Determinants of delayed diagnosis and treatment of tuberculosis in high-burden countries: a mixed-methods systematic review and meta-analysis

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Research

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Abstract

Background: Globally, 30 countries with the highest tuberculosis (TB) burden bears 87% of the world's TB cases. Delayed diagnosis and treatment are detrimental to TB prognosis and sustain TB transmission in the community, making TB elimination a great challenge, especially in these countries. Our objective was to elucidate the determinants and duration of delayed diagnosis and treatment of pulmonary TB in high TB burden countries.

Methods: We conducted a systematic review and meta-analysis of quantitative and qualitative studies by searching four databases for literature published between 2008 and 2018 following PRISMA guidelines. For quantitative studies, we performed narrative synthesis of the covariates that were significantly associated with patient, health system, treatment, and total delays. The pooled median duration of delay and effect sizes of covariates were estimated using random-effects meta-analyses. We identified key qualitative themes using thematic analysis.

Results: We included 124 articles from 14 low-and lower-middle-income countries (LIC and LMIC) and five upper-middle-income countries (UMIC) in this review. The pooled median duration of patient, health system, and treatment delay were 28 days (95%CI 20–30), 11.5 days (95%CI 3.9–24.7), and six days (95%CI 1–28.4), respectively. We found that the duration of delays was consistently shorter among UMIC compared to LIC and LMIC. There was consistent evidence that being female and rural residence was associated with longer patient delay. Furthermore, patient delay was also associated with other individual, interpersonal, and community risk factors such as poor TB knowledge, long chains of care-seeking through private/multiple providers, perceived stigma, financial insecurities, and poor access to healthcare. Health system and treatment delay were mediated by organizational and policy factors. These factors included the lack of resources and complex administrative procedures and systems at the health facilities. We identified data gaps in 11 high burden countries.

Conclusions: This review detailed the determinants of delayed TB diagnosis and treatment in high burden countries. The gaps identified at different socio-ecological levels could be addressed through tailored approaches, education, and at a higher level, through health system strengthening and provision of universal health coverage to reduce delays and improve access to TB diagnosis and care.

Background

In 1993, the World Health Organization (WHO) declared global tuberculosis (TB) emergency to make TB a high priority [1]. Twenty-five years on, TB remains one of the leading infectious causes of illness and death worldwide [2]. Despite that TB is both preventable and curable, and efforts such as the implementation of directly observed treatment short course and coordinated national TB programs worldwide, approximately 10 million people fell ill with TB, of which 1.5 million died from the disease in 2018 [2]. The cumulative reduction in the TB incidence rate globally between 2015 and 2018 stood at 6% [2], imposing a significant delay in reaching the end TB milestone of 20% [3] reduction by the year 2020. TB control and elimination is a critical challenge in many countries. However, the burden is disproportionately borne by 30 countries, mostly in Asia and Africa, accounting for 87% of the world's TB (both pan-TB and drug-resistant TB) and TB/HIV cases [2].

In 2018, nearly one-third of the people with TB were estimated to be undiagnosed globally [2]. The delay in diagnosis and treatment is not only detrimental to the patients' prognosis but also perpetuates TB transmission in the community [4] and thus poses a great challenge to eliminate TB. Therefore, identifying the factors that lead to delayed TB diagnosis and treatment is imperative in developing interventions to achieve a substantial reduction in TB incidence. Collectively, recent systematic reviews have provided empirical evidence associating socio-demographic, clinical, health system, and economic factors with delayed diagnosis and treatment of TB in different countries and regions [5–11]. However, delays in diagnosis and treatment vary across countries with a different burden of the disease. From what we know, no systematic reviews have addressed delayed diagnosis and treatment of TB among countries bearing most of the global TB burden. There is also a lack of reviews that triangulate qualitative and quantitative findings to provide a more complete and all-inclusive view of the matter. Therefore, a systematic review and meta-analysis were undertaken to derive the determinants and duration of diagnosis and treatment delay of pulmonary TB in the high TB-burden countries.

Methods

We structured this review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement. The protocol of this systematic review was published [12] and registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42018107237).

