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Review

Tuberculosis outcomes among international migrants living in Europe compared with the nonmigrant population: A systematic review and meta-analysis

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ABSTRACT

Objectives: Migration status refers to socioeconomic factors that challenge access to the health care system and increase the risk of developing tuberculosis (TB) with worse outcomes. This systematic review and meta-analysis aimed to investigate the outcomes of TB among international migrants arriving in Europe compared with the nonmigrant population.

Methods: A systematic review and meta-analysis were conducted to identify studies investigating TB-related outcomes among migrants and nonmigrants in Europe. Six investigators searched PubMed, Scopus, and Web of Science from inception to March 2024 and screened the abstracts of potentially eligible articles. Studies reporting TB-related outcomes in both migrants and nonmigrants were also included. Studies with migrant definitions other than the one from the inclusion criteria, with no control group, and with no discernible data, including nonhuman samples or written in a non-English language, were excluded. Data were reported as relative risks (RRs) or odds ratios with their 95% confidence intervals (CIs). The risk of bias was assessed using the Newcastle–Ottawa Scale (PROSPERO Registration number: CRD42024529629).

Results: Of the 1,109 papers screened, 34 were included, consisting of 601,293 participants (459,670 nonmigrants and 141,623 migrants). The meta-analysis, adjusted for potential confounders, showed that migrants presented a lower mortality risk (RR = 0.391, 95% CI: 0.276-0.554; P <0.0001; I^2 = 71.6%), a lower rate of treatment completion (RR = 0.313; 95% CI: 0.163-0.600; P <0.0001), and a higher rate of loss to follow-up (RR = 4.331, 95% CI: 1.542-12.163, P = 0.005; I^2 = 55.8%). Treatment success, cure, not evaluated, and sustained treatment success showed no significant differences between migrants and nonmigrants. No adjusted analyses could be performed for cure, not evaluated, and sustained treatment success. Only three studies had a high risk of bias.

Conclusions: Migrants living in Europe have lower mortality rates; however, TB management is affected by a higher risk of loss to follow-up and discontinuation. Therefore, migrant-targeted TB care is necessary to improve the fight against TB in Europe.

Introduction

Migrants represent a fundamental target in the fight against tuberculosis (TB) [1]. Endemic exposure, vaccination status, and predisposing conditions, such as HIV seroprevalence and nutritional status, are more commonly encountered among people from different geographic areas [2,3]. However, these factors alone cannot fully explain the higher incidence of TB in the migrant population.

The identification of TB as a syndemic underscores the role of social determinants in TB outcomes [4]. From this perspective, migrants are generally included among vulnerable categories, alongside people experiencing homelessness, incarcerated people, and people living with

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drug/alcohol dependency [5]. Scientific literature acknowledges that migration status is closely linked to social barriers to health care, as well as unhealthy and challenging living conditions. In addition, language barriers and different cultural perspectives contribute to further difficulties [6]. The recurrent need to renew residence and job permits also affects access to the welfare state [7].

An interesting issue is that the migration flow towards Europe is characterized by people moving from low-middle-income countries (LMICs) to high-income countries (HICs). This transition implies not only a change in medical resource settings but also a shift from high-burden to low-burden TB contexts. In 2023, the average incidence of TB in Europe was 24 cases per 100,000 inhabitants. Conversely, the African, Southeast Asian, and Eastern Mediterranean regions show significantly higher incidences (206, 234, and 116 cases per 100,000 inhabitants, respectively) [8]. These regions include many of the most common countries of origin involved in the migration phenomenon in Europe [9]. In support of this, the TB diagnostic rate among foreign-born individuals is 33.3% [10]. Interestingly, in recent decades, the percentage of TB diagnoses among people of foreign origin in the European Union and European Economic Area (EU/EEA) has increased from 28 to 33.3% [11], whereas the general trend has decreased by 5.5% [10]. In addition, the authors noted that access to health care for migrants varies among different European countries and that collective efforts are needed in this area [12]. The challenges faced by migrants in HICs are complex and include basic material needs, bureaucratic issues, and psychological stress stemming from the residual effects of travel-related violence and abuse, as well as the influence of anti-immigrant movements in host countries [7].

