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The effect of internal displacement due to armed conflict on tuberculosis treatment outcomes in northwest Syria, 2019–2020

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ABSTRACT

Background: Northwest Syria accounts for over 4 million people of whom more than half are internally displaced persons (IDPs). More than 1 million IDPs reside in camps and many more live in settings which are overcrowded and poorly ventilated. Suboptimal social living conditions leave these populations susceptible to tuberculosis (TB) morbidity and mortality. This study aimed to assess the effect of internal displacement due to armed conflict on the risk of unsuccessful treatment outcomes among TB patients in northwest Syria.
Methods: All patients registered to start TB treatment at three centres in northwest Syria between the 1st June 2019 to the 31st December 2020 were included. Unsuccessful TB treatment outcome was defined as a composite outcome combining the WHO TB treatment outcomes of treatment failure, loss to follow-up, and death. We assessed the association between internal displacement and unsuccessful TB treatment outcomes using multivariable logistic regression. We also explored the risk of an unsuccessful treatment outcome by internal displacement setting (camp, village or city).
Results: Of the total 737 registered patients included in the analysis, 400 (54%) were documented as internally displaced. The median age of IDPs was 30 (IQR: 21.5–48) and the median age of residents was 34 (IQR:22–50). A significantly higher percentage of those who were IDPs had an unsuccessful treatment outcome compared to residents (40% vs 18%, $p<0.001$). After adjustment for confounders, the relative risk of having unsuccessful TB treatment was two-fold higher in internally displaced TB patients compared to residents (95% CI: 1.5–2.6). IDPs living in villages had a 30% lower risk of an unsuccessful treatment outcome compared to IDPs living in camps (RR 95% CI: 0.50–0.91), and IDPs living in cities had a 13% lower risk of an unsuccessful treatment outcome (RR 95% CI: 0.57–1.18).
Conclusion: This is one of few studies which aims to quantify the effect of internal displacement on TB treatment outcomes during times of conflict. Our findings starkly highlight how social determinants contribute to poor TB outcomes and act as a starting point for much needed research on how best to manage TB in humanitarian crisis settings.

Introduction

Tuberculosis (TB), caused by the bacillus *Mycobacterium tuberculosis* (*M.tb*), is among the top ten causes of death worldwide despite significant progress in TB prevention and care in recent years. The World Health Organisation (WHO) estimated that there were globally 5.8 million new cases of TB and 1.3 million deaths from the disease in 2021 (Word Health Organization, 2020a). Any event which perturbs the fabric of society leading to mass population displacement will impact the TB epidemic through mechanisms which aid *M.tb* transmission or make hosts more vulnerable to TB disease, even in settings where TB has hitherto not been a major cause of morbidity or mortality (Njuki and Abera, 2018). Armed conflict leads to significant societal disruption and a significant proportion of the population being forcibly displaced. This results in mass movement of people relocating to camps, informal settlements or other underserved temporary shelters, where exposure to risk factors such as overcrowding, poor shelter, food insecurity, malnutrition and stress can increase the risk of *M.tb* exposure, infection

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and progression to disease (World Health Organization 2016; Nuzzo et al., 2015; Greenaway et al., 2011; Kimbrough et al., 2012). Health care disruption as result of attrition of health professionals, poor governance and funding, interrupted or inadequate access to diagnostics, lack of medications and suspension of disease surveillance, and delayed health service utilisation due to insecurity exacerbate the situation and derail TB prevention and care (Checchi et al., 2017). Despite recognition that these events potentially drive the development of multidrug-resistant TB (MDR TB), increase *M.tb* transmission and increase TB-related morbidity and mortality (Checchi et al., 2017; Ejeta et al., 2018; Dudnyk et al., 2015; Doğru and Döner, 2017), there is a paucity of evidence in the published literature in conflict settings.

