181/375$, 48%, 95% CI: 43–53) compared with people without HIV ($n = 834/1373$, 61%, 95% CI: 58–63). More people living with HIV also died ($n = 106$, 28%, 95% CI: 24–33) compared with those without HIV ($n = 224$, 16%, 95% CI: 14–18). Applying the new 2021 definition of XDR-TB, i.e. where second-line injectable drugs were replaced by moxifloxacin, levofloxacin, bedaquiline, and linezolid, only 27% ($n = 9/34$, 95% CI: 14–45) had a successful outcome. All patients receiving BPaL ($n = 24$) treatment had a successful outcome.

Several risk factors associated with an unsuccessful outcome were identified (Table 4) [10]. In the multivariable model, using imputed data, XDR-TB (aOR 3.23; 95% CI: 1.88–5.53), low total protein (aOR 2.79; 95% CI: 1.93–4.04), psychiatric illness (aOR 2.79; 95% CI: 1.46–5.33), age at TB diagnosis >65 years (aOR 2.50; 95% CI: 1.42–4.42), and alcohol misuse (aOR 2.48; 95% CI: 1.89–3.26) were

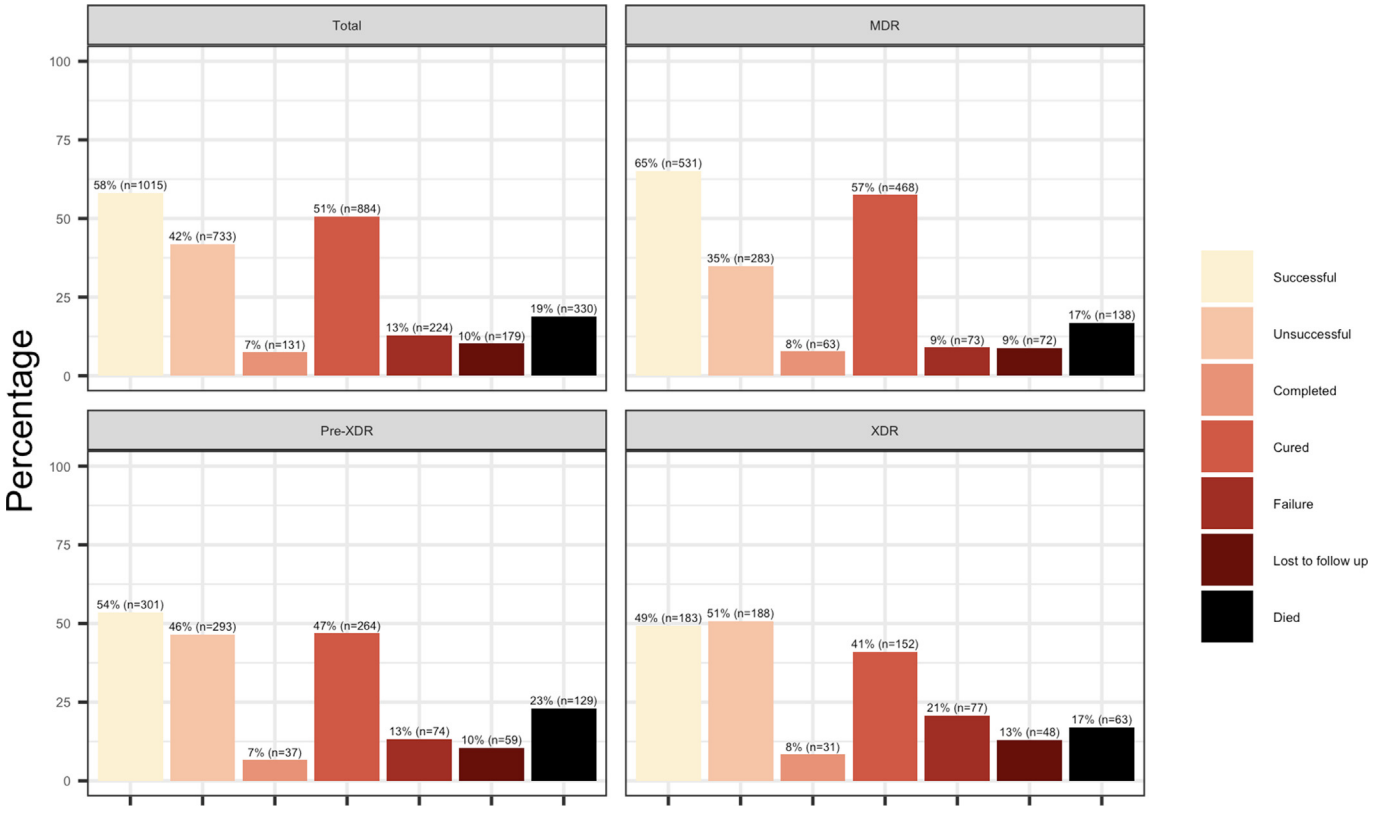

Fig. 1. Treatment outcomes (%) by type of drug resistance. Data were consecutively collected from 2020 to 2021 among the largest central tuberculosis (TB) dispensaries in 15 of 24 Ukrainian oblasts. Study sites were included at different periods in early 2020 and then participated consecutively for 1 year each. Patients were excluded if pheno- or genotypic drug resistance patterns were not available ($n = 38$), or if treatment outcomes were not evaluated, including patients still on treatment ($n = 5$). A few patients had missing outcomes ($n = 3$). Treatment outcomes were defined as recommended by the WHO [12]. A successful outcome was defined as the sum of 'cured' and 'treatment completed', whereas an unsuccessful outcome was defined as the sum of 'lost to follow-up', 'treatment failure', and 'died'. Multidrug-resistant TB and extensively drug-resistant TB were defined using WHO 2006 standards [10,11], whereas pre-extensively drug-resistant TB was defined using the definition most commonly used in clinical practices and research until 2021.