Given this context, the phenomenon of migration can be examined through the lens of the latest document by the World Health Organization (WHO) on TB outcome definitions [13]. According to the 2020 revised guidelines, TB treatment outcomes are categorized as either successful or unsuccessful, with the latter including patients who are lost to follow-up (LTFU). This outcome highlights a critical issue: Physicians frequently encounter challenges in ensuring that patients complete their treatment regimen [14].

Investigating the outcomes of TB can help assess the preparedness of health care systems to address the interactions between social determinants and diseases. Specifically, we aim to investigate TB outcomes among one of the most representative categories in public health and social studies' influence on clinical medicine: migrants [15].

With this systematic review and meta-analysis, we aimed to explore TB-related outcomes between migrants and nonmigrants living in European countries.

Materials and methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under CRD42024529629. The protocol can be consulted at the following link PROSPERO (york.ac.uk) using the indicated registration number. The revised 2020 PRISMA guidelines were followed for this study [16]. The data are available and can be requested from the corresponding author. The PRISMA checklist is presented in Supplementary Table 1 and Supplementary Table 2.

Search strategy

The study protocol was registered on March 28, 2024. Six investigators, in pairs, independently searched PubMed, Web of Science, and Embase for studies on migration as a potential risk factor for unfavorable outcomes in migrants living in Europe affected by TB. The detailed search strategy for each database is shown in Supplementary Table 3. This search was conducted until March 28, 2024 and included articles from the databases' inception. Finally, we manually searched for eligible articles in reviews pertinent to the topic as well as in the papers included in this systematic review.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (i) data collected from observational (i.e., longitudinal or retrospective) studies; (ii) investigate WHO-endorsed outcomes [11] in migrants (any individual residing in the EU/EEA but born outside of the country where the study was conducted or any individual recorded as migrant in the EU/EEA or any second-generation individual, meant as any individual born in a country where at least one of the parent entered as a migrant, regardless his/her citizenship) affected by TB, regardless of age; (iii) studies conducted in Europe, meant as any countries included in the EEA or in the United Kingdom; (iv) had at least one control group of nonmigrants in a European country; and (v) studies written in English. Articles were excluded if: (i) they did not include a control group of nonmigrant people; (ii) studies with no clearly identifiable migrant population, or in which the definition of a migrant conflicted with our own (e.g., defining migrant status on the basis of ethnicity); (iii) studies with nonhuman samples and animal models; and (iv) articles were reviews, letters, *in vivo* or *in vitro* experiments, commentaries, posters, or case reports. Titles and abstracts were screened by six independent researchers in pairs, using the Rayyan Web app for systematic reviews. Any inconsistencies were resolved by consensus with the senior author.

Data extraction

Each article was screened for eligibility first by title and abstract, followed by a full-text assessment. Both screening phases were conducted in pairs with two junior researchers (RP, LF, CP, GD, VG, and SC) independently evaluating the articles for inclusion. Any conflicts were resolved by consensus with the senior researchers (FVS, FDG, and NV). Titles and abstracts were screened using the Rayyan web app for systematic reviews. Any inconsistencies were resolved by consensus with the senior author (NV).

The extracted data included the first author's name, publication date, country in which the study was conducted, participant age, percentage of females, study design, sample size, region of origin, percentage of multidrug resistance/rifampicin resistance (*Mycobacterium tuberculosis* strains showing resistance to rifampicin, isoniazid, and other second-line drugs) [17], HIV-positive status, and the presence of extrapulmonary forms of TB. The confounders used in the multivariate analyses (if any) and data on the outcomes of interest were also collected (RP, LF, CP, GD, VG, and SC). The data were extracted using a structured REDCap form (RP, LF, CP, GD, VG, and SC). Data extraction was revised by an additional researcher, (SC) and disagreements between the members of the pairs were resolved by three independent authors (NV, FDG, and FVS).

Risk of bias

Quality assessment of the studies was conducted by a data extraction supervisor (SC) in pairs, using the Newcastle–Ottawa Scale. This scale assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome. Consistent with previous works using Newcastle–Ottawa Scale grading, we classified studies as having a high risk of bias (<5 stars), moderate risk of bias (5-7 stars), or low risk of bias (≥8 stars). A senior author (FVS) was available to resolve any discrepancies.

