Risk factors associated with unsuccessful tuberculosis treatment outcomes in Hunan Province, China

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Abstract
Objectives: Globally, China has the third highest number of tuberculosis (TB) cases despite high rates (85.6%) of effective treatment coverage. Identifying risk factors associated with unsuccessful treatment outcomes is an important component of maximising the efficacy of TB control programmes.

Methods: Retrospective cohort study to evaluate the outcomes of 306,860 drug-susceptible TB patients who underwent treatment in Hunan Province, China between 2013 and 2018. Univariable and multivariable logistic regression models were used to identify factors associated with unsuccessful TB treatment outcomes.

Results: A successful treatment outcome was recorded for 98.6% of patients, defined as the sum of patients who were cured (36.2%) and completed treatment (62.4%). An unsuccessful treatment outcome was recorded for 1.8% of patients, defined as the sum of treatment failure (1.1%), deaths (0.5%) and lost to follow up (0.2%). The odds of an unsuccessful treatment outcome showed an increasing trend in more recent years of registration (2018 adjusted odds ratio (AOR): 1.43; 95% Confidence Interval (CI) 1.31, 1.57 relative to 2013). Other significant risk factors were male sex (AOR: 1.17; 95% CI 1.10, 1.25); increasing age (AOR:1.02 per year increase; 95% CI 1.02,1.02); being severely ill (AOR: 1.50; 95% CI 1.33, 1.70); having a history of TB treatment (AOR: 2.93; 95% CI 2.69, 3.20); not being under systematic management (AOR: 16.10 (14.49, 17.88) and treatment regimens that differed from full course management.

Conclusions: The increasing likelihood of an unsuccessful treatment outcome over time necessitates the need for further research.

KEYWORDS
China, risk factors, treatment outcome, tuberculosis

Sustainable Development Goals: Good health and well-being, Reduced inequalities
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INTRODUCTION

Throughout history *Mycobacterium tuberculosis* (MTB), the pathogen responsible for tuberculosis (TB), is thought to have claimed more lives than any other microorganism [1]. With an estimated 1.4 million lives lost to the disease in 2019, TB continues to be one of the leading infectious causes of death globally [2]. Tuberculosis is associated with poverty and it fuels the cycle of deprivation and vulnerability [3].

Tuberculosis can be cured, but if left untreated the mortality rate is high, with 10-year case fatality rates ranging between 54 and 86% in human immunodeficiency virus (HIV) negative patients [4]. For drug-susceptible TB, a 6-month treatment regime containing four first-line antibiotics (i.e. isoniazid, rifampicin, ethambutol and pyrazinamide) is recommended, which has an 85% success rate [3]. Successful treatment is key to curing the disease, preventing transmission of infection and preventing the development of drug resistance [3]. Drug-resistant TB is an escalating global health security threat [2], projected to cost the world US$ 16.7 trillion by 2050 [5].

Previous studies have found a number of factors to be associated with unsuccessful TB treatment outcomes, including positive HIV status, male sex, ethnicity, low body mass index (BMI), substance abuse, other co-morbidities, previous treatment, drug resistance, low level of education, lack of knowledge on treatment duration and the importance of treatment completion, household income, the requirement for hospitalisation during treatment, side effects of medication, improved symptoms resulting in the cessation of therapy, lack of family support and unsupervised treatment administration [6–13]. The factors relating to unsuccessful treatment outcomes need to be understood and addressed to maximise the efficacy of TB control programmes and prevent escalating drug resistance.

In 2014, the World Health Assembly adopted the *End TB Strategy*, which is integral to Sustainable Development Goal 3.3 that aims to end the TB epidemic by 2030 [14,15]. By 2030, the End TB Strategy aims to reduce TB deaths by 90%, reduce TB incidence by 80% and eliminate catastrophic costs faced by TB households [15].

In terms of 2019 TB cases numbers, China ranks third with 8.4% of the global total [3], despite effective treatment coverage being estimated at >85.6% [16]. In 2019, China had the second-greatest burden (14%) of multidrug-resistant TB (MDR-TB), which was estimated to occur in 7.1% of new and 23% of previously treated cases [3]. To address the burden of disease, China has initiated a National Tuberculosis Control Programme (NTP) based on the Directly Observed Treatment Short-course (DOTS) strategy recommended by WHO [17]. Although the NTP aims to provide TB diagnosis and treatment services free of charge, patients often face significant out of pocket expenses and financial hardship [18].