Inclusion and exclusion criteria

In this review, we considered all studies conducted in the WHO high TB-burden countries—Angola, Bangladesh, Brazil, Cambodia, Central African Republic, China, Congo, Democratic People's Republic of Korea, Democratic Republic of Congo, Ethiopia, India, Indonesia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, the Philippines, Russian Federation, Sierra Leone, South Africa, Tanzania, Thailand, Vietnam, Zambia, and Zimbabwe. We included studies that reported on individual and interpersonal risk factors, social and physical environment, health systems, and policies associated with delayed TB diagnosis and treatment initiation published between 2008 and 2018. The factors could be self-reported, ascertained by health providers, or abstracted from medical charts or programs/administrative records.

We included study populations that comprised presumptive TB cases and people with TB (new diagnosis, previously treated, and those without a known history of previous TB treatment) regardless of HIV and bacteriological status. We included both observational (cross-sectional, case-control, retrospective, and prospective cohort design) and qualitative studies published in either English or Chinese language. Systematic reviews, meta-analyses, scoping reviews, intervention studies, publications in the form of letters and reviews, and studies lacking and/or unclear reporting of key outcomes were excluded.

Our primary outcomes were—1) patient delay: the time interval between the onset of symptoms and the first encounter with healthcare professionals; 2) health system delay: the time interval between the first encounter with healthcare professionals and the diagnosis of pulmonary TB; 3) treatment delay: the time interval between TB diagnosis and TB treatment initiation; and 4) total delay: the time interval between onset of symptoms and TB treatment initiation. As there were no universal cut-offs [8] to a duration that constituted delay, we treated delay in this review as to how they were defined in individual studies.

Literature search strategy and study selection

First, we conducted a preliminary search of articles on PubMed and EMBASE to develop a set of appropriate Medical Subject Heading terms, index terms, and keywords [12]. Using these identified search terms structured with Boolean logic operators (AND and OR), we searched PubMed, EMBASE, CINAHL, and PsycInfo. We also reviewed the reference list of key articles for additional studies. We managed all identified citations into EndNote X8 (Clarivate Analytics, Philadelphia, USA). Duplicates were removed and citations were exported to Microsoft Excel (Microsoft Corporation, Washington, USA) for further assessment. AKJT and SRS independently screened the titles, abstracts, and full-text articles based on the inclusion and exclusion criteria. Interrater agreements for the titles and abstract screening between the reviewers were high (agreement = 98%, Cohen's kappa = 0.95, and Krippendorff alpha = 0.95) and discrepancies were discussed. The search and selection process was conducted and presented in accordance with the PRISMA guidelines.

Data extraction

Study characteristics and data on risk factors were extracted independently by two authors (AKJT and SRS). We recorded study and participants' characteristics, exposure variables (various factors associated with delays reported by individual study), primary outcome measures, and study quality assessment scores using a standard form. Data on variables to be included in the meta-analysis were extracted by one author (AKJT) and subsequently reviewed by a second author (KP). This included duration of delay (median and interquartile range/range and mean and standard deviation) and the effect sizes for exposures of interest.

Quality assessment

The quality of the selected non-randomized (quantitative) and qualitative studies was critically evaluated using the Newcastle-Ottawa Scale for cross-sectional studies, case-control studies, and cohort studies, and the Critical Appraisal Skills Program (CASP) tool, respectively [13–15]. For non-randomized quantitative studies, the assessment was made based on four main domains - selection of samples (representativeness, sample size, definition and selection of cases and controls (for case-control studies), and non-response rate), comparability of groups included in the analyses, and the ascertainment of exposures and outcomes, including the statistical tests applied in the studies. A score of 1 was given to individual questions if the criterion was satisfied, and 0 was given if the criterion was not satisfied or not justified. The highest possible score for cross-sectional studies was 10 (5 for selection, 2 for comparability, and 3 for outcomes). The highest possible score for case-control studies was 9 (4 for selection, 2 for comparability, and 3 for exposure). The highest possible score for cohort studies was 9 (4 for selection, 2 for comparability, and 3 for exposures). Studies that scored 0–3 were regarded as low quality (LQ), 4–6 were regarded as moderate quality (MQ), and ≥ 7 were regarded as high quality (HQ).