Outcomes

The outcomes of our systematic review were as follows: (i) mortality, (ii) treatment failure, (iii) cure, (iv) treatment completion, (v) LTFU,

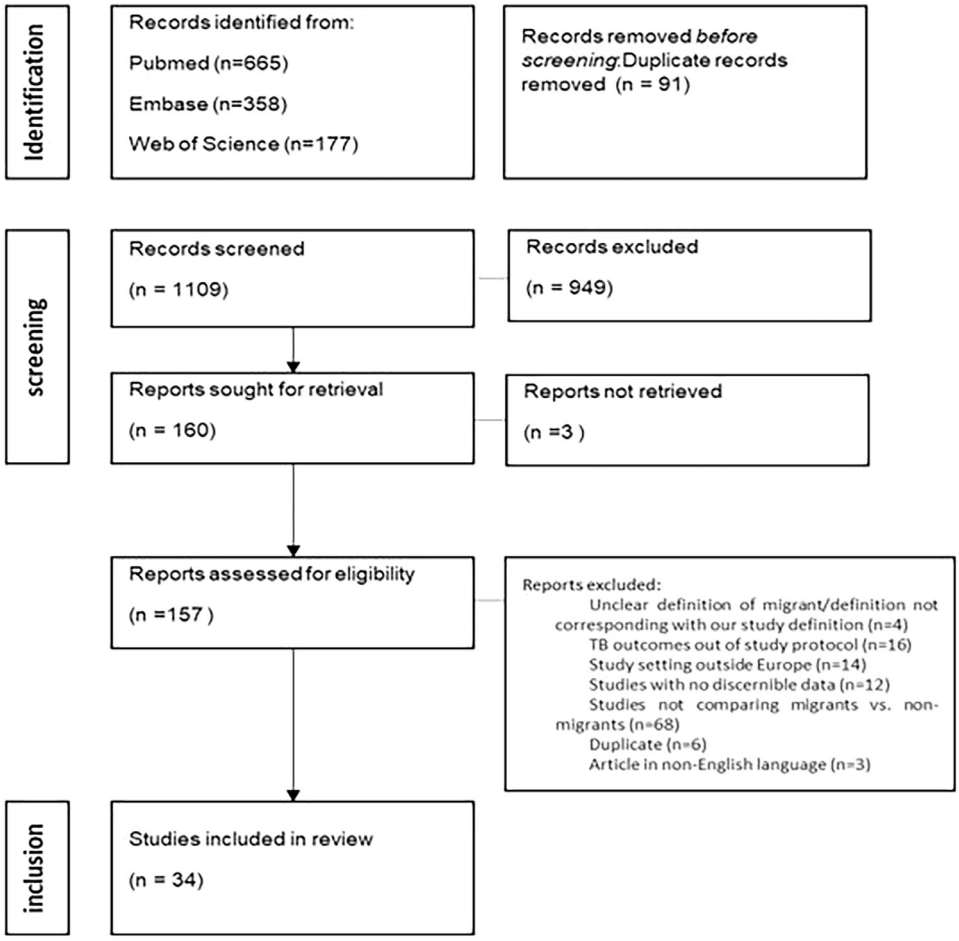

Figure 1. PRISMA flowchart.

(vi) treatment success, (vii) sustained treatment success, and (viii) not evaluated.

The outcome definition is adopted from the latest updated WHO definition [13] and is defined as follows:

- Mortality: Patients who died before starting treatment or during the course of treatment.
- Treatment failure: A patient whose treatment regimen needs to be terminated or permanently changed to a new regimen or treatment strategy.
- Cured: Patients with pulmonary TB with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriologic response and no evidence of failure.
- Treatment completion: A patient who completed treatment as recommended by the national policy, whose outcome does not meet the definition of cure or treatment failure.
- LTFU: A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
- Treatment success: The sum of cured and treatment completed.
- Sustained treatment success: An individual assessed at 6 months (for drug-susceptible TB and drug-resistant TB) and at 12 months (for drug-resistant TB only) after successful TB treatment who is alive and free of TB.
- Not evaluated: A patient with TB for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit, as well as cases for whom the treatment outcome is unknown to the reporting unit.