Syria has one of the largest humanitarian and displacement crises worldwide due to the uprising in 2011 and the escalation into armed conflict by the summer of 2012 when the uprising was violently suppressed by the Syrian government. In 2023, approximately 15.3 million people are in need of humanitarian support (OCHA, 2023) and 6.8 million people were internally displaced, the highest figure due to armed conflict across the world in 2022. (IDMC, 2022) Pre-conflict, the national TB prevalence had declined from 85/100,000 in 1990 to 23/100, 000 in 2011. (Ismail et al., 2018) In 2017, the Syrian Ministry of Health (MoH) reported 3820 pulmonary TB cases (19 per 100,000) with 10% treatment failure. (World Health Organization, 2017) However, these figures are most likely to be an underestimate due to the collapse of the health system and associated TB surveillance since the start of the conflict. Other challenges include a lack of TB specialists in Syria pre-conflict, limited access to TB diagnostics and treatment, and difficulties transporting supplies due to security risks, multiple checkpoints and destruction of road infrastructure. (Abbara et al., 2020) There are no official figures from northwest Syria that we are aware of as this area remains largely under opposition control.

This study aims to investigate the association between internal displacement due to armed conflict and the risk of unsuccessful TB treatment outcomes among patients with drug-sensitive TB in northwest Syria. Unsuccessful TB treatment outcomes among internally displaced persons (IDPs) in different settings, such as within camps, villages, and cities, will also be explored.

Methods

Study design

This study was a retrospective cohort study of all eligible TB cases in the only three specialised TB facilities in northwest Syria, namely in Idlib city, Afrin, and Azaz, from June 1st 2019 to the December 31st 2020.

A conceptual framework outlining the relationship between internal displacement and TB treatment outcomes was developed by combining clinical and epidemiological evidence on TB and plausibility considerations (Fig. 1).

Study setting

After more than ten years of armed conflict, northwest Syria (Idleb and parts of Aleppo governorates) remains the only part of Syria in the hands of non-state actors. Several waves of IDPs have reached this area after fleeing their homes from different parts of Syria. This area is under permanent siege and access to surrounding areas is limited. Over 2.7 million people are estimated to be displaced in northwest Syria, with more than one million residing in 1302 IDP sites (UNHCR, 2021; OHCHR, 2022; UNHCR, 2020). The health system in northwest Syria is heavily disrupted due to systematic attacks on healthcare facilities, a shortage of resources, and loss of medical expertise (Ekzayez et al., 2020). In mid-2019, through coordination among humanitarian actors three specialised TB centres were set up in three different locations of northwest Syria (Idlib, Azaz and Afrin) (Fig. 2) to serve as referral facilities for all suspected TB patients (World Health Organization, 2021; Alashavi et al., 2021).

Study population

The study population for this analysis included: 1) all patients (residents and IDPs) with microbiologically confirmed or clinically diagnosed TB who were registered to receive care at one of the three specialised TB treatment facilities in northwest Syria; and 2) patients with a TB treatment outcome at 6 months for pulmonary TB (PTB) and/or lymph node TB, 9 months for extrapulmonary TB (EPTB) and/or spinal TB, and 12 months for central nervous system (CNS) or spinal TB with cord involvement. TB patients found to have any confirmed TB drug resistance at treatment initiation were excluded from the study.

Variables

The exposure of interest was internal displacement due to armed conflict. The outcome variable was a binary variable defined as unsuccessful treatment outcome. This was a composite variable and included treatment failure, loss to follow-up (LTFU) and death, all of which individually constitute an unsuccessful treatment outcome. Standardised WHO definitions were used to define a TB case, TB classification and treatment outcome categories (World Health Organization, 2020b).