For qualitative studies, the assessment was made based on 10 questions regarding the results and its validity, and the value of the research. We gave a score of 1 if the paper fulfilled a criterion, 0.5 if we could not tell if the paper fulfilled a criterion, and 0 if the paper did not fulfill a criterion. A score of 0–5 equated to LQ study, a score of 6–7 equated to MQ study, and a score of ≥ 8 equated to HQ study. The final synthesized qualitative findings were graded based on the dependability and credibility of the findings using the ConQual approach [16].

Data synthesis and analyses

We described the studies by the populations, countries, study designs, and sample sizes. We reported the independent variables that were significantly associated with patient, health system, treatment, and total delays. In studies that reported both bivariate and multivariable analyses, results from the multivariable analyses preceded that of bivariate.

Median and interquartile range/range for the duration of delay in days were extracted and used to estimate a pooled median, i.e. median of study-specific medians [17]. For independent variables (risk factors), effect sizes were extracted and used to calculate pooled odds ratio and their 95% confidence interval (CI). We pooled effect sizes of covariates if data were available in more than two studies and duration of delays by meta-analysis using R (R Foundation for Statistical Computing, Vienna). Where adjustments for covariates had been performed, the data were extracted from the adjusted model. We quantified between-study heterogeneity using Chi-square statistic Q , I^2 , and Tau [18]. For each meta-analysis, we estimated the pooled odds ratio (OR) and its 95% CI using a random-effect model which accounts for between-study heterogeneity [19]. The estimates for Tau and I^2 statistics were presented together with the pooled estimates and the 95% CI. We assessed the association of the primary outcomes and 1) sociodemographic and economic variables: sex, marital status, urbanicity; 2) behavioral variables: smoking, alcohol use, stigma, TB knowledge; and 3) clinical and health services-related variables: cough, hemoptysis, weight loss, fever, chest pain, night sweats in the meta-analyses.

We extracted qualitative findings and sample quotes reported in qualitative and mixed-method studies verbatim. The extracted data were annotated and analyzed using NVIVO 12 (QSR International). We retrieved references deductively and applied thematic analyses to categorize the textual references. Two authors (AKJT and SRS) coded the data independently. Discrepancies, code definitions, and the emergence of sub-themes were discussed. The results were presented by income categories that the high-burden countries represent.

Results

Study selection

The systematic review process is presented in Fig. 1. A total of 4878 records were identified from electronic database searches. Following the removal of duplicates ($n = 1189$), and non-relevant titles and abstracts ($n = 3451$), 238 full-text articles were retrieved and assessed. Of these, 114 articles were further excluded. A total of 124 articles were reviewed—36, 86, and two articles were included for qualitative synthesis; quantitative and narrative synthesis; and qualitative, quantitative, and narrative synthesis, respectively. Thirteen (87%) meta-analyses had large heterogeneity ($I^2 > 50\%$), and 10 (67%) meta-analyses had very large heterogeneity ($I^2 > 75\%$).

Study characteristics and quality assessments

These studies described data from 149,901 presumptive TB cases and people with TB,[20–107] 1659 in-depth and structured interviews, and 87 focus groups [44, 94, 108–143] from 19 countries in three continents (Table 1). A total of 14 countries were classified as lower-income (LIC) and lower-middle-income economies (LMIC), and five were classified as upper-middle-income economies (UMIC) [144]. Patient delay was reported in 103 studies, health system delay in 29 studies, treatment delay in 18 studies, and total delay in 21 studies. Of the 30 high TB-burden countries, 11 countries were not included in this review, either due to data unavailability or lack of key outcome data (Fig. 2). After assessments of study quality, a total of 81 HQ studies, 40 MQ studies, and one LQ study were identified. Two mixed-methods studies scored MQ/HQ and HQ/MQ for the quantitative and qualitative components, respectively. The final synthesized qualitative findings were rated HQ (55%) and MQ (45%) using the ConQual method. Details of the assessments were illustrated in the Supplementary Materials. Based on the outcome of quality assessments, no studies were excluded; instead, the information was considered during data synthesis and interpretation.

