SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Quantifying the risk of tuberculosis recurrence in Asia: A systematic review of hazard estimates

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ABSTRACT

Introduction: Recurrence of tuberculosis (TB) is a major challenge to its control in Asia, even though there is a high treatment success rate of drug-susceptible diseases. TB recurrence contributes to ongoing disease transmission in the community, increases drug resistance and leads to higher TB mortality rates. The study aimed to examine and synthesise the current evidence on determinants of TB recurrence occurring after completed treatment in the Asian setting.

Materials and Methods: The PRISMA 2020 framework is used as a guide for this systematic review. A systematic search in PubMed/MEDLINE, Scopus and Web of Science (WOS) until September 30, 2025 was conducted. The eligible studies were cohort studies implemented in Asian countries and reported post-treatment TB recurrence and adjusted risk estimates. The Newcastle-Ottawa Scale was used to assess the methodological quality of the included studies. Since the methodological heterogeneity is rather significant, a narrative synthesis was conducted.

Results: The review included a total of 15 cohort studies with sample sizes ranging from 508 to more than 10 million individuals. TB recurrence was 1.5 to 15.1% or 0.47 to 6.5 per 1,000 person-years, with the highest rates seen within two years of post-treatment. Recurrence risk was higher when there were comorbidities like diabetes, chronic lung or kidney disease, low body mass index and behavioural factors like smoking. Additionally, environmental exposure to fine particulate matter ($PM_{2.5}$) and socioeconomic disadvantage were also significant variables. Protective variables observed were high levels of treatment compliance, extended treatment period, the use of fixed-dose combination (FDC) therapy, treatment during the directly observed therapy (DOT) era, smoking cessation, and residential greenness. The quality of the included study was moderate to high.

Conclusion: Multiple determinants drive TB recurrence; thus, improving post-treatment surveillance as well as integrating clinical, behavioural and environmental interventions are important to reduce the incidence and mortality of TB recurrence cases.

KEYWORDS:
Tuberculosis; Recurrence; Reactivation; Time-to-event analysis; Determinants

INTRODUCTION

Tuberculosis (TB) is a significant public health concern in Asia and contributes to more than 55% of the global TB burden. According to the World Health Organization (WHO) Global TB Report 2025, as in 2024, it is estimated that 10.7 million individuals contracted TB and 1.23 million died of the disease, which demonstrates that TB is the leading cause of death from an infectious agent after a few years, being replaced by COVID-19.[1-2] The WHO South-East Asia Region is reported to have the highest TB incidence, which makes up to 34% of global cases, closely followed by the Western Pacific Region with 27% and the African region (25%).[2] The Asian region has a complex epidemiological pattern that is affected by multiple factors, including socio-economic determinants and health system insufficiency, making the region a critical focus for research.[3-4] Despite the success rate of the standard WHO regime for drug-susceptible TB (DS-TB) being more than 85%, TB recurrence, which is defined as a new TB episode after completed TB treatment or cured during the previous episode, may still occur and continues to be a challenge to TB control efforts.[5-6]

TB recurrence may contribute to continuous disease transmission in the community, drug resistance and higher mortality, hindering the TB control efforts, especially in Asian high-burden settings.[7] The local epidemiological data on TB in Malaysia also support that TB recurrence has led to ongoing spread in the population and contributes to poor treatment outcomes.[8-10] There are two mechanisms of TB recurrence: either from the relapse of the original strain of *Mycobacterium tuberculosis* or reinfection with a new strain, especially in high-burden settings where sustained exposure is common.[11-12] In Asia, the risk of TB recurrence is increased with population ageing, high prevalence of diabetes mellitus, persistent tobacco use and socioeconomic inequalities. These factors contribute to negative impacts on immune response as well as on treatment outcomes and may help to explain why TB recurrence is significant in Asian populations.[13-14] The epidemiology of TB in the region is also influenced by rapid urbanisation and environmental exposures like ambient air pollution, which increase susceptibility to infection and the development of respiratory diseases in densely populated urban centres across Asia.[15]

TB recurrence is an insufficiently explored challenge to TB control in Asia. Existing studies have reported widely varying estimates, most probably due to heterogeneity in study design, definitions used for recurrence, different lengths of follow-up and analytical approaches. This inconsistency has

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restricted quantitative synthesis and translations of evidence into action, in turn creating a gap in understanding the true burden, determinants and implications of TB recurrence in the region.[16] As a result, although countries with DS-TB have high rates of treatment success, policy-wide integration of recurrence data has not been comprehensive. A structured synthesis of the available evidence is therefore needed to identify the determinants of TB recurrence within Asian populations.[17] Understanding these context-specific determinants may help inform post-treatment surveillance and risk stratification plans that will support the WHO End TB Strategy. Thus, this review aimed to synthesise the existing evidence on the determinants of TB recurrence in Asia.

MATERIALS AND METHODS

Study Design and Reporting Framework

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist.18 The review protocol was developed prior to the literature search and followed established methods for evidence synthesis. This systematic review has been registered at PROSPERO (registration no: CRD42024612771).

PECOT Framework

The search strategy was developed using the PECOT framework to ensure a structured and comprehensive approach to identifying studies relevant to the research question. P (Population) refers to individuals of any age who have completed treatment for active TB, documented as cured or treatment completed and studies conducted in Asian countries (as defined by WHO regions or United Nations geographic classification). E (Exposure) refers to post-treatment exposure to one or more risk factors for TB recurrence, including but not limited to demographic, clinical, behavioural, socioeconomic and environmental factors. C (Comparison) refers to individuals who have completed TB treatment without exposure to the specified risk factor(s). O (Outcome) refers to TB recurrence, defined as a new episode of active TB occurring after treatment completion or cure, including relapse (same strain) and reinfection (different strain), where molecular typing is available. T (Time) refers to observational studies (e.g. cohort studies, case-control studies, cross-sectional studies) and randomized controlled trials reporting post-treatment TB recurrence.