Hunan province, located in south-central China, carries a high burden of TB despite significant investments that have been made by the Hunan government to combat the disease [19–21]. An understanding of the risk factors associated with unsuccessful treatment outcomes in province-specific TB patient populations could help reduce the burden of disease by informing targeted interventions, for example, systematic drug supervision, sex-specific TB education/messaging. Few of the studies on risk factors associated with unsuccessful TB outcomes have been conducted in China. To our knowledge, only one study has evaluated treatment default and mortality in TB patients that were registered in Hunan between 2005 and 2006 [22]. Our study aimed to evaluate the rate of treatment success and the risk factors associated with unsuccessful treatment outcomes among drug-susceptible TB (DS-TB) patients in Hunan Province who were undergoing treatment between 2013 and 2018.

METHODS

Study design and data sources

This is a retrospective cohort study conducted on patients undergoing treatment for pulmonary and extrapulmonary DS-TB in Hunan Province, China between 2013 and 2018 inclusive. Within China, TB is a category II notifiable disease and health professionals are responsible for the collection and entry of data from notified patients into an Internet-based TB management information system [23]. Within Hunan, the TB management information system is managed by the Tuberculosis Control Institute of Hunan Province (TBCIH), which provided access to the data for this study. Clinical data relating to the date of treatment commencement, date of treatment completion, treatment outcome and type of treatment management were available, as were demographic data such as ethnicity, age, sex, occupation and residential address.

Definitions

We used the WHO definitions of treatment outcomes: [24]

| Outcome       | Definition                                                                 |
|---------------|---------------------------------------------------------------------------|
| Cured         | A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion. |
| Treatment completed | A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable. |
| Treatment failed | A TB patient whose sputum smear or culture is positive at month five or later during treatment. |
| Died          | A TB patient who dies for any reason before starting or during the course of treatment. |
| Outcome                           | Definition                                                                 |
|----------------------------------|---------------------------------------------------------------------------|
| Lost to follow up                | A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more. |
| Not evaluated                    | A TB patient 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. |
| Treatment success                | The sum of cured and treatment completed                                    |

To dichotomise data into successful and unsuccessful treatment outcomes, treatment success was classified as ‘cured’ plus ‘treatment completed’ and an unsuccessful outcome as the sum of ‘treatment failed’, ‘died’ and ‘lost to follow-up’. Definitions pertaining to the other demographic descriptors/variables analysed are detailed in Table 1.

**Results**

Figure 1 details the patient record selection process: 318,792 records were available after translation and data cleaning. The data set included patients on treatment between 2013 and 2018; we were in receipt of this in 2018 and so some patients were yet to complete their course of treatment and were excluded (n = 10,679). Of the patients that had completed treatment (n = 308,113), records for those transferred out (n = 1,253) were excluded, as their treatment outcomes were not recorded on the TBCIH database.

**Socio-demographic and clinical characteristics of the TB patients**

The sociodemographic characteristics of the final patient cohort (n = 306,860) are detailed in Table 2. The mean age of the patient population was 51.6 years (SD 17.6), the majority was male (72.6%), employed in agriculture (78.3%) and new patients (95.9%).

**Unsuccessful TB treatment outcomes**

A successful treatment outcome was recorded for 98.24% of the patient population (treatment completed 62.04% and cured 36.20%). An unsuccessful treatment outcome was recorded for 1.76% of the patient population (treatment failure 1.08%, death 0.46% and lost to follow up 0.21%).

**Risk factors associated with an unsuccessful TB treatment outcome**

Table 3 shows results of univariable and multivariable logistic regression models and factors associated with an unsuccessful treatment outcome. In the univariable analysis, demographic factors such as male sex, increasing age, occupation (i.e. agriculture housekeeping, childcare, retired and un-employed) and year of enrolment; and clinical factors such as severe illness, non-systematic management and supervision process were significantly associated with unsuccessful TB treatment outcomes.