Table 1
Characteristics of included observational and qualitative studies

Income group ^a	Country	Study population	Study design	Sample size and study		
				Newcastle-Ottawa scale score ^b		
				HQ	MQ	LQ
Patient delay						
LIC	Ethiopia	People with TB	Cross-sectional	216[20], 296[21], 360[22], 382[23], 398[24], 425[25], 605[26], 706[27], 924[28]	129[29], 201[30], 226[31]	
		Presumptive TB cases	Case-control	838[32]		
			Cross-sectional	476[33], 843[34], 1006[35]	663[36], 763[37]	
	Mozambique	People with TB	Cross-sectional		622[38]	
	Tanzania	People with TB	Cross-sectional	639[39]	206[40]	
		Presumptive TB cases	Cross-sectional	3388[41]		
LMIC	Angola	People with TB	Cross-sectional	385[42]		
	Bangladesh	People with TB	Cross-sectional		7280[43]	
	Cambodia	People with TB	Mixed-methods		96[44]	
	India	People with TB	Cross-sectional	216[45], 234[46]	150[47], 261[48]	
		People with TB (children)	Cross-sectional		175[49]	
		Presumptive TB cases	Cross-sectional	437[50]		
	Indonesia	Presumptive TB cases	Cross-sectional	194[51]	746[52]	
	Kenya	People with TB	Cross-sectional			230[53]
		Presumptive TB cases	Cross-sectional		426[54]	
	Nigeria	People with TB	Cross-sectional	160[55], 450[56]	102[57]	
	Zambia	Presumptive TB cases	Cross-sectional	6708[58]		
	Zimbabwe	People with TB	Cross-sectional	383[59]		
UMIC	Brazil	People with TB	Cross-sectional	139[60], 153[61]	97[62], 101[63], 199[64], 218[65], 304[66]	
		TB-HIV co-infection	Prospective cohort	201[67]		

CASP, critical appraisal skills program; FGD, focus group discussions; HQ, high quality, IDI, in-depth interviews; LIC, low-income countries, LMIC, lower-middle-income countries, LQ, low quality; MQ, moderate quality, TB, tuberculosis, UMIC, upper-middle-income countries,

^aBased on World Bank classification. Low-income economies—gross national income (GNI) per capita \$1,025 or less in 2018; lower middle-income economies—GNI per capita between \$1,026 and \$3,995; upper middle-income economies—GNI per capita between \$3,996 and \$12,375

^bStudy quality was assessed using the Newcastle-Ottawa scale. Highest possible score for cross-sectional studies was 10 (5 for selection, 2 for comparability, and 3 for outcome). Highest possible score for case-control studies was 9 (4 for selection, 2 for comparability, and 3 for exposure). Highest possible score for cohort studies was 9 (4 for selection, 2 for comparability, and 3 for exposure). Studies that scored 0–3 were regarded as LQ, 4–6 were regarded as MQ, and ≥ 7 were regarded as HQ.

^cAll papers were pre-ranked (high, moderate, low) and the levels were adjusted according to the dependability and credibility of the findings. We pre-ranked all papers as high. The ranking remained high if the papers were regarded as dependable and the findings were unequivocal. We downgraded the paper from high to moderate if the papers scored 3 or less in terms of dependability or scored a mix of unequivocal and credible in terms of credibility.

^dCASP for qualitative study had 10 questions to critically appraise the paper. We gave a score of 1 if the paper fulfilled a criterion, 0.5 if we couldn't tell if the paper fulfilled a criterion, and 0 if the paper did not fulfil a criterion. A score of 0–5 equated to LQ study, a score of 6–7 equated to MQ study, and a score of ≥ 8 equated to HQ study.