Research question

Among individuals who have completed TB treatment (P), does exposure to specific risk factors (E), compared with no exposure (C), increase the risk of TB recurrence (O) based on evidence from observational and experimental studies (S)?

Information Sources and Search Strategy

A comprehensive literature search was conducted across multiple electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science (WOS), from database inception to the most recent search date. The searches have been conducted using MeSH terms, combined key terms, text words and search strings taken from the review questions. To access the records, the following combination key terms was used: ("Survival Analysis" OR "Time-To-Event Analysis" OR "Cox Proportional Hazard" OR "Kaplan Meier") AND (Tuberculosis) AND ("Recurrent" OR "Relapse" OR "Reinfection" AND "previously treated" OR "Retreatment" OR "Reactivation"). Table I shows the search strategy for PubMed, Scopus and WOS databases.

Eligibility Criteria

Studies were selected based on the following inclusion criteria: Original observational studies including prospective or retrospective cohort studies; involving TB patients who successfully completed treatment (defined as cured or treatment completed); reporting TB recurrence as an outcome, including relapse, reinfection, or recurrent TB. examining risk factors, determinants, or predictors of TB recurrence; conducted in Asian countries; published in English between 1 January 2000 and 30 September 2025. The exclusion criteria: Case reports, case series, reviews, editorials, commentaries, conference abstracts, and modelling studies without primary data; studies focusing exclusively on treatment failure, loss to follow-up, or mortality without recurrence outcomes; involving exclusively multidrug-resistant TB populations; without clear post-treatment follow-up or recurrence definitions.

Selection Process

All retrieved articles were imported into EndNote for reference management and duplicate removal. The selection process was conducted in three stages: title and abstract screening; Two independent reviewers screened studies for relevance to TB recurrence; full-text assessment: articles meeting initial criteria were reviewed in full to confirm eligibility, and consensus resolution: disagreements were resolved through discussion with a third reviewer.

Data Extraction

Data from all included studies were extracted using a standardised extraction form. From the selected studies, important information was extracted, such as study design, study setting, sample size, population characteristics, statistical methods used, definitions and measurements of recurrence, length of follow-up, outcomes of TB recurrence, and reported determinants with their effect estimates and confidence intervals (CI) when available. To minimise the error, two independent reviewers extracted the data, and any discrepancies were resolved by cross-checking and consensus.

Quality Assessment

The quality and risk of bias of the included studies with a cohort as a study design were assessed by using the Newcastle-Ottawa Scale (NOS).19 The evaluation was done based on three domains: First, selection of study groups, whether they were well-defined, had reliable exposure measurement and were representative, allocated with a maximum of four stars. Second, comparability of cohorts that evaluated whether the confounding variables were examined and had well-adjusted analyses for reducing bias were allocated a maximum of two stars. Third, ascertainment of outcomes evaluated whether the outcome measurement and follow-up were appropriate, valid and reliable were allocated with a maximum of three stars. Overall, the total possible score was nine stars for each study.

Table I: The search strategy for PubMed, Scopus and Web of Science (WOS) databases

Database	Search Strategy
PubMed	("Survival Analysis"[Mesh] OR "Proportional Hazards Models"[Mesh] OR "Time-to-Event" OR "time to event" OR "survival analysis" OR "Cox proportional hazard*" OR "Cox model*" OR "Kaplan Meier" OR "Kaplan–Meier" OR "hazard ratio" OR "incidence rate*" OR "person-year*" OR "competing risk*") AND ("Tuberculosis, Pulmonary"[Mesh] OR "Tuberculosis"[Mesh] OR tuberculosis OR TB) AND (recurrent OR recurrence OR relapse OR reinfection OR "previously treated" OR retreatment OR reactivation) AND (adult*[Title/Abstract] OR "Aged"[Mesh] OR "Young Adult"[Mesh] OR "Middle Aged"[Mesh])
Scopus	(("survival analysis" OR" time to event" OR "time-to-event" OR "Cox proportional hazards" OR "Cox proportional hazard" OR "Cox model" OR "Kaplan Meier" OR "hazard ratio" OR "competing risks" OR "competing risk") AND (tuberculosis OR "pulmonary tuberculosis) AND (recurrent OR recurrence OR relapse OR reinfection OR "previously treated" OR retreatment OR reactivation))
WOS	(("survival analysis" OR "time to event" OR "Cox proportional hazard*" OR "Kaplan Meier" OR "hazard ratio" OR "competing risk*") AND (tuberculosis OR TB) AND (recurrent OR recurrence OR relapse OR reinfection OR "previously treated" OR retreatment OR reactivation))

By using standard practice, each NOS item allocated with stars and a total score (0-9) was calculated for each study to facilitate comparison across the studies.[19-20] The total scores were classified as follows: high methodological quality and low risk of bias, seven to nine stars, moderate risk of bias, four to six stars, and high risk of bias, zero to three stars. Any discrepancy in scoring was resolved through discussion.