Statistical analysis

The outcomes of interest were treated using the cumulative incidence for dichotomous variables (raw data) and relative risks (RRs) reported in the original studies adjusted for the largest number of factors available. The extracted data were meta-analyzed using pooled RRs with their 95% confidence intervals (CIs). In all analyses, random-effects models were applied because of anticipated clinical heterogeneity. In the case of zero events in the unadjusted analysis, a continuity correction (0.5) was used.

Statistical heterogeneity was assessed using the I^2, categorized as low (30-49%), moderate (50-74%), or high (≥75%). For all outcomes, publication bias was assessed by visually inspecting funnel plots and the Egger bias test; in the case of publication bias, a fill and trim analysis was planned. All analyses were performed using STATA/MP 14.0 and MedCalc Version 22.016, considering a *P*-value of <0.05 as statistically significant.

Results

Figure 1 shows the literature search for this systematic review. Of the 1,109 articles initially considered, 157 were examined. Of these, 123 were excluded mainly because they did not compare migrants vs nonmigrants (n = 68) or because they were conducted in non-European countries (n = 14), TB outcomes were out of the study protocol (n = 16), had unclear definitions of migrants, did not correspond with our study definition (n = 4), were published in a non-English language (n = 3), had no discernible data (n = 12), or were duplicates (n = 6). A list of excluded articles with specific reasons for exclusion is provided in Supplemen-

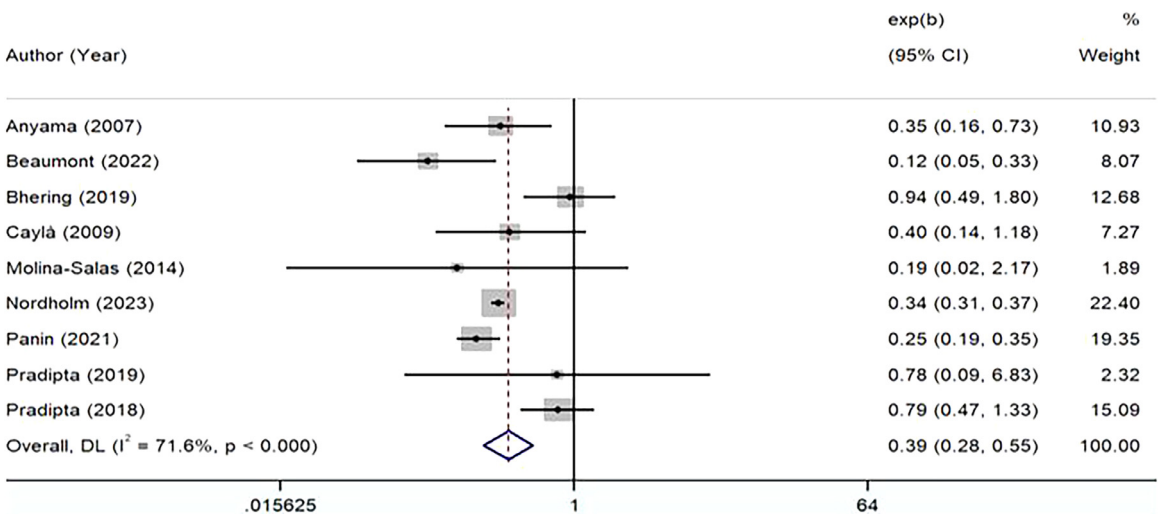

Figure 2. Adjusted result for mortality.
Note: weights are from random-effects model
CI, confidence interval.

tary Table 4. Finally, 34 full-text articles were included in this systematic review. The entire list of references is presented in Supplementary Table 5.