The following demographic and clinical variables were collected: gender, age, residency setting (rural or urban), displacement setting (camp, village or city), education level, socioeconomic status (poor or middle-income, as defined by the World Bank definitions of $2.15 and

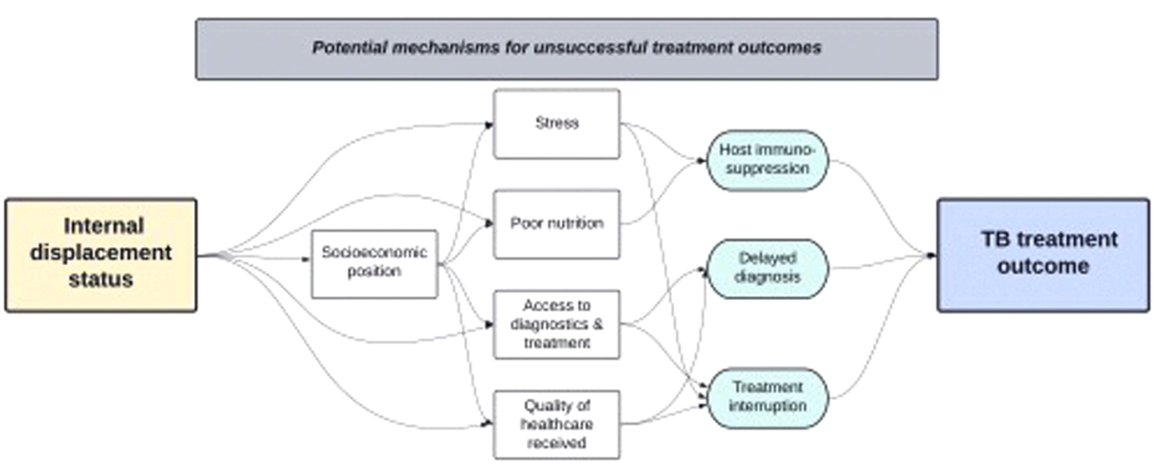

Fig. 1. Conceptual framework of the association between forced displacement and unsuccessful TB treatment.