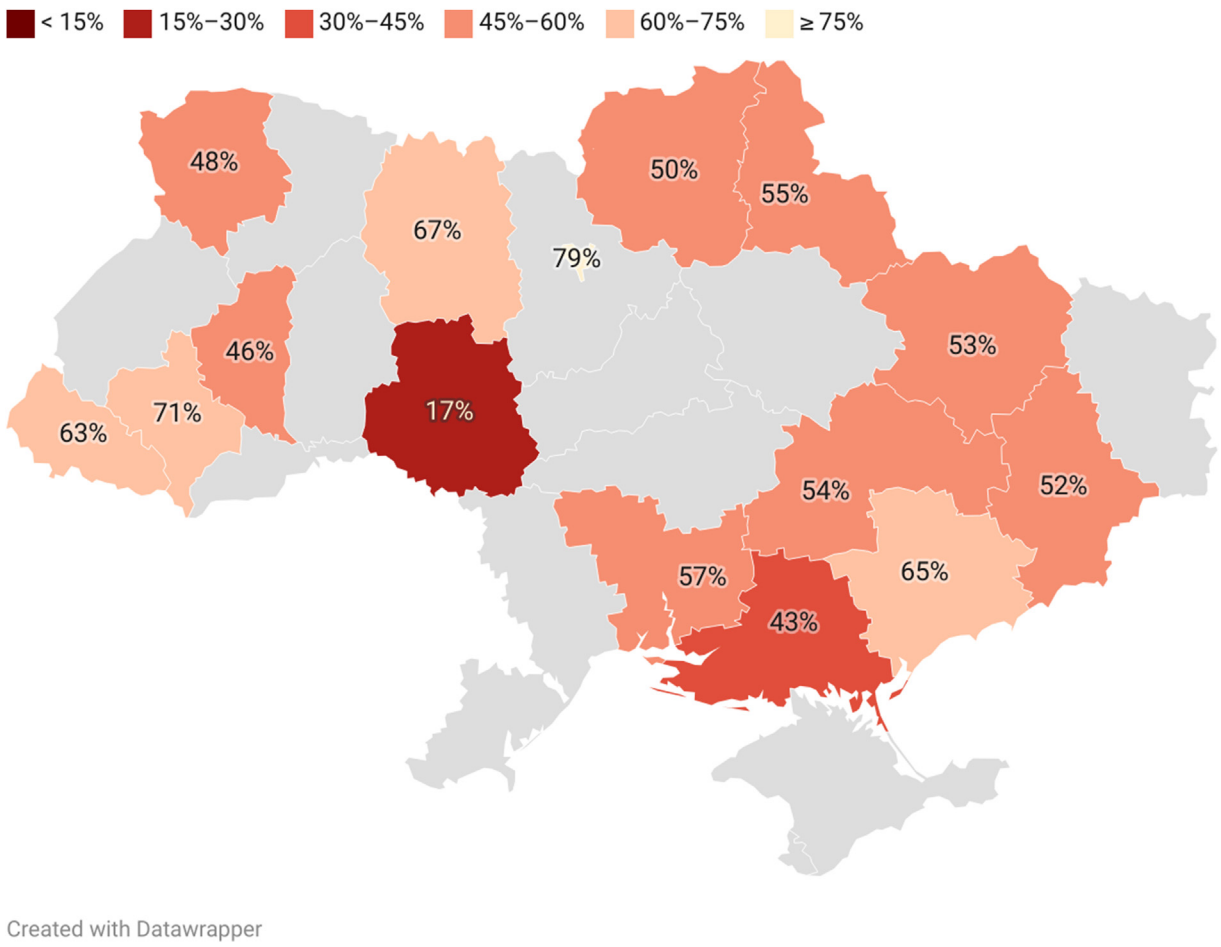

Fig. 2. Patients with successful treatment outcomes (%) by Ukrainian oblasts. The notably low rate of success in the oblast of Vinnytsia is undoubtly explained by the COVID-19 lockdown. During the lockdown, only one TB centre in the region continued accepting patients and experienced much lower treatment adherence than usual, thus explaining the low rate of success.

the strongest risk factors for an unsuccessful outcome that also increased the odds of an unsuccessful outcome consistently across all 3 models. Calculating unadjusted ORs using complete case analysis did not change the direction of the estimates (data not shown).

Discussion

With 1748 patients enrolled from 15 of 24 Ukrainian oblasts in 2020–2021, this is the most recent and comprehensive cohort study assessing treatment outcomes of Ukrainian patients with highly drug-resistant TB. In total, 58% had a successful treatment outcome. For MDR-, pre-XDR-, and XDR-TB, the proportions were 65%, 54%, and 49%, respectively. The strongest risk factors for an unsuccessful outcome were XDR-TB, low total protein, psychiatric illness, age at TB diagnosis >65 years, and alcohol misuse all resulting in 2–3-fold higher odds of an unsuccessful outcome.

Previous studies assessing outcomes of Ukrainians with MDR-TB, with the most recent enrolment period ending in 2016, have estimated that 18–44% achieve a successful outcome [2,4–6]. Our study demonstrates that treatment of drug-resistant TB in Ukraine has improved considerably and has now surpassed the overall global success rate [3,16]. It is reasonable to consider whether such an improvement could be explained by wider implementation of novel anti-TB drugs in Ukraine. Yet, although 98% of patients in our study received