Data Synthesis

A narrative synthesis was conducted due to the expected methodological diversity among the included studies, such as differences in study design, populations, measurement approaches, and outcome reporting. Key study characteristics, including sample size, setting, participant demographics, exposure definitions, and outcome measures, were extracted and summarised in tables. Due to significant clinical, methodological and statistical heterogeneity between studies on the definition of recurrence, duration of follow-up, study populations and analysis methodologies, a quantitative meta-analysis was not performed. Instead, a structured narrative synthesis was performed. Findings were synthesised thematically across key domains, including sociodemographic factors, disease severity factors, behavioural factors, comorbidity-related factors, treatment-related factors and environmental factors. Consistency and direction of associations were examined across studies, with emphasis on adjusted estimates derived from multivariable models.

RESULTS

Study Selection

A total of 2229 records were identified through database searching, including PubMed (n=218), Scopus (n=1717), and WOS (n=294). Prior to screening, 1032 records were removed, comprising 283 duplicate records, 651 records marked as ineligible by automation tools, and 98 records removed for other reasons. The remaining 1197 records were screened based on titles and abstracts, of which 1108 records were excluded for not meeting the inclusion criteria.

Following the screening stage, 89 reports were sought for full-text retrieval; however, 5 full-text articles were not available and were therefore excluded. Consequently, 84 full-text articles were assessed for eligibility. Of these, 68 articles were excluded for the following reasons: irrelevant exposure or outcome (n=20), failure to report risk factors (n = 30), did not assess after successfully treated TB cases (n = 9), and ineligible study design (n=10).

Ultimately, 15 studies met the eligibility criteria and were included in the systematic review. Figure 1 shows the flowchart of the selection of suitable journals using the PRISMA flowchart.

Characteristics of Included Studies

Across 15 cohort studies conducted in Asia, TB recurrence after treatment completion ranged from approximately 1.5 to 15.1%, or 0.47 per 100 person-years to 6.62 per 1,000 person-years, with a higher risk observed during the first two years post-treatment. Most studies used retrospective registry-based designs and Cox proportional hazards models. Consistent risk factors for TB recurrence observed were markers of high mycobacterial burden (cavitation, smear or culture positivity, delayed 2-month conversion), prior TB history, older age, male sex, and drug resistance. Comorbidities such as diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and low body mass index (BMI) were repeatedly associated with elevated risk. Behavioural and social determinants, including smoking, homelessness, and low socioeconomic status, also contributed. Treatment-related factors such as treatment duration, adherence, and regimen type were protective in several studies. The characteristics of included studies, recurrence definition and frequency, statistical approaches, and adjusted risk factors for recurrent TB in Asia are shown in Table II.

Countries settings

Variation in TB recurrence was observed across 15 studies conducted in East Asia, Southeast Asia, and the Middle East. Studies from high-income settings such as South Korea, Taiwan, and Hong Kong generally reported lower recurrence proportions from approximately 1.5% to 3.5%. Meanwhile, studies from China, Vietnam and Iran reported wider recurrence estimates ranging from 2.6% to 15.1% across different study populations and follow-up periods.

Study setting and study design

All studies utilise cohort study designs, with the majority of them being retrospective cohorts (11/15, 73.3%) based on national registries, surveillance systems, or administrative databases, and the remaining ones were prospective cohorts.

Table II: Characteristics included studies, recurrence definition and frequency, statistical approaches, and adjusted risk factors for TB recurrence in Asia