Income group ^a	Country	Study population	Study design	Sample size and study		
				Newcastle-Ottawa scale score ^b		
				HQ	MQ	LQ
	China	People with TB	Cross-sectional	314[68], 1126[69], 2280[70]	146[71], 259[72], 314[73], 323[74], 819[75], 1083[76]	
			Prospective cohort		202[77]	
			Retrospective cohort	4677[78], 10356[79]	75401[80]	
		Presumptive TB cases	Cross-sectional		1005[81]	
	Russia	People with TB	Cross-sectional	105[82]		
	South Africa	General population	Cross-sectional		1020[83]	
		Presumptive TB cases	Cross-sectional		104[84]	
		TB-HIV co-infection	Prospective cohort	891[85]		
	Thailand	People with TB	Cross-sectional	443[86]	199[87]	
Health system delay						
LIC	Ethiopia	People with TB	Cross-sectional		201[30]	
	Nigeria	People with TB	Cross-sectional	470[88]		
LMIC	Angola	People with TB	Cross-sectional	385[42]		
UMIC	Brazil	People with TB	Cross-sectional		218[65], 304[66], 305[89]	
	China	People with TB	Cross-sectional	314[68]	146[71]	
			Prospective cohort		202[77]	
			Retrospective cohort	4677[78]		
	South Africa	TB-HIV co-infection	Cross-sectional	480[90]		
Treatment delay						
LIC	Tanzania	People with TB	Cross-sectional	1161[91]		
LMIC	Bangladesh	People with TB	Cross-sectional		123[92]	
	Cambodia	People with TB	Mixed-methods		96[44]	
<p>CASP, critical appraisal skills program; FGD, focus group discussions; HQ; high quality, IDI, in-depth interviews; LIC; low-income countries, LMIC; lower-middle-income countries, LQ; low quality; MQ; moderate quality, TB; tuberculosis, UMIC; upper-middle-income countries,</p> <p>^aBased on World Bank classification. Low-income economies—gross national income (GNI) per capita \$1,025 or less in 2018; lower middle-income economies—GNI per capita between \$1,026 and \$3,995; upper middle-income economies—GNI per capita between \$3,996 and \$12,375</p> <p>^bStudy quality was assessed using the Newcastle-Ottawa scale. Highest possible score for cross-sectional studies was 10 (5 for selection, 2 for comparability, and 3 for outcome). Highest possible score for case-control studies was 9 (4 for selection, 2 for comparability, and 3 for exposure). Highest possible score for cohort studies was 9 (4 for selection, 2 for comparability, and 3 for exposure). Studies that scored 0–3 were regarded as LQ, 4–6 were regarded as MQ, and ≥ 7 were regarded as HQ.</p> <p>^cAll papers were pre-ranked (high, moderate, low) and the levels were adjusted according to the dependability and credibility of the findings. We pre-ranked all papers as high. The ranking remained high if the papers were regarded as dependable and the findings were unequivocal. We downgraded the paper from high to moderate if the papers scored 3 or less in terms of dependability or scored a mix of unequivocal and credible in terms of credibility.</p> <p>^dCASP for qualitative study had 10 questions to critically appraise the paper. We gave a score of 1 if the paper fulfilled a criterion, 0.5 if we couldn't tell if the paper fulfilled a criterion, and 0 if the paper did not fulfil a criterion. A score of 0–5 equated to LQ study, a score of 6–7 equated to MQ study, and a score of ≥ 8 equated to HQ study.</p>						