In the final multivariable analysis, male sex (AOR: 1.17; 95% CI 1.10, 1.25), increasing age (AOR: 1.02 per year increase; 95% CI 1.02, 1.02) and being severely ill (AOR: 1.50; 95% CI 1.33, 1.70) were significant risk factors for unsuccessful treatment outcomes. The odds of an unsuccessful treatment outcome were greater where a patient was not systematically managed (AOR: 16.10; 95% CI 14.49, 17.88) and when they were under full process supervision (AOR: 1.51 (95% CI 1.37, 1.66); intensive phase supervision (AOR: 1.39; 95% CI 1.26, 1.55) or self-administered medication (AOR: 1.98; 95% CI 1.53, 2.55) relative to full course management. Registration in the years 2016–2018 was also associated with an unsuccessful treatment outcome relative to 2013 (2016

**Ethical approval**

Ethics approval was obtained from Curtin University (HRE2019-0581) and permission to access the data was obtained from TBCIH. As this study used secondary and routinely collected clinical data, informed consent was not obtained from the study participants. Medical records were anonymised by TBCIH to maintain patient confidentiality.
| Variable                  | Definition                                                                                                                                                                                                 |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Residential address      |                                                                                                                                                    |
| Local                    | Patients who reside in local counties                                                                                                                |
| Intra-provincial         | Patients who reside in other counties within the province                                                                                           |
| Inter-provincial         | Patients who reside in provinces other than Hunan                                                                                                  |
| Foreign nationality     | Patients who reside in other countries                                                                                                               |
| Registration category    |                                                                                                                                                    |
| New patient              | PTB patients who have never taken anti-TB drugs, or who have been receiving irregular treatment for less than one month                                                                                     |
| Relapse                  | PTB patients with a history of disease, who complete a full course of chemotherapy and appear cured according to symptoms, but who return a smear positive sputum sample |
| Return after default     | PTB patients who receive chemotherapy for ≥1 month but discontinue therapy for ≥2 months and then return for treatment                                                                                     |
| Initial treatment failed | New sputum smear positive PTB patients with positive sputum smear microscopy results at the end of the 5th month or after completion of therapy; and sputum smear negative PTB patients with a positive smear result for any sputum sample |
| Chronic patient          | Positive sputum examination results after several episodes of irregular therapy                                                                                                                                      |
| TB diagnosis results     |                                                                                                                                                    |
| Etiological examination negative | TB cases confirmed on basis of symptoms                                                                                                                |
| Smear positive           | Positive Acid-Fast Bacillus test                                                                                                                        |
| Extrapulmonary TB        | TB identified in organs other than the lungs                                                                                                         |
| Culture positive         | Positive sputum culture                                                                                                                              |
| Molecular biology positive | TB confirmed on basis of molecular diagnosis                                                                                                      |
| Severely ill             | Patients with miliary TB, cavities, TB empyema or serious damage to one or more organs caused by TB infection.                                                                                               |
| Drug resistance pattern  |                                                                                                                                                    |
| Drug susceptible TB      | *M. tuberculosis* that is susceptible to first line antibiotics (isoniazid, rifampin, ethambutol, and pyrazinamide)                                                                                       |
| MDR-TB                   | *M. tuberculosis* resistant to isoniazid and rifampicin                                                                                                |
| Mono-resistant TB        | *M. tuberculosis* resistant to a single first line antibiotic                                                                                         |
| History of TB treatment  |                                                                                                                                                    |
| No (Initial treatment)   | • a patient who has never taken anti-TB drugs; or<br>• a patient receiving standardized TB treatment but who has not completed the full course of treatment; or<br>• a patient receiving irregular TB treatment for less than one month. |
| Yes (Retreatment)        | • a patient receiving irregular anti-TB drugs for one month or longer; or<br>• initial treatment failure and relapse                                                                                         |
| TB treatment outcomes [50] |                                                                                                                                                    |
| Treatment completed      | A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable. |
| Cured                    | A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion. |
| Treatment failure        | A TB patient whose sputum smear or culture is positive at month five or later during treatment.                                                                                                               |
| Death                    | A TB patient who dies for any reason before starting or during the course of treatment.                                                                                                                        |
| Lost to follow-up        | A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more                                                                                              |
| Successful treatment outcome | The sum of cured and treatment completed                                                                                                           |
| Unsuccessful treatment outcome | The sum of treatment failure, death and lost to follow up                                                                                         |
DISCUSSION

This study found a treatment success rate of 98.24% amongst DS-TB patients undergoing therapy between 2013 and 2018 in Hunan Province, China. This figure is higher than the 94% success rate reported for new cases across China in 2018 [25], and the WHO target of 85% [26]. It is noted, however, that the exclusion of patients who were transferred out, may have increased the reported success rate.