No.	Author (year)	Country / Setting	Study design	Study population & sample size	Key recurrence findings	Main limitations
1.	Chung et al., 2024.[14]	South Korea (nationwide)	Retrospective national cohort; Cox regression Incidence:982.1 per 100,000 person-years	Drug-susceptible PTB patients from national registry; n=66,690; recurrence ≈3.1% (over 39 months median follow-up), with 50.3% (occurred within 1 year after treatment completion)	Lower household income was associated with recurrence (aHR 1.76, 95% CI 1.49–2.07), with stronger effects observed among males (aHR 2.08, 95% CI 1.71–2.52).	Income used as proxy for socioeconomic status; residual confounding possible.
2.	Golub et al., 2019.[13]	South Korea	Large prospective cohort; time-varying Cox models	Adults with previous TB from national cohort; n= 1,267564; Age standardised recurrence rate≈ 759.4/100000	Diabetes mellitus significantly increased TB recurrence risk (aHR 1.67, 95% CI 1.12–2.48) and TB-related mortality.	Recurrence identified using administrative data; limited clinical detail. TB recurrence was defined using claim-based in person with prior TB episode, limiting the differentiation between relapse after cure and re-treatment cases.
3.	Hsu et al., 2025.[21]	Taiwan	Retrospective cohort; Cox regression	Successfully treated non-HIV PTB patients; n=1,875; recurrence ≈2.0% (median follow-up: 72 months). The highest rate was seen within 2 years of treatment completion	Low BMI (<20 kg/m²) (aHR 4.38, 95% CI 1.70–11.30), prior history of TB (aHR 4.28, 95% CI 1.77–10.35), and 2-month culture non-conversion (aHR 3.37, 95% CI 1.36–8.38) predicted recurrence.	Single centre; limited generalizability
4.	Shen et al., 2017.[22]	China (Shanghai)	Retrospective cohort with molecular genotyping; Cox regression	Successfully treated bacteriologically confirmed PTB; n=13,417; recurrence≈ 5.3% or 755 cases per 100,000 person-years. Relapse cases occurred earlier, within 3 years after treatment completion while reinfection cases increased as time progressed.	Male sex (aHR 1.40, 95% CI 1.11–1.77), age 30–59 (aHR 1.24, 95% CI 1.03–1.47), cavitation (aHR 1.27, 95% CI 1.06–1.51), diabetes (aHR 1.42, 95% CI 1.13–1.79), smear positive (aHR 2.13, 95% CI 1.19–1.51) and MDR-TB (aHR 2.90, 95% CI 2.20–3.84) increased recurrence; 58.2% due to relapse with similar genotype.	Genotyping was limited (approximately only 27.4% had paired isolates to differentiate the mechanism of recurrence); immigrant populations were excluded.
5.	Ruan et al., 2022.[23]	China (Hangzhou)	Retrospective population cohort; Cox regression	Successfully treated smear-positive non-MDR PTB; n=9,828; recurrence ≈4.9%. More than 50% of recurrences occurred within 1-year post-treatment completion (median follow-up: 51.4 months	Recurrence risk increased with male sex (aHR 1.61, 95% CI 1.30–2.00), age ≥60 (aHR 2.03, 95% CI 1.70–2.44), cavitation (aHR 1.51, 95% CI 1.25–1.82), and 2-month sputum positivity (aHR 1.39, 95% CI 1.12–1.82); prolonged treatment was protective (aHR 0.73, 95% CI 0.61–0.88).	Retrospective design; with potential case underestimation. Lack of socioeconomic (income and employment status) and clinical data (adherence)
6.	Li et al., 2024.[24]	China (national registry)	Retrospective national cohort; Cox regression	Successfully treated PTB cases (2005–2021); n=1,0482271; recurrence≈3.9% or 0.47 per 100 person-years. 48.9% of recurrences occurred within the first 2 years.	Age 65 to 85 years (aHR 2.54, 95% CI 1.65–3.92), minority ethnicity (aHR 1.55, 95% CI 1.25–1.91), treated in general hospital (aHR 2.35, 95% CI 1.26–4.41) increased recurrence, while negative sputum at 2 months (aHR 0.31, 95% CI 0.16–0.58) was a protective factor.	Registry-based data; relapse vs reinfection not distinguished.
7.	Wang et al., 2024.[25]	China (Jiangsu)	Retrospective cohort; Cox regression	Successfully treated PTB patients; n=12,509; recurrence ≈3.5% or 6.62 per 1000 person years (median follow-up: 65.5 months)	Diabetes mellitus (aHR 2.40, 95% CI 1.68–3.45), age ≥60 (aHR 1.39, 95% CI 1.15–1.70), male sex (aHR 1.30, 95% CI 1.03–1.64), and etiologic positivity (aHR 2.42, 95% CI 2.00–2.92) increased recurrence risk, while FDC (aHR 0.77, 95% CI 0.61–0.95) reduced recurrence risk.	No strain typing; reliance on routine surveillance variables.
8.	Yen et al., 2014.[26]	Taiwan	Retrospective cohort; Cox regression	Successfully treated TB patients; n=5,567; recurrence≈1.5%	Heavy smoking (>10 cigarettes/day) doubled recurrence risk (aHR 2.03, 95% CI 1.29–3.18); homelessness (aHR 3.75, 95% CI 1.17–12.07); comorbidities (aHR 2.66, 95% CI 1.22–5.79) and smear positivity (aHR 2.27, 95% CI 1.47–3.49) were additional predictors.	Smoking exposure self-reported; residual socioeconomic confounding.

Table II: Characteristics included studies, recurrence definition and frequency, statistical approaches, and adjusted risk factors for TB recurrence in Asia

No.	Author (year)	Country / Setting	Study design	Study population & sample size	Key recurrence findings	Main limitations
9.	Lin et al., 2024.[27]	China	Prospective cohort; Cox regression	TB patients completing treatment; n=634; followed up to 7 years recurrence≈15.1%	Dose–response relationship between smoking intensity and recurrence; smoking cessation during treatment reduced recurrence risk. Heavy smoker who smokes 30+ cigarettes/day (aHR 6.488, 95% CI 2.16–19.46) had the highest recurrence risk compared with non-smokers.	Claim-based smoking status with no biochemical verification; residual confounding such as comorbidities.
10.	Lee et al., 2023.[28]	Taiwan (National Health Insurance Database)	Retrospective database cohort; time-to-event analysis	New TB patients (2008–2017); n=33,298; 2-year recurrence≈ 1.54%	Incomplete adherence (80–89%: aHR 1.57, 95% CI 1.27–1.96; 90–99%: aHR 1.63, 95% CI 1.29–2.07), diabetes (aHR 1.40, 95% CI 1.15–1.70), and COPD (aHR 1.28, 95% CI 1.06–1.55) increased recurrence.	Claims-based adherence and outcome definitions; limited clinical detail.
11.	Di et al., 2025.[15]	China (Quzhou)	Population-based retrospective cohort; Cox regression	PTB registry patients; n=6,732; recurrence≈ 8.2%	High $PM_{2.5}$ exposure markedly increased recurrence risk in a dose-response manner (aHR 15.48, 95% CI 9.28–25.82); residential greenness was protective (aHR 0.86, 95% CI 0.75–0.98 per 0.1 NDVI).	Environmental exposure estimation subject to spatial misclassification.
12.	Leung et al., 2015.[29]	Hong Kong	Prospective cohort; registry linkage; Cox regression	Successfully treated patients; n=13,349; recurrence≈ 3.2% or 396 per 100,000 person-years	Recurrence risk increased from never-smokers to ex-smokers (HR 1.33, 95% CI 1.04–1.71) to current smokers (HR 1.63, 95% CI 1.29–2.06).	Observational design; smoking exposure may be imperfect as it is not quantified.
13.	Huyen et al., 2013.[30]	Vietnam	Prospective cohort with genotyping; Cox regression	Smear-positive PTB patients; n=1,068; recurrence 3.3% (over 18 months follow-up) or 1.39 per 100 person-years. Of recurrent cases, 66% were relapse cases	Beijing genotype infection (aHR 5.48, 95% CI 2.06–14.55) and isoniazid resistance (aHR 5.91, 95% CI 2.16–16.16) strongly predicted relapse.	Limited follow-up time and lack of HIV and radiographic data for confounding adjustment.
14.	Mehrbakhsh et al., 2024.[31]	Iran (Golestan)	Retrospective cohort; penalised Cox models	Smear-positive PTB patients; n=1,548. Recurrence≈ 2.6% (median follow-up time:136.87months)	Relapse associated with age >35 (HR 2.77), CKD (HR 5.36), and married patients (HR 8.49); penalised Cox models improved prediction.	Single centre; covariate availability limited (smoking, alcohol)
15.	Wang et al., 2015.[32]	Taiwan (nationwide)	Retrospective population-based cohort; Cox regression	HIV-infected TB patients who completed anti-TB treatment; n=508; recurrences n=18 (3.5%)	Anti-TB treatment duration 6 to 9 months (>270 days) significantly reduced recurrence risk (aHR 0.24, 95% CI 0.08–0.73); treatment during the DOT era was protective (aHR 0.34, 95% CI 0.12–0.97).	CD4+ and HAART were not included which are common predictors for recurrence in HIV patients. Limited clinical detail (e.g. cavitation, smear conversion).