Income group ^a	Country	Study population	Study design	Sample size and study		
				Newcastle-Ottawa scale score ^b		
				HQ	MQ	LQ
	India	People with TB	Cross-sectional	234[46], 344[93]	150[47]	
			Mixed-methods	2027[94]		
			Retrospective cohort	662[95], 1800[96]		
	Zimbabwe	People with TB	Retrospective cohort	2443[97]		
UMIC	China	People with TB	Cross-sectional	314[98]		
			Retrospective cohort	4677[78]		
	South Africa	People with TB	Cross-sectional	210[99]		
Total delay						
LIC	Ethiopia	People with TB	Cross-sectional	216[20], 296[21], 328[100], 382[23]	201[30]	
	Mozambique	People with TB	Cross-sectional		622[38]	
	Tanzania	People with TB	Cross-sectional		206[40]	
LMIC	Bangladesh	People with TB	Cross-sectional		7280[43]	
	India	People with TB	Cross-sectional	216[45], 289[101]		
			Retrospective cohort	656[102]		
	Indonesia	People with TB	Cross-sectional		1116[103]	
	Nigeria	People with TB	Cross-sectional	450[56]		
	Pakistan	People with TB	Cross-sectional	844[104]	252[105], 269[106]	
UMIC	Brazil	People with TB	Case-control	242[107]		
			Cross-sectional		304[66]	
	South Africa	People with TB	Cross-sectional	210[99]		
		TB-HIV co-infection	Prospective cohort	891[85]		
	Thailand	People with TB	Cross-sectional	443[86]		
Qualitative studies						
CASP, critical appraisal skills program; FGD, focus group discussions; HQ, high quality, IDI, in-depth interviews; LIC, low-income countries, LMIC, lower-middle-income countries, LQ, low quality; MQ, moderate quality, TB, tuberculosis, UMIC, upper-middle-income countries,						
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Income group ^a	Country	Study population	Study design	Sample size and study		
				Newcastle-Ottawa scale score ^b		
				HQ	MQ	LQ
Income group ^a	Country	Study population	Methods of analysis	Study and sample size	ConQual rating ^c	CASP score ^d
LIC	Ethiopia	People with TB, contacts of people with TB, and health care workers	Phenomenological analysis	5 IDIs and 2 FGDs[108]	HQ	HQ
		People with TB	Thematic analysis	26 IDIs[109]	HQ	HQ
		People with TB and policy makers	Thematic analysis	19 IDIs[110]	HQ	HQ
	Mozambique	Caretakers of people with TB	Content analysis	35 IDIs[111]	HQ	HQ
	Tanzania	People with TB and traditional healers	Content analysis	32 IDIs[112]	HQ	HQ
LMIC	Bangladesh	People with TB	Qualitative analysis of open ended survey questions	229 interviews[113]	MQ	MQ
		People with TB and health care workers	Qualitative analysis using a priori codes	24 IDIs[114]	HQ	HQ
	Cambodia	People with TB, health care workers, and community volunteers	Thematic analysis	43 IDIs and 6 FGDs[44]	MQ	HQ
		People with TB and general population		13 FGDs[115]	HQ	HQ
	India	Health care workers	Thematic analysis	16 IDIs[116]	HQ	HQ
		People with TB	Not presented in the article	76 IDIs[117], 75 structured interviews[94]	MQ	MQ
				108 structured interviews[118]	MQ	HQ
				229 interviews[113]	MQ	MQ
		People with TB and health care workers	Qualitative analysis using a priori codes	19 IDIs[119]	MQ	HQ

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Income group ^a	Country	Study population	Study design	Sample size and study		
				Newcastle-Ottawa scale score ^b		
				HQ	MQ	LQ
	Indonesia		Thematic analysis	71 IDIs[120]	HQ	HQ
		People with TB and community volunteers	Thematic analysis	67 IDIs and 6 FGDs[121]	HQ	HQ
		People with TB, TB survivors, village leaders, and community volunteers	Not presented in the article	50 IDIs and 3 FGDs[122]	HQ	HQ
	Nigeria	General population	Thematic analysis	56 IDIs[123]	MQ	HQ
	Philippines	People with TB and general population	Thematic analysis	22 IDIs and 3 FGDs[124]	HQ	HQ
	Zambia	People with TB and community volunteers	Thematic analysis	30 IDIs and 6 FGDs[125]	MQ	HQ
	Zimbabwe	Presumptive TB cases	Grounded theory	20 IDIs[126]	HQ	HQ
UMIC	Brazil	Health care workers	Discourse analysis	16 IDIs[127]	MQ	HQ
		People with TB	Content analysis	23 IDIs[128]	MQ	HQ
			Thematic analysis	7 IDIs[129]	MQ	HQ
			Discourse analysis	7 IDIs[130]	HQ	MQ
	China	People with TB	Qualitative analysis of open ended survey questions	70 interviews[131]	MQ	MQ
		People with TB (migrants)	Thematic analysis	34 IDIs[132]	MQ	HQ
		People with TB (migrants), presumptive TB cases, and health care workers	Framework approach	60 IDIs and 12 FGDs[133]	MQ	HQ
		People with TB, health care workers, policy makers, and community volunteers	Thematic analysis	47 IDIs and 5 FGDs[134]	MQ	HQ
	Russia	People with TB	Grounded theory	5 FGDs[135]	HQ	HQ
		People with TB and health care workers		32 IDIs and 11 participants in FGDs (number of FGDs not specified) [136]	HQ	HQ