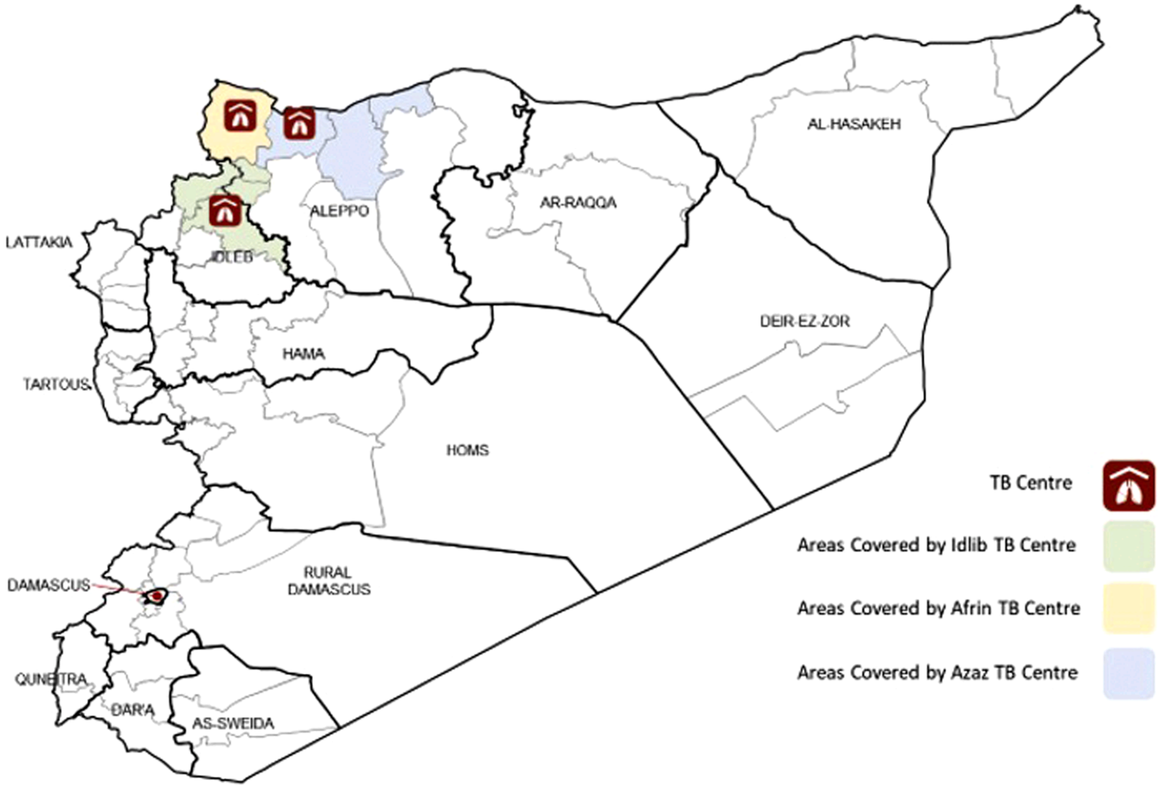

Fig. 2. Map of TB centre locations in northwest Syria.

$3.65 per person per day respectively (The World Bank ,2022)), smoking status, TB classification by site of disease (PTB and/or EPTB), TB classification by diagnostic category (smear or culture-status), treatment history (new or retreatment), and treatment unit (Idlib, Afran, Azaz).

Data sources and management

Data used in this study were collected as part of the TB program in northwest Syria which was established in 2019. Data collection tools for the TB program monitoring were developed by the non-governmental organisations (NGOs) Syria Relief and Development (SRD), Hand and Hand for Aid and Developement (HIHfAD) and Bahar who were operating in the area under the supervision of the WHO. Demographic and clinical data were extracted from patient registers in the three TB facilities by a trained data clerk under the direction of the medical officer in each area. To ensure data quality during data collection, the data clerk and field health officer in the three facilities received training and data were checked regularly by project team. The extracted data were entered into a data collection system and then imported into Microsoft Excel. All participant data were anonymised in the dataset through unique patient IDs known only to clinical staff.

Data were checked, cleaned, and exported to Stata version 16 (Stata Corp, College Station, TX, USA) (Stata, 2022) for data management and analysis.

Statistical approach

Data on demographic and clinical characteristics were summarised with standard descriptive statistics. We used a mixed effect logistic regression model to analyse the association between internal displacement status and unsuccessful TB treatment outcome with a random intercept to account for clustering at the treatment unit (primary analysis). All *p*-values of the logistic regression models were generated by likelihood ratio tests.

A priori confounders included age, gender, education level, and residency setting. Supplementary Figure S1 outlines the directed acyclic graph underpinning the analysis (Tennant et al., 2021). We did not include socioeconomic status as a confounder as this variable was only measured at the time of TB treatment initiation through a direct question on the total monthly income of the patient and their family income. It is therefore on the causal pathway rather than a confounder of the association of interest.

We conducted a secondary analysis in which we restricted the analysis to IDPs. The exposure variable was stratified into three categories to reflect the internal displacement setting, i.e., living in a camp, village or city as an IDP.

For ease of interpretation, results of mixed effects logistic regression models were presented as predicted probabilities of unsuccessful TB treatment outcomes with 95% confidence intervals (CIs) and relative risk (RR) using marginal standardisation methods. The predicted probability of an unsuccessful TB treatment outcome is adjusted to a weighted average reflecting the confounder distribution in the total population (Muller and Maclehose, 2014). All analyses were undertaken using Stata Statistical Software, version 16; StataCorp, College Station, TX (Stata, 2022).

Ethical approval

The study was approved by the ethics committee of the London School of Hygiene and Tropical Medicine (Ref: 26002). Ethics approval was also obtained from the Syrian MoH and Syrian Interim Government (Ref:102). Authorising permissions were obtained from the NGOs managing the specialised TB centres (Syria Relief and Development, Hand and Hand for Aid and Development, and Bahar) to use patient data for this study under the condition of anonymising all patients' names.