Notes:
PTB: Pulmonary tuberculosis; NDVI: Normalised Difference Vegetation Index; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; DOT: Directly observed therapy; HIV: Human immunodeficiency virus; BMI: Body mass index; FDC: Fixed-dose combination; MDR: Multidrug-resistant; $PM_{2.5}$: Fine particulate matter; HAART: Highly active antiretroviral therapy; aHR: Adjusted hazard ratio; CI: Confidence interval.

Table III: Stratified Adjusted Hazard Ratios for Determinants of TB Recurrence

Domain	Factor	Adjusted Hazard Ratio (Range)	Strength of Association*
Sociodemographic	▪ Male sex	1.30 – 1.61	Mild–Moderate
	▪ Older age (≥60 years)	1.39 – 2.54	Mild–Moderate
	▪ Age 30–59 years	1.24 – 1.50	Mild–moderate
	▪ Marital status (married)	8.49 (single study)	Strong (isolated)
	▪ Low household income	1.76 (1.49–2.07)	Moderate
	▪ Minority ethnicity	1.55 (1.25-1.91)	Moderate
	▪ Homelessness	3.75 (1.17–12.07)	Strong
Behavioural	▪ Current smoking	1.63 (1.29 – 2.06)	Moderate
	▪ Heavy smoking (>30+ cigarettes/day)	2.03 – 6.49	Moderate–strong
	▪ Smoking (dose–response)	↑ HR with intensity	Gradient effect
	▪ Smoking cessation	0.63 (0.46–0.86)	Protective
Comorbidities	▪ Diabetes mellitus	1.44 – 2.40	Moderate
	▪ Low BMI (<18.5- 20 kg/m²)	1.63 – 4.38	Moderate–strong
	▪ COPD	1.28 (1.06–1.55)	Mild
	▪ CKD	5.36 (single study)	Strong
	▪ HIV infection	Recurrence 3.5%	Elevated risk
Disease Severity / Microbiological	▪ Cavitary disease	1.27 – 1.51	Mild–Moderate
	▪ Smear/culture positivity/	1.67 – 4.09	Moderate–strong
	▪ 2-month non-conversion	1.39 – 3.37	Moderate–strong
	▪ Prior TB history	4.28 (1.77–10.35)	Strong
	▪ Any drug resistance	2.90 – 2.94	Moderate
	▪ Isoniazid resistance	5.91 (2.16–16.16)	Strong
	▪ Beijing genotype	5.48 (2.06–14.55)	Strong
Treatment-related	▪ Incomplete adherence (80–89%)	1.57 (1.22–1.96)	Moderate
	▪ Incomplete adherence (90–99%)	1.63 (1.26–2.07)	Moderate
	▪ FDC	0.77 (0.61–0.95)	Protective
	▪ Treatment >270 days	0.24 (0.08–0.73)	Protective
	▪ Prolonged regimen	0.73 (0.61–0.88)	Protective
	▪ DOT era treatment	0.34 (0.12–0.97)	Protective
Environmental	▪ High $PM_{2.5}$ exposure	15.48 (9.28–25.82)	Very strong
	▪ Residential greenness (per 0.1 NDVI)	0.86 (0.75–0.98)	Protective

Notes:
BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; HIV: Human immunodeficiency virus; FDC: Fixed-dose combination; DOT: Directly observed therapy; $PM_{2.5}$: Fine particulate matter; NDVI: Normalised Difference Vegetation Index.
Strength of association based on adjusted hazard ratio (aHR): Protective: <1.0; Mild: 1.1-1.4; Moderate: 1.5-3.0; Strong: 3.1-10.0; Very strong: >10.[33-34]

Table IV: Risk of bias assessment of included studies using the Newcastle–Ottawa Scale (NOS)