at least one group A drug, only 0.8% received the BPaL combination. This is not surprising because, although Ukraine was the first country to initiate operational research on the performance of BPaL in clinical settings, such research only commenced after the enrolment period of this study [8]. Another possible explanation could be enhanced efforts to integrate patient-centred ambulatory health care systems into the MDR-TB management systems of the individual oblasts, such as those efforts that were part of the Challenge TB Project [17]. This explanation is supported by the fact that several of the identified risk factors for an unsuccessful outcome in our study are dependent on social resources and treatment adherence (i.e. psychiatric illness, alcohol misuse, among others). These factors are more likely to be addressed in patient-centred management.

Our study also showed that treatment outcomes were similar across the 15 different oblasts. However, Vinnytsia had a success rate of only 17% and Kyiv city as high as 79%. The low rate of success in Vinnytsia was undoubtedly a direct consequence of the COVID-19 lockdown. All TB centres in the region, except for one, were closed and repurposed as COVID-19 centres. The one TB centre that did accept patients throughout the lockdown experienced much lower treatment adherence than usual, explaining the low rate of success. Although TB services have reportedly been sustained throughout Ukrainian territories during the first year of the war [18], the results from Vinnytsia during the COVID-19 pandemic demonstrate the drastic impact of disrupted TB services on treatment outcomes. The high level of success in Kyiv city can be

Table 4
Uni- and multivariable analysis of risk factors for an unsuccessful treatment outcome