Our study found the likelihood of unsuccessful treatment outcome to be higher in the last three years of patient enrolment, with an increasing trend over time. Within the variables that contribute to an unsuccessful treatment outcome, there is an increasing trend in the mortality rate over recent years. Modelling studies have suggested that an increasing...
The trend of unsuccessful TB treatment outcomes may be related to the increasing prevalence of MDR-TB and the relatively low rate of MDR detection and treatment in China [3,27,28]. Further research is required to elucidate whether the increasing trend in mortality is related to an increasing prevalence of MDR-TB or whether it relates to other factors such as disease severity, age or co-morbidities. Among the causes for TB treatment default, economic hardship is cited as one of the most common reasons [7,9,18,27] with 2019 global figures estimating that 44% of people with DS-TB and 80% of people with MDR-TB face catastrophic costs [3]. Although the Chinese Action Plan to Stop TB (2019–2022) aims to provide drug susceptibility testing (DST) to 90% of bacteriologically confirmed cases by 2022 [27], the cost implications of the additional resources required to detect and treat MDR are not fully covered by Chinese health insurance schemes [18,27,29]. Interventions that identify and help patients facing catastrophic costs maybe an effective way of improving the efficacy of TB programme outcomes.

Within the Hunan study population, male sex and increasing age were associated with increased odds of unsuccessful treatment outcome. The finding supports sex specific TB education and messaging. Gender differences in TB treatment outcomes remain inconsistent, although a number of studies support our finding [30–33]. Possible explanations for sex disparities in TB treatment outcomes include male sex, increasing age, and history of TB treatment.TABLE 2 (Continued)

| Mean age 51.6 years (SD 17.6) | Number | Percent |
|-------------------------------|--------|---------|
| **Occupation** | | |
| Agriculture | 240,235 | 78.29 |
| Housekeeping, childcare, retired, un-employed | 29,144 | 9.50 |
| Education$^{a}$ | 10,341 | 3.37 |
| Commercial services/civil servant | 7,479 | 2.44 |
| Migrant worker | 2,531 | 0.82 |
| Healthcare | 962 | 0.31 |
| Hospitality | 586 | 0.19 |
| Other | 15,582 | 5.08 |
| **Ethnicity** | | |
| Han | 277,813 | 90.54 |
| Tujia | 12,354 | 4.32 |
| Miao | 8,168 | 2.66 |
| Dong | 8,168 | 2.66 |
| Yao | 3,888 | 1.27 |
| Bai | 2,621 | 0.85 |
| Mongolian | 496 | 0.16 |
| Other$^{b}$ | 337 | 0.11 |
| **Residential address** | | |
| Local | 298,844 | 97.39 |
| Intra-provincial | 5,896 | 1.92 |
| Inter-provincial | 2,071 | 0.67 |
| Foreign nationality | 49 | 0.02 |
| **Registration category**$^{c}$ | | |
| New patient | 294,355 | 95.92 |
| Relapse | 11,210 | 3.65 |
| Return after default | 328 | 0.11 |
| Initial treatment failed | 246 | 0.08 |
| Chronic patient | 120 | 0.04 |
| **TB diagnosis results** | | |
| Etiological examination negative | 182,343 | 59.42 |
| Smear positive | 117,491 | 38.29 |
| Extrapulmonary TB | 5,031 | 1.64 |
| Only culture positive | 1,154 | 0.38 |
| Only molecular biology positive | 637 | 0.21 |
| No etiological results | 637 | 0.21 |
| Only pathologically positive | 496 | 0.16 |
| Severely ill | 295,172 | 96.19 |
| Yes | 11,688 | 3.81 |