Author (Year)	Selection				Comparability	Outcome			Overall Score
	Cohort Representativeness	Non-exposed cohort selection	Exposure ascertainment	Outcome absent at baseline	Cohort comparability	Outcome ascertainment	Sufficient follow-up for outcome	Follow-up adequacy	(0–9)
Chung et al. (2024)	*	*	*	*	**	*	*	*	9
Golub et al. (2019)	*	*	*	*	**	*	*	–	8
Hsu et al. (2025)	*	*	*	–	**	*	*	–	7
Shen et al. (2017)	*	*	*	*	**	*	*	–	8
Ruan et al. (2022)	*	*	*	*	**	*	*	–	8
Li et al. (2024)	*	*	*	*	*	*	*	–	7
Wang et al. (2024)	*	*	*	*	**	*	*	–	8
Wang et al. (2015)	*	*	*	–	*	*	*	–	6
Yen et al. (2014)	*	*	*	*	*	*	*	–	7
Lin et al. (2024)	*	*	*	–	**	*	*	–	7
Lee et al. (2023)	*	*	*	*	*	*	*	–	7
Di et al. (2025)	*	*	*	*	*	*	*	–	7
Leung et al. (2015)	*	*	*	*	**	*	*	*	9
Huyen et al. (2013)	*	*	*	–	**	*	*	–	7
Mehrbakhsh et al. (2024)	*	*	*	–	**	*	*	–	7

Time-to-event analysis using Cox proportional hazards models was applied, including penalised and time-varying Cox approaches. However, only two studies distinguished between relapse and reinfection as mechanisms of recurrence using molecular genotyping. Heterogeneity arose from differences in data sources, time window of follow-up, study designs (retrospective or prospective) and modelling strategies.

Sample size and study population.
The included studies assessed TB recurrence across diverse post-treatment populations, with sample sizes ranging from 508 to over 1.2 million individuals, including one national registry study exceeding 10 million cases. Most focused on successfully treated pulmonary TB patients, including bacteriologically confirmed, smear-positive, and DS-TB cases; fewer examined new TB patients or human immunodeficiency virus (HIV) infected populations.

Determinants of TB Recurrence
The determinants of TB recurrence, as estimated by hazard ratios, are shown in Table III.

Across domains, the strongest associations with TB recurrence were observed for environmental exposures, particularly high fine particulate matter ($PM_{2.5}$) levels (aHR 15.48), drug resistance and bacterial genotype (aHR 5.48–5.91), prior TB history (aHR 4.28). Delayed microbiological response, such as two-month culture non-conversion (aHR 3.37), also showed a strong association. In contrast, modifiable factors were consistently protective, including smoking cessation, which reduced recurrence risk by approximately 35–40% (aHR 0.63), and extended treatment duration (>270 days), which was associated with up to a 76% lower risk of recurrence (aHR 0.24).

Summary of Study Limitations
Across the 15 studies, methodological limitations were common. Most studies used retrospective or registry-based designs, limiting causal inference and increasing residual confounding. About one-third relied on single-centre or single-province data, restricting generalisability. Over half (55–60%) used administrative or claims data, often lacked clinical detail and risked misclassification of recurrence. Relapse and reinfection were not differentiated in almost 80% of studies, as molecular genotyping was often available in selected populations or short follow-up. Exposure misclassification was noted, with self-reported behaviours in approximately 25–30% of the studies and spatial misclassification of environmental exposures. Collectively, these issues contributed to heterogeneity, limited synthesis, and reduced programmatic applicability.

Quality Assessment
The risk of bias of the included studies was assessed using the Newcastle-Ottawa Scale.[35] There were three domains: selection of study groups, comparability of groups and outcome ascertainment were evaluated. Table IV displays the summary of the risk of bias of the included studies. The included studies generally demonstrated high quality; 14 out of 15 studies (93.3%) had obtained total NOS scores of 7-9, signifying that the studies had a low risk of bias. Only one study scored six, thus it was categorised as having a moderate risk of bias, and no study was noted as having a high risk of bias. The selection domain was good, with all 15 studies rated three or four stars. In contrast, the comparability area had a lower strength, as only 60 per cent (9/15) received up to two stars for full confounder adjustment. All the studies on the outcome domain had at least two out of three stars, but the most overlooked parameter was the adequacy of follow-up. Generally, the results indicate that the findings should be interpreted with caution because residual confounders may potentially serve as a limitation.

DISCUSSION

The recurrence rates observed in our study range widely from 1.5% to 15% or 0.47 to 6.5 per 1,000 person-years reflecting a diverse epidemiological landscape of TB in Asia. Globally, the upper limit of this range is higher than the reported rate in regions with highly resourced healthcare systems such as the United States and Europe which reported rates between 1.1% and 5.7%.[36-38] Within our study cohort, we observed that high-income Asian countries (South Korea, Taiwan, and Hong Kong) generally reported lower recurrence compared to middle- and lower-income countries (China, Vietnam, and Iran), suggesting a role of economic resources in long-term disease management. In Asian setting, TB recurrence cannot be explained by one single factor, as there is a complex interaction of individual susceptibility and structural determinants of health. Multiple determinants have been found as the key predictors of TB recurrence, which can be divided into several domains: sociodemographic, behavioural, comorbidities, microbiological, treatment-related, and environmental factors.[16] This study demonstrates the importance of sociodemographic and structural determinants that contribute to TB recurrences. Male and older patients are more prone to have recurrence.[14,22-25] The high male incidence could suggest more occupational exposure and lower health-seeking behaviours, while older patients are more likely to have immunological deterioration and more comorbidities (e.g., diabetes, COPD), thereby making adherence and tolerance to treatment difficult and slow bacterial clearance.[39-41]