Risk factors	Successful outcome ($n = 1015$)	Unsuccessful outcome ($n = 733$)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	Adjusted OR based on imputed data (95% CI)[b]
Demographics, *n* (%)					
Age >65 years	39/1015 (3.8)	51/733 (7.0)	1.87 (1.22–2.89)	3.49 (1.75–7.07)	2.50 (1.42–4.42)
Male	754/1015 (74)	618/733 (84)	1.86 (1.46–2.38)	1.39 (0.88–2.21)	1.21 (0.86–1.71)
BMI <18.5 kg/m^2	236/1007 (23)	300/727 (41)	2.30 (1.87–2.83)	2.08 (1.45–2.99)	1.45 (1.09–1.93)
Unemployed, disabled, or retired	758/1006 (75)	639/724 (88)	2.46 (1.89–3.23)	1.96 (1.22–3.21)	2.01 (1.39–2.92)
No education, basic or complete school	557/854 (65)	486/636 (76)	1.73 (1.37–2.18)	0.91 (0.62–1.34)	1.02 (0.74–1.41)
Social risk factors, *n* (%)					
Homelessness	36/1015 (3.5)	54/733 (7.4)	2.16 (1.41–3.36)	1.57 (0.73–3.50)	1.62 (0.91–2.91)
Tobacco usage	694/1015 (68)	611/733 (83)	2.32 (1.84–2.94)	1.19 (0.76–1.89)	1.07 (0.77–1.51)
Alcohol misuse	322/1015 (32)	456/733 (62)	3.54 (2.91–4.33)	2.42 (1.71–3.42)	2.48 (1.89–3.26)
Drug abuse	98/1015 (9.7)	133/733 (18)	2.07 (1.57–2.75)	1.46 (0.87–2.46)	1.32 (0.87–2.00)
Previous incarceration	93/1015 (9.2)	146/733 (20)	2.47 (1.87–3.27)	2.32 (1.41–3.85)	1.86 (1.26–2.76)
Known MDR-TB contact	32/1015 (3.2)	25/733 (3.4)	1.08 (0.63–1.84)	—	—
Comorbidities, *n* (%)					
HIV positive	181/1015 (18)	194/733 (26)	1.66 (1.32–2.09)	1.15 (0.74–1.77)	1.45 (1.04–2.03)
HBV positive	23/1015 (2.3)	29/733 (4.0)	1.78 (1.02–3.12)	1.32 (0.54–3.31)	1.18 (0.56–2.48)
HCV positive	128/1015 (13)	107/733 (15)	1.18 (0.90–1.56)	—	—
Anaemia	175/1015 (17)	252/733 (34)	2.51 (2.01–3.15)	1.41 (0.97–2.03)	1.51 (1.11–2.06)
COVID-19	37/1015 (3.6)	31/733 (4.2)	1.17 (0.71–1.90)	—	—
Diabetes mellitus	43/1015 (4.2)	31/733 (4.2)	1.00 (0.62–1.59)	—	—
Renal insufficiency	17/1015 (1.7)	19/733 (2.6)	1.56 (0.80–3.06)	1.11 (0.35–3.44)	1.28 (0.51–3.22)
Psychiatric illness[c]	26/1015 (2.6)	46/733 (6.3)	2.55 (1.57–4.21)	2.65 (1.25–5.70)	2.79 (1.46–5.33)
Immunosuppression[d]	3/1015 (0.3)	9/733 (1.2)	4.19 (1.25–18.9)	3.82 (0.77–24.6)	4.31 (0.83–22.3)
Biochemistry, *n* (%)					
Low total protein[e]	85/945 (9.0)	175/692 (25)	3.42 (2.59–4.55)	2.41 (1.52–3.85)	2.79 (1.93–4.04)
Elevated ESR[f]	473/854 (55)	463/644 (72)	2.06 (1.66–2.57)	1.19 (0.83–1.69)	1.25 (0.94–1.68)
TB manifestation, *n* (%)					
Pulmonary TB	963/1015 (95)	687/733 (94)	Reference	—	—
Pulmonary and/or extrapulmonary TB	52/1015 (5.1)	46/733 (6.3)	1.24 (0.82–1.87)	—	—
Smear positive	703/1013 (69)	565/732 (77)	1.49 (1.20–1.86)	0.95 (0.65–1.39)	0.97 (0.72–1.31)
Cavitation	380/984 (39)	340/707 (48)	1.47 (1.21–1.79)	1.36 (0.95–1.95)	1.15 (0.86–1.53)
Multiple cavities	105/984 (11)	142/707 (20)	2.10 (1.60–2.77)	1.96 (1.19–3.26)	1.88 (1.28–2.77)
TB treatment, *n* (%)					
Retreatment	378/1015 (37)	393/733 (54)	1.95 (1.61–2.36)	1.43 (1.02–2.00)	1.84 (1.41–2.40)
Duration more than 275 d	712/1015 (70)	144/702 (21)	0.11 (0.09–0.14)	0.10 (0.07–0.14)	0.08 (0.06–0.11)
BPaL[g]	24/1015 (2.4)	0/616 (0)	—	—	—
Group A drug[h]	1015/1015 (100)	586/616 (95)	—	—	—
Injectable	170/1015 (17)	100/616 (16)	0.96 (0.73–1.26)	—	—
Resistance pattern, *n* (%)					
MDR-TB	531/1015 (52)	283/733 (39)	Reference	Reference	Reference
Pre-XDR-TB	301/1015 (30)	262/733 (36)	1.63 (1.31–2.04)	2.18 (1.37–3.48)	1.98 (1.38–2.84)
XDR-TB	183/1015 (18)	188/733 (26)	1.93 (1.50–2.48)	2.76 (1.36–5.67)	3.23 (1.88–5.53)
Drug resistance, *n* (%)					
Injectable(s)	337/870 (39)	311/665 (47)	1.39 (1.13–1.71)	0.65 (0.37–1.14)	0.68 (0.43–1.06)
Fluroquinolone(s)	330/876 (38)	327/672 (49)	1.57 (1.28–1.92)	—	—
Bedaquiline	0/620 (0)	8/471 (1.7)	—	—	—
Delamanid	16/595 (2.7)	12/451 (2.7)	0.99 (0.45–2.10)	—	—
Linezolid	15/778 (1.9)	23/572 (4.0)	2.13 (1.11–4.21)	1.01 (0.31–3.33)	2.18 (0.78–6.05)