Supplementary Table 6 shows the primary characteristics of the included studies. Overall, 34 studies included 601,293 people (459,670 nonmigrants compared with 141,623 migrants), with a mean age of 41.3 years (SD = 18.7), and 62.2% were males. Italy (n = 10) was the most frequent European country in terms of studies conducted, followed by Spain (n = 5). Extrapulmonary forms of TB were present in 38.9%of the participants. We observed the presence of multidrug-resistant forms of TB in 19.1% of the participants. Patients with HIV represented 12.6% of the participants included. Finally, where available, the analyses were adjusted for the mean of four potential confounders (Supplementary Table 7).

Table 1 presents the main analyses of the systematic review. When considering mortality, compared with nonmigrants, migrants experienced a significantly lower risk of this outcome in unadjusted (n = 24 studies, 455,619 participants; RR = 0.069, 95% CI: 0.026-0.184; P <0.0001; I^2 = 87.1%) and adjusted analyses (n = 9 studies, 29,642 participants; RR = 0.391, 95% CI: 0.276-0.554; P <0.0001; I^2 = 71.6%; Figure 2 and Supplementary Figure 1a). No outcomes were affected by publication bias. Conversely, migrants did not report any significant differences in treatment failure or cure in either the unadjusted or adjusted analyses (Figure 3 and Supplementary Figure 1b-1c).

In nine studies, we did not observe any difference between nonmigrants and migrants in terms of treatment completion in the unadjusted analyses (Supplementary Figure 1d), whereas in one study that included 503 patients, migrants reported a lower rate of treatment completion in the adjusted analyses (RR = 0.313; 95% CI: 0.163-0.600; P <0.0001).

The rate of LTFU was significantly higher in migrants than in nonmigrants in the nonadjusted (n = 12 studies, 455,598 patients; RR = 2.122, 95% CI: 1.414-3.184, P <0.0001; I^2 = 94%; Supplementary Figure 1e) and adjusted analyses (n = 3 studies, 986 patients; RR = 4.331, 95% CI: 1.542-12.163, P = 0.005; I^2 = 55.8%; Figure 4). The first outcome was affected by publication bias. The trim-and-fill analysis indicated a nonstatistically significant result after trimming six studies to the left of the mean.

Finally, no significant differences emerged between migrants and nonmigrants in terms of treatment success, not evaluated, and sustained treatment success in the unadjusted analysis (Supplementary Figure 1f-g). In four studies, the adjusted analyses did not show any significant differences in terms of treatment success (Supplementary Figure 2).

Supplementary Table 8 shows the evaluation of the risk of bias in the included studies. Overall, three studies had a high risk of bias (<5 stars), 11 had a moderate risk of bias (5-7 stars), and the remaining studies had a low risk of bias (≥8 stars). Representativeness of the exposed cohort was the most frequent source of bias.

Discussion

This systematic review and meta-analysis investigated the differences in TB outcomes between migrants and nonmigrants in Europe. Our findings indicate that migrants are at an increased risk of LTFU and treatment discontinuation. Conversely, the risk of mortality decreases.

In contrast, a meta-analysis conducted by Nellums et al. [18] reported no differences in TB outcomes between migrants and nonmigrants. Their study is similar to our study, although their measured outcome is overall “treatment adherence” as a proxy for general TB outcomes. Furthermore, Nellums et al. [18] focused on multidrug-resistant TB and suggested that outcomes improve in situations requiring more intensive care and engagement. Indeed, the authors found that the rate of nonadherence among migrants in their meta-analysis dropped from 20% to 11% when only LTFU and discontinued treatment were included. This suggests that treatment failure depends on the challenging conditions posed by multidrug-resistant TB rather than the patients’ predisposition to treatment adherence.

This highlights the pivotal role of LTFU among migrants. A systematic review by Lin et al. [19] assessed the risk factors for treatment adherence failure among migrants and found that irregular legal status and social factors reduced treatment adherence. It is evident that precarious living conditions represent a major barrier to health care access, significantly affecting the ability to follow up with migrant patients and prevent treatment discontinuation [15]. Consistent with this finding, our study highlights a significantly higher risk of LTFU and treatment discontinuation among migrants.