Socioeconomic disadvantage, such as homelessness, low household income, and being an ethnic minority, also exhibited a quite strong association with TB recurrence. A Korean study found the risk increases as income level decreases, shaped by barriers to high-quality care, increased exposure to transmission environments.[14] These structural determinants influence TB recurrence by impacting treatment adherence and weakened immune response. Homelessness further increases the risks through continuous barriers to healthcare access and suboptimal living conditions.[26,42-43] These factors suggest that TB recurrences are not purely biomedical failures; they represent a complex interaction between biological, social environment and health system. Behavioural factor like smoking is found to be modifiable determinants of long-term TB treatment outcomes, including recurrence.[26-27,29,44] In this analysis, the dose-response relationship in which heavier smoking is associated with higher hazards of TB recurrences is established. This is supported by a recent systematic review

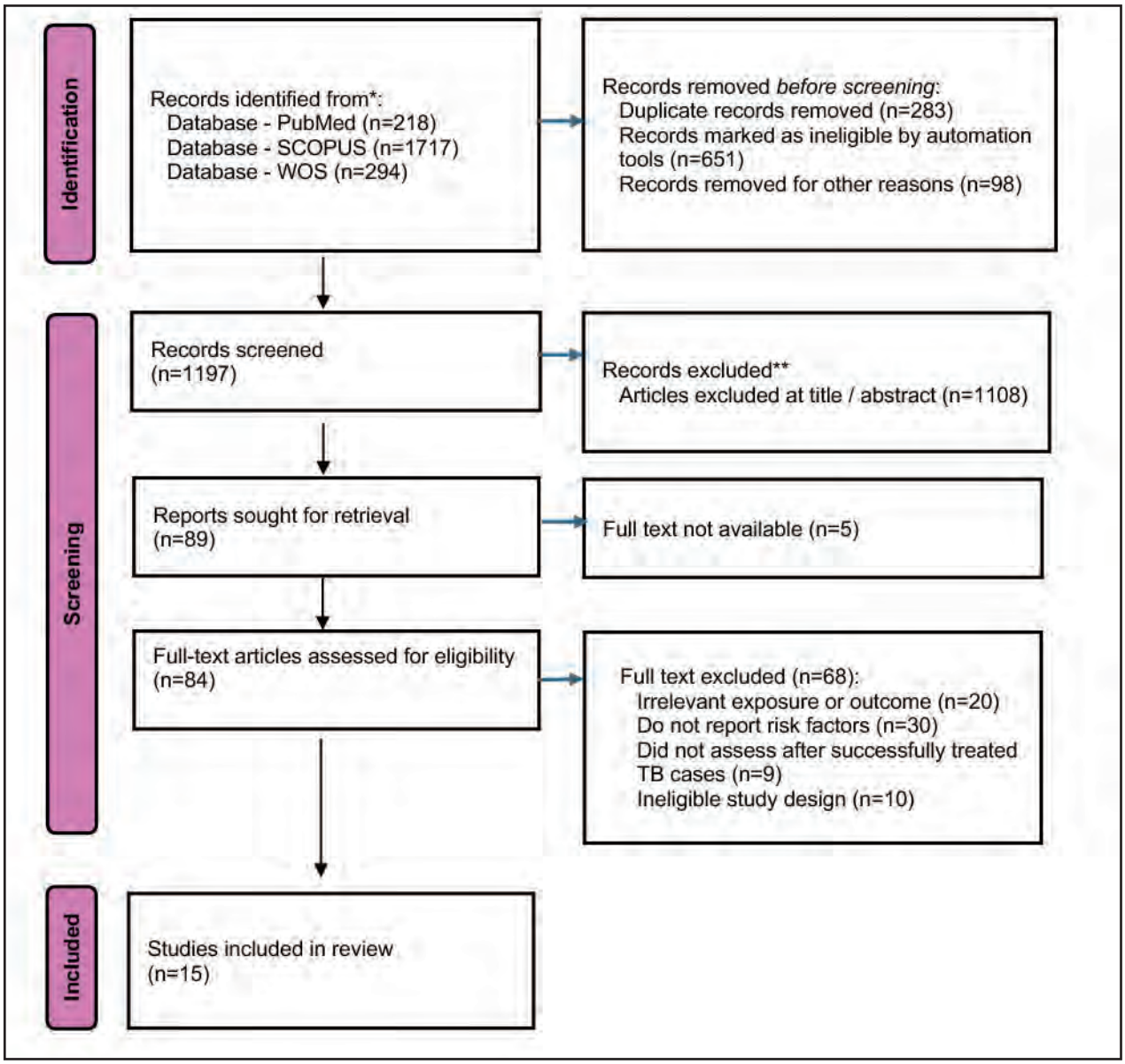

Fig. 1: The process of selecting suitable journals using the PRISMA flowchart

and meta-analysis showing that smoking cigarettes is linked to impaired immune defences, reduced macrophage function and delayed clearance of *M. tuberculosis*.[44] The consistencies in dose-responses gradient observed in several studies included in the review and the evidence of smoking cessation reduces the risk of TB recurrence support the biological plausibility, coherence, reversibility and strengthen causal inference under the Bradford Hill framework.[45]