Results

Study population

From the 1st of June 2019 to 31st of December 2020, a total of 753 TB cases were registered. Drug resistance was detected in 16 cases, of which 12 (75%) were IDPs, and were excluded from the analysis. Therefore 737 patients were included in the final analysis (Fig. 3). There were 435 (57.8%) TB cases reported from Idlib centre, 214 (28.4%) from Azaz centre and 104 (13.8%) from Afrin centre. Supplementary Figure S2 demonstrates the trends in notified TB cases across the three TB centres in northwest Syria between 2019 and 2020.

Demographic and clinical characteristics

Demographic and clinical characteristics of IDPs and residents are shown in Table 1. The male to female ratio of the IDP population was higher than the resident population, 1.3:1 compared to 1:1 respectively. The median age of IDPs was 30 (IQR: 21.5–48) and the median age of residents was 34 (IQR:22–50). Over 80% of IDPs were residing in rural areas compared to 62% of residents. Only 16.5% of the IDP population had an education level of secondary school and above compared to 48.1% of residents. Self-reported smoking was higher among IDPs (41.2%) compared to residents (29.1%).

Most of the TB cases amongst IDPs and residents were reported to be new (86.7%). PTB accounted for the majority of the overall number of TB cases (60.1%) and was more frequently reported among IDPs (63.5%) compared to residents (56.1%). The proportion of cases with clinically diagnosed PTB was similar among IDPs (27.2%) and residents (27.9%), while microbiologically confirmed PTB cases were higher in IDPs (36.3%) than residents (28.2%).

TB treatment outcomes

TB treatment outcomes amongst IDPs and residents are summarised in Table 2. The overall proportion of successful TB treatment outcomes among IDPs and residents was 70%. The proportion of unsuccessful treatment outcomes (treatment failed, died or LTFU) was higher amongst IDPs (40.1%) compared to residents (17.3%). LTFU contributed the most to the composite unsuccessful treatment outcome for both IDPs and residents (74.7%: 162/217). The proportion of patients who died was higher in the IDP population compared to residents, 6.7% versus 3.6% respectively. A comparison of TB treatment outcomes by TB treatment centre is shown in supplementary Table S1.

Our analysis was focused on the primary question of whether internal displacement status is associated with an unsuccessful TB treatment outcome, however the crude association of individual demographic and clinical characteristics with unsuccessful TB treatment outcome are shown in supplementary Table S2. There was no significant difference in unsuccessful treatment outcome between males and females. Patients aged more than or equal to 60 years were more likely to have an unsuccessful treatment outcome as compared to the youngest age group. TB patients who lived in urban areas, with higher education level and higher socioeconomic status at the time of treatment initiation were less likely to have an unsuccessful treatment outcome.

Association of internal displacement and treatment outcome

The multivariable analysis of the association between internal displacement status and unsuccessful treatment outcome is presented in Table 3. After adjustment for age, gender, education status and residency setting, the predicted probability of an unsuccessful outcome in residents was 0.19 compared to 0.38 in those who were internally displaced at the time of treatment initiation. The adjusted relative risk of having an unsuccessful TB treatment was two-fold higher in patients who were internally displaced compared to residents (RR 2.02; 95% CI: 1.5–2.6). The output from the mixed effect logistic regression models used to estimate marginal predicted probabilities are shown in supplementary Table S3.

Table 4 shows the secondary analysis which was restricted to the IDP population. The exposure of interest for this analysis was categorised according to whether the IDP lived in a camp, village or city. The final model adjusted for age, gender and education status indicated that IDPs living in villages had a 30% lower risk of an unsuccessful treatment outcome compared to IDPs living in camps (RR 95% CI: 0.50–0.91). IDPs living in cities had a 13% lower risk of an unsuccessful treatment outcome (RR 95% CI: 0.57–1.18), although the 95% confidence interval included 1. Mixed effect logistic regression models used to estimate marginal predicted probabilities for this analysis are shown in supplementary Table S4.