Notably, Nellums et al. [18] did not include mortality data in their study. In our study, mortality is the only outcome that favors migrants over nonmigrants. A more detailed evaluation of the included studies may provide a more detailed explanation. The lower mortality risk may be related to the differences between migrant and nonmigrant populations. Studies by Ködmön et al. and Kuehne et al. showed that the migrant population was consistently younger than the nonmigrant population. In addition, Nordholm et al. and Panin et al., who included approximately 20,000 patients from our study population, reported a

Table 1
Association between migration and outcomes of interest in people with tuberculosis in Europe.

Outcome[a]	Raw data							Adjusted data						
	Number of studies	Sample size	RR	95% CI	*P*-value	I^2	Publication bias	Number of studies	Sample size	RR	95% CI	*P*-value	I^2	Publication bias
Mortality	24	455619	0.069	0.026-0.184	<0.0001	87.1	No	9	29642	0.391	0.276- 0.554	<0.0001	71.6	No
Treatment failure	21	428089	1.020	0.461-2.256	0.96	98.8	No	7	10084	1.830	0.967- 3.466	0.06	77.8	No
Cure	8	5059	0.97	0.86-1.09	0.191	29.7	No	-	-	Not available				
Treatment completion	9	8444	0.982	0.924-1.044	0.56	0	No	1	503	0.313	0.163 -0.600	<0.0001	-	-
Lost follow-up	12	455598	2.122	1.414-3.184	<0.0001	94.0	Yes (RR = 1.228; 95% CI: 0.827-1.822, 6L)	3	986	4.331	1.542- 12.163	0.005	55.8	No
Not evaluated	8	408403	1.025	0.769-1.367	0.87	45.4	No	-	-	Not available				
Treatment success	21	895913	0.968	0.942-0.994	0.02	64.4	No	4	45028	4	0.750	0.443 -1.270	60.5	No
Sustained treatment success	1	2815	0.990	0.908 1.080	0.83	-	-	-	-	Not available				

CI, confidence interval; OR, odds ratio; RR, risk ratio.
[a] All data are reported as RR or OR with their 95% CIs.

lower prevalence of comorbidities among migrants. Thus, fewer comorbidities and a younger age could explain the reduced mortality among such a vulnerable population when accurate follow-up is completed. A study by Pittalis et al. [20] supports this observation, reporting a correlation between comorbidities and a negative prognosis. Although this study could not be included in our meta-analysis due to the inclusion criteria, it compared patient characteristics between nonmigrant and migrant populations.

Furthermore, a systematic review by Tavares et al. [21] investigates the differences between migrants and nonmigrants in HIV-TB coinfected populations. The authors identified four studies with discordant findings regarding reduced or increased mortality. These nonunivocal conclusions may be explained by the fact that the HIV population is more at risk of severe presentations but is also more closely monitored by specific health services.

Mortality risk related to migration status is a popular topic in global health. A meta-analysis by Aldridge et al. [22] reported an overall lower risk of mortality among migrants compared with nonmigrants. Notably, the pooled analysis showed a reverse trend in mortality due to infectious diseases, including TB. Nevertheless, data on TB mortality were extracted from only three articles, which contradicts our findings regarding the mortality advantage. One study focused strictly on asylum seekers [23]. In addition, all three studies evaluated standard mortality ratios based on national registries, whereas our study assessed mortality using relative risk measures [23–25]. As a general consideration, the inverse trend in mortality and follow-up loss rates among the migrant population highlights the complexity of migrant health. It seems that the most important role in outcomes is not influenced by the severity of the disease itself but by the nonmedical characteristics of the patient, such as all social aspects that influence access to health. For this reason, TB is once again confirmed as a "social disease" [26,27]. A similar finding was reported for HIV/AIDS in a meta-analysis by Segala et al. [28], which compared HIV-related outcomes between migrants and nonmigrants. Although no differences were observed in mortality, all other outcomes influenced by treatment adherence and related social barriers (e.g., LTFU, virologic failure, and treatment discontinuation) were found to be worse among migrants [28].

For this reason, in 2015, Lönnroth et al. [29] revised an action framework to emphasize the composite plan required to fight TB among hard-to-reach populations, such as migrants in low-incidence countries; pre- and post-entry screening, international communication between health institutions, inclusion of migration stakeholders such as nongovernmental organizations, and outreach structures are all factors that have proven to be crucial in reaching the migrant population in TB programs.