BMI, body mass index; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; MDR-TB, multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

[a] For complete case analysis, 1010 patients had no missing data in any variable.

[b] Multiple imputation by chained equations with 20 imputations. The method creates multiple imputations for missing data based on fully conditional specification (or sequential regression imputation), imputing one variable at a time, conditional on all the other variables in the data set. For categorical and binary variables, data were imputed using polytomous logistic and logistic regression.

[c] Psychiatric illnesses were diagnosed by a psychiatrist at the individual study sites according to ICD-10 diagnostic codes. The most prevalent illness was schizophrenia, but the definition also included other psychiatric diagnoses (anxiety, depression, bipolar disorder, among others).

[d] Defined as treatment with either cytostatics, TNF-alpha inhibitors, and/or corticosteroids.

[e] Protein levels were considered low if below 62 g/L in adults and below 57 g/L for children and adolescents (<18 years).

[f] Erythrocyte sedimentation rate was considered elevated if above 20 mm for females between 0 and 50 years and above 30 mm for females older than 50 years. For males older than 50 years, above 20 mm was considered elevated, and above 15 mm for younger males.

[g] Delamanid and pretomanid were equally considered part of a BPaL regimen.

[h] Group A drugs according to WHO: Bedaquiline, linezolid, levofloxacin, moxifloxacin [10].

explained by several factors: the urban population in Ukraine is presumably more committed to TB treatment, there are fewer problems with transportation, the standard of living is higher than in other regions, and anti-TB drugs are more accessible because all drugs and reagents are distributed from Kyiv.

We found that only 0.7% of all patients with tested isolates had bedaquiline resistance at time of diagnosis. Compared with neighbouring countries such as Moldova, where acquired bedaquiline drug resistance has been reported in as many as 15% of patients with MDR-TB [19], the prevalence was reassuringly low. Still, we did not have data on acquired drug resistance. Concerningly, 40% of patients with MDR-TB, and more than half of the patients with XDR-TB, were subjected to retreatment; a known factor driving emergence of drug resistance [20]. It is reasonable to expect

an increasing number of retreated patients who have been exposed to bedaquiline in the future, especially if access to TB services is disrupted [21,22]. Ultimately, bedaquiline resistance is likely increase in the years to come.