Having comorbidities such as diabetes, COPD, CRF, HIV infection and low BMI tends to increase the risk of developing TB recurrence. From our analysis, those with diabetes have a two times higher risk of developing recurrence, possibly because the condition impairs innate and adaptive immunity and delays sputum conversion.[13,22,25,28] Low BMI and malnutrition are also associated with impaired cell-mediated immunity and reduced CD4 T-cell and interferon-gamma (IFN-γ) responses, thereby increasing the risk of unsuccessful TB outcomes and recurrences.[21,46] Additionally, broader immunosuppressive conditions and therapies, particularly the use of tumour necrosis factor-alpha (TNF-α) inhibitors, are identified as risk factors in other studies.[47-48] As TNF-α is essential for the formation and maintenance of granulomas that contain M. tuberculosis, patient receiving the therapy for inflammatory diseases (eg; rheumatoid arthritis) have compromised immune containment thus increasing their susceptibility to TB reactivation and recurrence.[48]

Furthermore, COPD is also found to have a higher hazard for developing recurrence due to structural lung damage and impaired mucociliary clearance, thus increasing susceptibility to reinfection and reactivation from residual foci, and this finding is supported by recent reviews.[28,49-50] Other than that, CKD also has an increased risk of recurrence, about five times compared to those without it; however, only one study included in our analysis reported

this association. Luczynski et al, through their systematic review, suggest that CKD has immune dysregulation, specifically uraemia-related dysfunction, which alters the pharmacokinetics of TB medication and leads to higher side effects and recurrence.[51] HIV is another common comorbidity associated with an increased risk of recurrence. Evidence from the study conducted on TB-HIV patients suggests that treatment duration and treatment during the DOT era influence the risks; however, this study relied on routine or claim-based data and the independent contribution of clinical aspects, such as CD4+ counts and HAART treatment, could not be fully assessed.[32]

Disease severity and certain microbiological characteristics are also consistently linked with TB recurrence.[16,25-26] Among them are cavitary disease, smear/culture positivity, prior TB and delayed two months smear conversion.[21-23] Pulmonary cavities may result from failure to contain *M. tuberculosis*, producing necrosis that harbours high bacterial loads, delays clearance and elevates the risk for unfavourable treatment outcomes and recurrence.[52] A prior TB episode is another strong risk factor for recurrence, likely reflecting residual cavity or fibrotic lung damage and increased susceptibility to recurrence. Additionally, a high baseline smear grade can act as a marker for high mycobacterial burden and is often associated with delayed conversion and incomplete clearance.[21] Drug resistance has shown strong associations with recurrence, with isoniazid resistance exhibiting the largest hazard ratios.[30] The resistance compromises bactericidal activity and slows its clearance, resulting in higher bacterial loads and an increased risk for recurrence.[53] In addition, Beijing strains were found to be a strong risk factor for recurrence as it frequently associated with higher virulence traits, superior intracellular survival and drug-resistance.[54-55]

The risk of TB recurrence is also contributed by several treatment-related factors. Those with incomplete treatment (80–99%) have a higher risk of recurrence compared to those who fully completed the treatment.[28] An effective cure requires sustained and uninterrupted treatment over a prolonged period. From our analysis, longer treatment which is six to nine months or >270 days, reduces the recurrence risk. To reduce pill burden and maximise adherence, a fixed-dose combination (FDC) was introduced by the WHO, and it is noted to have a protective effect towards disease recurrence compared to loose tablets.[25] Moreover, the directly observed therapy (DOT) strategy that is designed to ensure adherence has also been found to reduce the risk for recurrence.[32,56] Environmental factors, especially exposure to $PM_{2.5}$ are strongly associated with TB recurrence. Our analysis indicates that an individual exposed to high $PM_{2.5}$ has a higher risk, approximately 15 times higher than those in the lower exposure group.[15] $PM_{2.5}$ can penetrate the lungs and weaken the body's natural defence mechanisms, making it easier for TB bacteria to persist and reactivate even after treatment is completed.[57] On the contrary, residential green spaces help to improve air quality and support lung health and possibly reduce risk of respiratory infections and recurrence.[58] These findings suggest that TB recurrence is influenced not only by clinical care but also by the environmental conditions.

Clinical and Public Health Implications

In general, the consistency and strength of associations across multiple domains are suggestive of a multifactorial model of TB recurrence with several modifiable risk factors, which offer opportunities for early prevention. The identification of at-risk patients, including those with drug resistance, late sputum conversion, prior TB or significant environmental exposure, will help in making clinical decisions. This includes risk-stratified surveillance, possible extended and closer post-treatment follow-up to allow early detection of recurrence. These approaches promote more efficient use of health-care resources. Most importantly, an integrated intervention that combines clinical management, behaviour interventions (smoking cessation and adherence support) and environmental as well as living conditions adjustments required to prevent TB recurrences.

Strengths and Limitations of the Study

This study offers a comprehensive synthesis of TB recurrence risk determinants by integrating clinical, microbiological, behavioural and environmental factors. The inclusion of emerging environmental data such as $PM_{2.5}$ and residential greenness extends the traditional clinical scope of TB research. By identifying modifiable risk factors, this review provides high translational value for public health programs aiming to reduce TB recurrence. There are a few limitations that should be mentioned. First, the findings rely on observational data, which restricts the causal inference. Second, heterogeneity across studies in the measurement of treatment adherence and environmental exposure is quite high and may result in some misclassification bias.

CONCLUSION

The review demonstrates that clinical, microbiological, treatment-related, behavioural, and environmental factors interact to cause TB recurrence. The findings support a multifactorial model of recurrence and identify modifiable, prevention-ready targets. Risk-stratified care for high-risk patients, combined with adherence support, behavioural interventions, and environmental improvements, is essential. Integrated, patient-centred, and multisectoral strategies are therefore critical to achieving durable TB cure and reducing recurrent disease burden.

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CONFLICT OF INTEREST

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