Discussion

Few studies conducted in similar conflict settings have investigated the association of TB treatment outcomes with displacement status. This is the first epidemiological study assessing this relationship in northwest Syria, a highly challenging context with active conflict for over eleven years. Our study demonstrated evidence for a potential causal

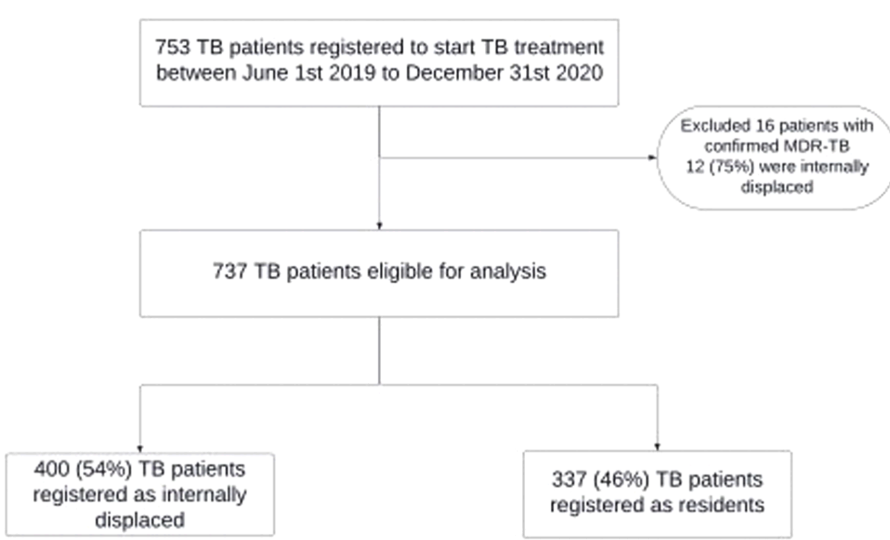

Fig. 3. Study flowchart.

Table 1
Demographic and clinical characteristics of registered TB cases in Idlib, Azaz, and Afrin TB units, northwest Syria, 2019–2020.

Characteristics at time of TB diagnosis	IDPs n (%)	Residents n (%)	Total n (%)
TB cases	400 (54.27)	337 (45.73)	737 (100)
Gender			
Male	222 (55.5)	168 (49.9)	390 (52.9)
Female	178 (44.5)	169 (50.1)	347 (47.1)
Age group (years)			
<15	28 (7)	20 (5.9)	48 (6.5)
15–29	154 (38.5)	124 (36.4)	276 (37.5)
30–44	103 (25.8)	87 (25.5)	188 (25.5)
45–59	61 (15.2)	60 (17.6)	121 (16.4)
> = 60	54 (13.5)	50 (14.7)	104 (14.1)
Residency setting			
Rural	337 (84.2)	208 (61.7)	545 (74)
Urban	63 (15.8)	129 (38.3)	192 (26)
Displacement setting			
Camp	209 (52.2)	–	–
Village	128 (32)	–	–
City	63 (15.8)	–	–
Education level			
None/primary school	334 (83.5)	175 (51.9)	509 (69.1)
Secondary school & above	66 (16.5)	162 (48.1)	228 (30.9)
Socioeconomic status			
Poor	368 (92)	221 (65.6)	589 (79.9)
Middle-income	32 (8)	116 (34.4)	148 (20.1)
Smoking status			
No	235 (58.8)	239 (70.9)	474 (64.3)
Yes	165 (41.2)	98 (29.1)	263 (35.7)
TB classification by site of disease.			
Pulmonary tuberculosis (PTB)	254 (63.5)	189 (56.1)	443 (60.1)
Extrapulmonary tuberculosis (EPTB)	146 (36.5)	148 (43.9)	294 (39.9)
TB classification by diagnostic category			
Microbiologically confirmed PTB[a]	145 (36.3)	95 (28.2)	240 (32.6)
Clinically diagnosed PTB[b]	109 (27.2)	94 (27.9)	203 (27.5)
EPTB[c]	146 (36.5)	148 (43.9)	294 (39.9)
EPTB site			
Lymph nodes	61 (41.8)	71 (48)	132 (44.9)
Pleura	28 (19.2)	37 (25)	65 (22.1)
Abdomen	13 (8.9)	10 (6.7)	23 (7.8)
Bone	15 (10.2)	8 (5.4)	23 (7.8)
Others[d]	29 (19.9)	22 (14.9)	51 (17.4)
TB classification by treatment history			
New	342(85.5)	297 (88.2)	639 (86.7)
Retreated[e]	19(4.7)	17 (5)	36 (4.9)
Referral (transfer in)	39(9.8)	23(6.8)	62 (8.4)
Treatment unit			
Idlib	228 (57)	201 (59.6)	439 (58.2)
Azaz	126 (31.5)	78 (23.2)	204(27.7)
Afrin	46 (11.5)	58 (17.2)	104 (14.1)