XDR-TB as a strong risk factor for an unsuccessful outcome is corroborated by findings from a previous Ukrainian study [5]. The strength of this association may be because of the long treatment duration, the many adverse effects related to historical treatment regimens, and the difficulties in eradicating the infection [23]. The substantial impact of XDR-TB on treatment outcomes highlights the urgency of implementing improved regimens, such as the all-oral short-course BPaL [7]. Several previous studies have also identified clinical factors, such as pre-XDR-/XDR-TB, smear positivity, and untreated HIV, as important predictors of an unsuccessful outcome in drug-resistant TB [2,4–6]. However, many of the risk factors identified in our study were related to, or influenced by, socioeconomic determinants, such as higher age, psychiatric illness, unemployment, alcohol misuse, malnutrition (low total protein considered as proxy), and previous incarceration. Thus, our results demonstrate that TB elimination requires significant efforts in targeting factors beyond effective treatment, particularly social and economic aspects of the disease. This was also highlighted by the recently published Reducing Activation of Tuberculosis by Improvement of Nutritional Status trial that demonstrated how simple nutritional supplementation dramatically reduces the incidence of TB among household contacts and improves outcomes by increasing adherence to treatment, reducing mortality, and decreasing treatment failure [24]. Another risk factor that often seems neglected in clinical practice is psychiatric illness. A recent study found that psychiatric illness was present in about one third of patients who were initiated on drug-resistant TB treatment [25]. Integration of psychiatric care into TB management yielded outcomes such as those achieved in patients without psychiatric illness [25]. Psychiatric illness has also been associated with a higher risk of TB [26]. In war-stricken countries, such as Ukraine, the mental health is undoubtedly impacted, and the burden of psychiatric illness may increase in the years to come [27]. Altogether, our results support that addressing mental health, nutritional status, and other social determinants is crucial in treatment of drug-resistant TB.

The study had limitations. Although many oblasts were included, there was not a complete national coverage. The absence of patients from certain regions may have skewed our results for better or worse. Still, considering that most oblasts were included in the cohort, the external validity of our results is presumably high within the context of Ukrainian patients with drug-resistant TB. Moreover, although many variables were reported for all patients, missing values may have resulted in bias. Nevertheless, most significant predictors in the adjusted model remained significant in the adjusted model with imputed data, indicating valid estimates. Finally, despite adjusting for many potential confounders, residual confounders could still have affected the results.

Conclusion

In the years leading up to the war in Ukraine, the overall success rate among Ukrainians with highly drug-resistant TB was 58%, a substantial improvement compared with previous years. The rate of success remains low for XDR-TB. The strongest risk factors for an unsuccessful outcome were XDR-TB, low total protein, psychiatric illness, age at TB diagnosis >65 years, and alcohol misuse, all resulting in 2–3-fold higher odds of an unsuccessful outcome. Our results demonstrate that addressing factors beyond effective treatment are crucial for achieving better outcomes, highlighting the importance of patient-centred care. Finally, although we found a low prevalence of bedaquiline resistance, it will most likely increase in the future. In perspective, considering the ongoing war, the achieved improvements in TB management in Ukraine are at risk of deteriorating. Going forward, comprehensive surveillance of highly drug-resistant TB management is warranted.

Author contributions

OSP: conceptualization, methodology, formal analysis, data curation, writing—original draft, writing. TB: investigation, writing—review and editing. VK: investigation, writing—review and editing. VM: investigation, writing—review and editing. MK: investigation, writing—review and editing. LH: investigation, writing—review and editing. SK: investigation, writing—review and editing. NB: investigation, writing—review and editing. OR: investigation, writing—review and editing. AF: investigation, writing—review and editing. AB: investigation, writing—review and editing. MT: investigation, writing—review and editing. OA: investigation, writing—review and editing. IK: investigation, writing—review and editing. OK: investigation, writing—review and editing. ZK: investigation, writing—review and editing. TS: investigation, writing—review and editing. NC: investigation, writing—review and editing. NK: investigation, writing—review and editing. OP: investigation, writing—review and editing. IS: investigation, writing—review and editing. MO: investigation, writing—review and editing. IM: investigation, writing—review and editing. LM: investigation, writing—review and editing. VS: investigation, writing—review and editing. VL: investigation, writing—review and editing. NH: investigation, writing—review and editing. LB: investigation, writing—review and editing. VH: investigation, writing—review and editing. VND: conceptualization, methodology, validation, formal analysis, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision, project administration, funding acquisition. DB: conceptualization, methodology, investigation, resources, writing—original draft, writing—review and editing, supervision, project administration.

Transparency declaration

VND is a member of the advisory board for Nordicinfu Care Denmark who distributes ARIKAYCE® (amikacin liposome inhalation suspension) for INSMED (outside of the scope of this work). All other authors declare no competing interests.

Funding

This research was supported by the grants from the National Institute of Allergy and Infectious Diseases/US Civilian Research & Development Foundation, CRDF Global (DAA9-19-66199), and the Ministry of Health of Ukraine (#0123100178). The study funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Data availability

Data can be made available on reasonable request.

Acknowledgements

We appreciate the valuable advice provided by statistician Nils Trolle Andersen from Biostatistical Research Unit at Department of Public Health, Aarhus University. The responsibility for and the interpretation of the analyses remains solely with the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.12.001.

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