This study has some limitations. Although most of the included studies had a low risk of bias, only a few were specifically designed to compare differences in TB outcomes between the two populations. As a result, stratified data on sex, age, and specific conditions such as HIV status and resistance patterns could not be extracted to perform a focused subanalysis. Interestingly, no studies targeting the pediatric population were included, suggesting a gap in knowledge about TB among the child migrant population. In addition, the definitions of migrants are not uniform among the included studies. The International Organization for Migration provides a UN-endorsed definition but notes that no definition exists under international law [30]. Although highly profiled and institutionally endorsed, we did not directly adopt this definition as an inclusion criterion for three reasons. First, the European context does not justify equating migrants and internally displaced people as the International Organization for Migration definition does, and other study designs are warranted to evaluate health outcomes among internal migrants in HICs. Second, in some cases, the current scientific literature focuses on European territories overall; hence, some reports assume migrants as individuals moving to the EU/EEA borders. In our opinion, this literature deserves consideration, but it does not allow us to distinguish between migrants and nonmigrants based on residence outside the country of birth, especially because the definitions of migrants are

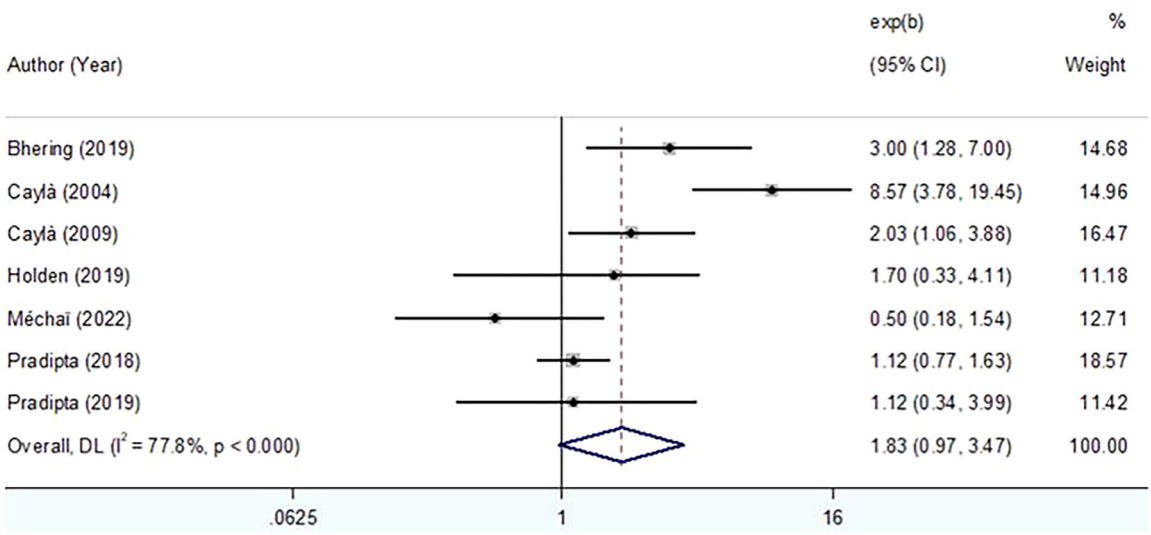

Figure 3. Adjusted result for treatment failure.
Note: weights are from random-effects model
CI, confidence interval.