$^{a}$Education includes both teachers and students.
$^{b}$Other are represented by 21 separately defined ethnic groups. NB ethnicity data are not available for four patients.
$^{c}$Patient registration category not available for 601 patients.
| Risk factor for n TB treatment outcome | TB treatment outcome | No Successful (%) | No. Unsuccessful (%) | Univariable estimate | Univariable p value | Multivariable estimate | Multivariable p value |
|--------------------------------------|----------------------|-------------------|---------------------|----------------------|---------------------|----------------------|----------------------|
| Ethnicity                            |                      |                   |                     |                      |                     |                      |                      |
| Han                                 | 272,912 (98.24)      | 4,91 (1.76)       | 1.00                | 1.00                |                     |                      |                      |
| Tujia                                | 13,031 (98.32)       | 223 (1.68)        | 0.95 (0.83, 1.09)   | 0.485               | 0.93 (0.81, 1.07)   | 0.337                |                      |
| Miao                                 | 8,018 (98.16)        | 150 (1.84)        | 1.04 (0.88, 1.23)   | 0.625               | 1.08 (0.92, 1.28)   | 0.334                |                      |
| Dong                                 | 3,816 (98.15)        | 72 (1.85)         | 1.05 (0.83, 1.33)   | 0.680               | 1.20 (0.95, 1.53)   | 0.130                |                      |
| Yao                                  | 2,583 (98.55)        | 38 (1.45)         | 0.82 (0.59, 1.13)   | 0.224               | 0.69 (0.49, 0.97)   | 0.033                |                      |
| Bai                                  | 492 (99.19)          | 4 (0.81)          | 0.45 (0.17, 1.21)   | 0.115               | 0.42 (0.16, 1.13)   | 0.083                |                      |
| Mongolian                            | 331 (98.22)          | 6 (1.78)          | 1.01 (0.45, 2.26)   | 0.982               | 1.11 (0.49, 2.49)   | 0.803                |                      |
| Other*                               | 274 (98.21)          | 5 (1.79)          | 1.02 (0.42, 2.46)   | 0.972               | 1.22 (0.50, 2.98)   | 0.660                |                      |
| Sex                                  |                      |                   |                     |                      |                     |                      |                      |
| Female                               | 82,847 (98.54)       | 1,230 (1.46)      | 1.00                | 1.00                |                     |                      |                      |
| Male                                 | 218,614 (98.13)      | 4,169 (1.87)      | 1.28 (1.20, 1.37)   | <0.0001             | 1.17 (1.10, 1.25)   | <0.0001             |                      |
| Age (mean, years)                    | 51.4                 | 58.4              | 1.02 (1.02, 1.03)   | <0.0001             | 1.02 (1.02, 1.02)   | <0.0001             |                      |
| Occupation                           |                      |                   |                     |                      |                     |                      |                      |
| Comm services/civil servant          | 7,384 (98.73)        | 95 (1.27)         | 1.00                | 1.00                |                     |                      |                      |
| Agriculture                          | 235,774 (98.14)      | 4,461 (1.86)      | 1.47 (1.20, 1.80)   | <0.0001             | 1.04 (0.84, 1.29)   | 0.707                |                      |
| At home<                            | 28,618 (98.20)       | 526 (1.80)        | 1.43 (1.15, 1.78)   | 0.001               | 0.99 (0.79, 1.24)   | 0.917                |                      |
| Education                            | 10,263 (99.25)       | 78 (0.75)         | 0.59 (0.44, 0.80)   | 0.001               | 0.98 (0.72, 1.33)   | 0.878                |                      |
| Migrant worker                       | 2,506 (99.01)        | 25 (0.99)         | 0.78 (0.50, 1.21)   | 0.260               | 0.74 (0.48, 1.17)   | 0.196                |                      |
| Healthcare                           | 956 (99.38)          | 6 (0.62)          | 0.49 (0.21, 1.12)   | 0.089               | 0.57 (0.25, 1.31)   | 0.186                |                      |
| Hospitality                          | 575 (98.12)          | 11 (1.88)         | 1.49 (0.79, 2.79)   | 0.217               | 1.74 (0.91, 3.31)   | 0.093                |                      |
| Other                                | 15,385 (98.74)       | 197 (1.26)        | 1.00 (0.78, 1.27)   | 0.970               | 0.91 (0.71, 1.17)   | 0.473                |                      |
| Year                                 |                      |                   |                     |                      |                     |                      |                      |
| 2013                                 | 53,660 (98.38)       | 886 (1.62)        | 1.00                | 1.00                |                     |                      |                      |
| 2014                                 | 53,501 (98.37)       | 886 (1.63)        | 1.00 (0.91, 1.10)   | 0.951               | 1.01 (0.92, 1.12)   | 0.768                |                      |
| 2015                                 | 53,051 (98.47)       | 824 (1.53)        | 0.94 (0.85, 1.04)   | 0.210               | 0.97 (0.88, 1.07)   | 0.526                |                      |
| 2016                                 | 47,634 (98.26)       | 842 (1.74)        | 1.07 (0.97, 1.18)   | 0.160               | 1.12 (1.02, 1.23)   | 0.022                |                      |
| 2017                                 | 47,407 (98.20)       | 869 (1.80)        | 1.11 (1.01, 1.22)   | 0.030               | 1.12 (1.02, 1.23)   | 0.022                |                      |
| 2018                                 | 46,208 (97.69)       | 1,092 (2.31)      | 1.43 (1.31, 1.57)   | <0.0001             | 1.43 (1.31, 1.57)   | <0.0001             |                      |
| Residential address                  |                      |                   |                     |                      |                     |                      |                      |
| Local                                | 293,564 (98.23)      | 5,280 (1.77)      | 1.00                | 1.00                |                     |                      |                      |
| Intra-provincial                     | 5,808 (98.51)        | 88 (1.49)         | 0.84 (0.68, 1.04)   | 0.113               | 0.92 (0.74, 1.15)   | 0.467                |                      |
| Inter-provincial                     | 2,040 (98.50)        | 31 (1.5)          | 0.84 (0.59, 1.21)   | 0.353               | 1.16 (0.80, 1.66)   | 0.434                |                      |
| Foreign nationality                  | 49 (100)             | –                 | –                   | –                   | –                   | –                   |                      |
| Severely ill                         |                      |                   |                     |                      |                     |                      |                      |
| No                                   | 290,085 (98.28)      | 5,087 (1.72)      | 1.00                | 1.00                |                     |                      |                      |
| Yes                                  | 11,376 (97.33)       | 312 (2.67)        | 1.56 (1.39, 1.76)   | <0.0001             | 1.50 (1.33, 1.70)   | <0.0001             |                      |
| History of TB treatment              |                      |                   |                     |                      |                     |                      |                      |
| No                                   | 289,756 (98.41)      | 4,683 (1.59)      | 1.00                | 1.00                |                     |                      |                      |
| Yes                                  | 11,705 (94.24)       | 716 (5.76)        | 3.78 (3.49, 4.10)   | <0.0001             | 2.93 (2.69, 3.20)   | <0.0001             |                      |
| Treatment management                 |                      |                   |                     |                      |                     |                      |                      |
| Full course management               | 40,860 (98.74)       | 521 (1.26)        | 1.00                | 1.00                |                     |                      |                      |