[a] Smear or culture-positive PTB.
[b] Clinically diagnosed PTB, including smear-negative PTB and pulmonary smear unknown/not done.
[c] EPTB microbiologically confirmed or clinically diagnosed.
[d] Other TB sites such as breast, skin, muscle, meninges, and genitourinary tract.
[e] Retreated includes treatment after failure, LTFU or relapse.

Table 2
TB treatment outcomes among IDPs and residents.

TB Treatment outcomes	IDPs n (%)	Residents n (%)	Total n (%)
Total cases	400 (54.3)	337 (45.7)	737 (100)
Successful treatment	238 (59.9)	278 (82.7)	516 (70.4)
Cured	25 (6.2)	43 (12.8)	68 (9.2)
Treatment completed	213 (53.2)	235(69.7)	448 (60.8)
Unsuccessful treatment	159 (40.1)	58 (17.3)	217 (29.6)
Treatment failed	13 (3.2)	3 (0.9)	16 (2.2)
Died	27 (6.7)	12 (3.6)	39 (53.0)
Loss to follow-up	119 (29.7)	43 (12.8)	162(22.0)
Not evaluated	3 (0.4)	1 (0.2)	4 (0.5)

association between internal displacement due to armed conflict and risk of having an unsuccessful treatment outcome among TB patients registered in northwest Syria between 2019 and 2020.

After controlling for age, gender, residency setting (rural, urban), and education status, the relative risk of having unsuccessful TB treatment was 2-fold higher in TB patients who were internally displaced compared to residents (RR 95% CI: 1.5–2.6). Of the TB patients defined as IDPs, living in a village setting had a 30% lower risk of an unsuccessful treatment outcome compared to IDPs residing in camps (RR 95% CI: 0.50–0.91). IDPs living in cities had a 13% lower risk of an unsuccessful treatment outcome (RR 95% CI: 0.57–1.18). The finding that the overall proportion of successful TB treatment outcomes among IDPs and residents was 70% highlights how affected TB care has been in this setting as it is much lower than global target of >90% and lower than the proportion found in a similar context (Word Health Organization, 2020a; Muller and Maclehose, 2014).

The results from our study are consistent with other settings including Ethiopia, Sudan, and Pakistan which have shown that displaced patients living in camps are more likely to have unsuccessful TB treatment outcomes than residents living in cities or villages (Ejet et al., 2018; Khan et al., 2021; Legesse et al., 2021a, 2021b; Gele and Bjune, 2010). Our study also highlighted that LTFU contributed the most to an unsuccessful treatment outcome among both IDPs and residents, although the proportion of LTFU was nearly 30% compared to 13% respectively. This finding of a higher LTFU in IDPs is expected as almost half of the displaced population in northwest Syria has experienced displacement more than once (OHCHR, 2022). Reducing LTFU is a key area for quality improvement in all TB programmes (Arsenault et al., 2019), but is especially pertinent in conflict settings and should be at the forefront of policy-making to improve TB treatment outcomes in these populations. Implementation research on how best to reduce LTFU in situations with unstable and dynamic population movement is urgently needed as the standard interventions such as health education through community health workers, electronic networks and efficient follow-up systems, referral services and treatment support programmes require significant infrastructure which are usually drastically reduced in complex crisis settings.