CASP, critical appraisal skills program; FGD, focus group discussions; HQ, high quality, IDI, in-depth interviews; LIC, low-income countries, LMIC, lower-middle-income countries, LQ, low quality; MQ, moderate quality, TB, tuberculosis, UMIC, upper-middle-income countries,

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^bStudy quality was assessed using the Newcastle-Ottawa scale. Highest possible score for cross-sectional studies was 10 (5 for selection, 2 for comparability, and 3 for outcome). Highest possible score for case-control studies was 9 (4 for selection, 2 for comparability, and 3 for exposure). Highest possible score for cohort studies was 9 (4 for selection, 2 for comparability, and 3 for exposure). Studies that scored 0–3 were regarded as LQ, 4–6 were regarded as MQ, and ≥ 7 were regarded as HQ.

^cAll papers were pre-ranked (high, moderate, low) and the levels were adjusted according to the dependability and credibility of the findings. We pre-ranked all papers as high. The ranking remained high if the papers were regarded as dependable and the findings were unequivocal. We downgraded the paper from high to moderate if the papers scored 3 or less in terms of dependability or scored a mix of unequivocal and credible in terms of credibility.

^dCASP for qualitative study had 10 questions to critically appraise the paper. We gave a score of 1 if the paper fulfilled a criterion, 0.5 if we couldn't tell if the paper fulfilled a criterion, and 0 if the paper did not fulfil a criterion. A score of 0–5 equated to LQ study, a score of 6–7 equated to MQ study, and a score of ≥ 8 equated to HQ study.

Income group ^a	Country	Study population	Study design	Sample size and study		
				Newcastle-Ottawa scale score ^b		
				HQ	MQ	LQ
	South Africa	Contacts of people with TB, health care workers, policy makers, and people with TB (miners)	Thematic analysis and grounded theory	104 applied ethnography using formal/informal IDIs, FGDs, field notes, and participant observations[137]	HQ	HQ
		Health care workers, village leaders, and researchers	Thematic analysis	12 IDIs[138]	HQ	HQ
		People with TB		41 IDIs[139]	MQ	HQ
		People with TB, contacts of people with TB, and health care workers		25 IDIs and 4 FGDs[140]	HQ	HQ
		People with TB, general population, and community volunteers		93 reports from participatory research and participants observation[141]	HQ	HQ
		People with TB and general population	Thematic analysis and grounded theory	8 IDIs[142]	HQ	HQ
	Thailand	People with TB (migrants) and health care workers	Thematic analysis	12 IDIs and 11 FGDs[143]	MQ	HQ
CASP, critical appraisal skills program; FGD, focus group discussions; HQ, high quality, IDI, in-depth interviews; LIC, low-income countries, LMIC, lower-middle-income countries, LQ, low quality; MQ, moderate quality, TB, tuberculosis, UMIC, upper-middle-income countries,						
^a Based on World Bank classification. Low-income economies—gross national income (GNI) per capita \$1,025 or less in 2018; lower middle-income economies—GNI per capita between \$1,026 and \$3,995; upper middle-income economies—GNI per capita between \$3,996 and \$12,375						
^b Study quality was assessed using the Newcastle-Ottawa scale. Highest possible score for cross-sectional studies was 10 (5 for selection, 2 for comparability, and 3 for outcome). Highest possible score for case-control studies was 9 (4 for selection, 2 for comparability, and 3 for exposure). Highest possible score for cohort studies was 9 (4 for selection, 2 for comparability, and 3 for exposure). Studies that scored 0–3 were regarded as LQ, 4–6 were regarded as MQ, and ≥ 7 were regarded as HQ.						
^c All papers were pre-ranked (high, moderate, low) and the levels were adjusted according to the dependability and credibility of the findings. We pre-ranked all papers as high. The ranking remained high if the papers were regarded as dependable and the findings were unequivocal. We downgraded the paper from high to moderate if the papers scored 3 or less in terms of dependability or scored a mix of unequivocal and credible in terms of credibility.						
^d CASP for qualitative study had 10 questions to critically appraise the paper. We gave a score of 1 if the paper fulfilled a criterion, 0.5 if we couldn't tell if the paper fulfilled a criterion, and 0 if the paper did not fulfil a criterion. A score of 0–5 equated to LQ study, a score of 6–7 equated to MQ study, and a score of ≥ 8 equated to HQ study.						