(Continues)
include immunological, socio-cultural and clinical factors [30,34–36]. Socio-cultural factors are complex and varied, and clinical factors are patient-specific, highlighting the need for detailed data to determine and address the underlying causes. Patient specific data on clinical factors, for example, co-morbidities may also be of value in identifying the underlying causes of age as a risk factor [37,38]. As a result of China’s aging demographic, diabetes, which is associated with unsuccessful TB treatment outcomes, is becoming significantly more prevalent [39,40]. Although China has a policy of treating HIV patients at separate institutions, screening for and clinical management of confounders such as diabetes may be of benefit in improving TB treatment outcomes [40,41].

For the patient population in this study, systematic and full process treatment management were associated with more favourable treatment outcomes and as such these treatment regimens are recommended where resources allow. Directly Observed Treatment, Short-course (DOTS) continues to be key to the WHO’s Stop TB Strategy [42], a component of which includes the direct observation of drug intake [43]. The significant reduction in TB prevalence that has been achieved in China is primarily attributed to the implementation of DOTS [44,45]. There is, however, debate in the literature on how much credit should be attributed to DOTS and to what extent other factors are responsible [46,47]. This raises the question of which strategies and interventions are really achieving the most resource-effective outcomes [47].
The same is true of the conclusions drawn from this study. Are the risk factors themselves responsible for unsuccessful treatment outcomes or are confounders such as comorbidities, malnutrition, substance abuse, underlying causes of unsuccessful treatment outcomes? This ambiguity highlights the need for access to detailed data if TB control programs are going to succeed in reducing the personal and societal burden of this disease.

A limitation of this study is the lack of detailed data that would have allowed potential confounders (e.g., diabetes mellitus, substance abuse) to be interrogated. However, the large size of the patient cohort is a significant strength. Despite the large cohort, it is acknowledged that these data may not be representative of Hunan's total TB patient population. Although TB reporting is mandatory in China, there may be potential under-reporting [48]. Patients may also seek care from traditional healers and therefore not be captured in the database [49].

CONCLUSION

This study found that demographic (e.g., sex, age) and clinical factors (e.g., year of patient registration, illness severity, history of TB treatment and management regime) were significantly associated with unsuccessful TB treatment outcomes. The underlying causes of the demographic and clinical risk factors need to be interrogated so that effective strategies can be implemented to achieve the End TB Strategy. Consideration is required on data requirements to maximise the efficacy of TB control programmes. Both TB programmes and their associated data requirements need to evolve as the disease and confounders change over time.

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