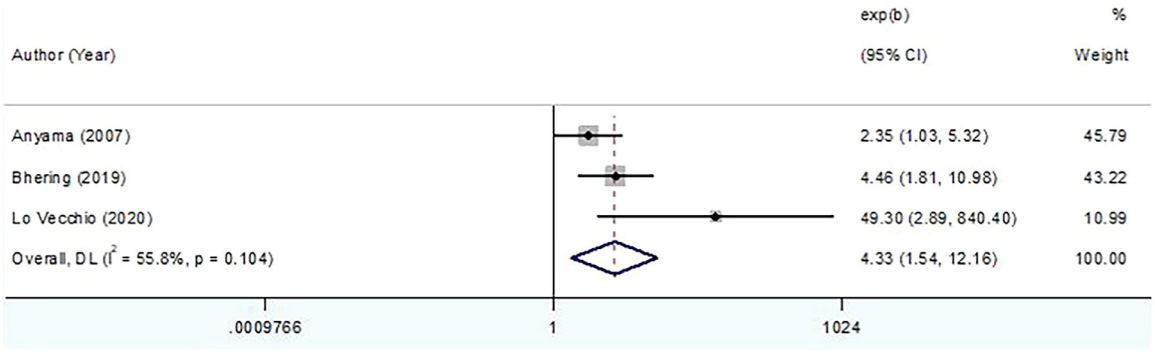

Figure 4. Adjusted result for lost-to-follow-up.
Note: weights are from random-effects model
CI, confidence interval.

not uniform across several European countries [31,32]. Third, although second-generation migrants never experienced the migration journey, it is acknowledged that the condition of being raised in a migrant setting predisposes them to similar social determinants. This has been observed in both general health outcomes and TB-specific studies [33,34]. Furthermore, the condition of being a second-generation migrant has been coded by the European Commission due to its high social significance, and for this reason, a study focusing on migration in Europe should include it [35].

In view of this, the definitions accepted as inclusion criteria for our study vary from general foreign-born/migrant individuals to local legal definitions. One of the most evident biases in this limitation is that second-generation migrants are not unequivocally considered. Furthermore, the distinction between migrants from LMICs and high-TB-burden countries was aggregated with those from low-TB-burden and HICs. This could theoretically equate a highly paid French citizen moving to Geneva with a Ukrainian or Malian refugee facing precarious circumstances. However, given the large size of our population and the predominance of migration from LMICs [30], this bias is likely reduced. Lastly, one limitation is, once again, closely tied to the heterogeneity of EU/EEA countries in terms of migration policies. Migrant individuals face varying material conditions owing to differences in welfare systems and resource settings across the countries where they reside. This may influence TB outcomes; however, this was not captured by the data analyzed in this study.

Conclusion

In this systematic review and meta-analysis, we found that migrants with TB in Europe had a lower rate of treatment completion and a higher rate of LTFU. This finding highlights that migration status is a major determinant of health, as being out of one's environment exposes individuals to increased difficulties in daily life management [36,37]. One of the first pieces of evidence for this vulnerability is the difficulty in adhering to the demand for antitubercular therapy.

Nevertheless, the literature often treats the migration status as an isolated phenomenon, as if the social status of migrants cannot be modified. Future researchers should focus on comparing TB outcomes between migrants and nonmigrants when specific vulnerabilities such as low income or homelessness are removed or adjusted.

Despite these limitations, our meta-analysis underscores that a crucial factor in the fight against TB among migrants is the capacity of the health care system to engage in this precarious social category. Policymakers and institutions should prioritize recommendations and programs that facilitate access to and follow-up on TB treatment for both migrants and health care providers. Future research should aim to gather prospective long-term data on TB outcomes among migrants and develop effective strategies to enhance care retention. To achieve this goal, comprehensive culturally sensitive communication and targeted health facility programs, including general attention to legal and nonmedical issues, should be developed. These efforts are essential for shaping poli-

cies and practices that mitigate health risks and improve the treatment of migrants with TB.

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Declarations of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Cotugno Sergio: Writing – original draft, Writing – review & editing, Data curation. **Guido Giacomo:** Conceptualization, Writing – review & editing, Investigation. **Segala Francesco Vladimiro:** Conceptualization. **Frallonardo Luisa:** Data curation. **Papagni Roberta:** Data curation. **Giliberti Vincenzo:** Data curation. **Polizzotto Carla:** Data curation. **Di Franco Giuseppina:** Data curation. **Piccione Ercole:** Supervision. **Affronti Marco:** Supervision. **Gualano Gina:** Supervision. **Palmieri Fabrizio:** Supervision. **Barbagallo Mario:** Project administration. **Veronese Nicola:** Methodology, Visualization. **Saracino Annalisa:** Project administration. **Di Gennaro Francesco:** Conceptualization, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2024.100564.

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