Next steps include untangling the mechanisms of how internal displacement due to armed conflict increases the risk of unsuccessful TB treatment among IDPs to be able to implement mitigating interventions. The more frequent occurrence of microbiologically confirmed PTB among IDPs than among residents may point to delayed diagnosis and/or increased disease severity among IDPs. Ongoing attacks on health facilities in north Syria are likely to have deterred attendance to healthcare facilities and healthcare-seeking for non-life-threatening conditions. Persistent stigma and poor understanding of TB may also have contributed to delayed treatment seeking, particularly among IDPs living in villages and cities (Abbara et al., 2020). Severe poverty among the displaced population due to an economic collapse, lack of job opportunities and loss of income sources (land, factories, governmental jobs, and agriculture) may also have led to inadequate nutritional intake, which results in weakened immunity and increased vulnerability to TB morbidity and mortality. Furthermore, displaced TB patients are at high risk of developing mental health disorders, particularly anxiety, depression and post-traumatic stress. Mental health disorders are known to reduce treatment adherence and delay treatment-seeking (Abbara et al., 2020).

Despite the importance of these data there are limitations to our findings. These include retrospective data collection with limited resources, which may have impacted data quality. Despite efforts to ensure data validity, there was a high turnover rate among staff which could have negatively impacted quality. No data were collected about the change of displacement status during the treatment period and we also did not consider the number of times displacement had occurred nor the duration of displacement. Furthermore, other potential confounders associated with unsuccessful treatment outcomes, such as diagnostic

Table 3
The association between internal displacement and unsuccessful TB treatment outcome.

Exposure	Unadjusted analysis $N = 737$			Adjusted analysis $N = 737$ Adjusted for age, gender, education status, and residency setting (urban or rural)		
	Marginal predicted probability (95% CI)	Crude relative risk (95% CI)	*p*-value	Marginal predicted probability (95% CI)	Adjusted relative risk (95% CI)	*p*-value
Residents	0.18 (0.13–0.22)	reference		0.19 (0.14–0.23)	reference	
IDPs	0.40 (0.35–0.45)	2.27 (1.67- 2.86)	<0.001	0.38 (0.33–0.43)	2.02 (1.47–2.59)	<0.001

Table 4
The association between internal displacement by setting and unsuccessful TB treatment outcome.

IDPs by displacement setting	Unadjusted analysis $N = 400$			Adjusted analysis $N = 400$ Adjusted for age, gender, and education status		
	Marginal predicted probability (95% CI)	Crude relative risk (95% CI)	*p*-value	Marginal predicted probability (95% CI)	Adjusted relative risk (95% CI)	*p*-value
Camp $N = 209$	0.45 (0.39–0.52)	reference		0.45 (0.38–0.52)	reference	
Village $N = 128$	0.31 (0.23–0.39)	0.69 (0.48–0.89)	0.002	0.32 (0.24–0.40)	0.70 (0.50–0.91)	0.004
City $N = 63$	0.39 (0.26–0.51)	0.85 (0.56–0.1.15)	0.32	0.39 (0.27–0.52)	0.87 (0.57–1.18)	0.41

delay, occupation, other co-morbidities, treatment adherence and medication side effects, and distance to TB centre were not included as data were not available resulting in residual confounding.

Conclusion

Our study showed evidence of a strong association between internal displacement status due to armed conflict and the risk of having unsuccessful treatment among TB patients in northwest Syria. These data are essential to alert policy makers, NGOs, donors, and health authorities to the problem in order to motivate for better TB prevention and care for affected populations. Failure to address suboptimal TB prevention and care during the Syrian conflict will affect the current and future control of TB in Syria with potential consequences beyond the borders through refugee movements. Our findings starkly highlight how social determinants contribute to poor TB treatment outcomes and act as a starting point for much needed research on how best to manage TB in humanitarian crisis settings.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jmh.2023.100195.

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