Patient delay

The pooled median patient delay (Fig. 3) in LIC and LMIC was 30 days (95% CI 17.9–45). The pooled median patient delay in UMIC was 24.5 days (95% CI 13.2–30). The overall median patient delay in high TB burden countries was 28 days (95%CI 20–30). In the meta-analysis and narrative synthesis of quantitative data (Table 2), females were more likely to delay care-seeking for TB (Fig. 4). Qualitative studies highlighted limitations for women to seek healthcare [113, 115, 123, 124, 128]. Women reported economic constraints and power imbalances in the decision-making process as barriers to care-seeking [113, 115, 123, 124]. We further stratified the analysis by sex, and we found that women were disproportionately affected by risk factors for patient delay (Fig. 5) such as unemployment, poor TB knowledge, and having difficulties or to travel a long distance to visit health facilities [39, 47]. Long-distance to health facilities was also reported by qualitative studies as a barrier to care-seeking [44, 109, 110, 112, 115, 124, 129, 134, 135, 138, 140, 143]. In addition to physical barriers, financial insecurities and economic challenges also compounded patient delay [21, 24, 29, 34–36, 39, 46, 47, 62, 63, 65, 68, 72, 73, 79, 81, 85, 86]. Among qualitative studies (Table 3), seven articles reflected on participant's experiences where competing priorities of livelihoods and commitment to work and family led to individual care-seeking delay [44, 123–125, 132, 136, 143]. We also found that being rural residents in LIC and LMIC was associated with patient delay. No studies from the UMIC were included in the meta-analysis for urbanicity. This review also identified other sociodemographic and economic risk factors for patient delay, such as being older, lower education level, unmarried, being unemployed, absence of health insurance, and high cost of treatment and transportation to health facilities (Table 2).

Table 2

Summary of risk factors for patient delay, health system delay, and treatment delay in high TB burden countries

Patient delay		Health system delay		Treatment delay		Total delay	
LIC and LMIC	UMIC	LIC and LMIC	UMIC	LIC and LMIC	UMIC	LIC and LMIC	UMIC
Socio-demographic and economic							
Female[34, 35, 57]	Female[65, 78, 80, 81]	Sub-urban residence[42]	Female[65]	Older age[44, 91, 93]	Low income[98]	Female[106]	Rural residence[85]
Male[52, 54, 58]	Male[84]	Low income[88]	Older age[90]	Younger age[92]		Male [56, 100, 105]	Unemployed [85]
Older age[23, 26, 27, 36, 57]	Older age[70, 79, 80]		Younger age[68]	Married[92]		Older age [30, 43, 56, 105, 106]	
Larger family size [23, 34, 45]	Low education[63, 67]		More working days per week [68]	Widowed/divorced/ separated/ not married[44]		Larger family size[23]	
Low education [22, 28, 29, 36, 42, 50, 54, 56]	Rural residence[80]		Long distance/ traveling time to health facility[68]	Reside in areas without health centers[95]		Low education[100]	
Rural residence [21, 22, 28–30, 43, 50]	Urban residence[87]			Long distance/ traveling time to health facilities[44]		Rural residence [21, 30, 43, 103, 106]	
Urban residence [24, 56, 58]	Widowed/divorced/ separated/not married[67, 75]			Cost of health care incurred before diagnosis[46]		Sub-urban residence[104]	
Widowed/divorced/ separated/ not married[53]	Low income [62, 68, 73, 79, 81]					Urban residence[56]	
Low income [21, 24, 29, 34, 46]	More working days per week[68, 73, 74]					Low income [21, 106]	
High income[37, 58]	Long distance/ traveling time to health facilities [68, 73, 79, 99]					High income[102]	
Long distance/ traveling time to health facilities [25, 29, 31, 32, 39, 48, 49, 51, 53]	Unemployed [63, 65, 85]					Long distance/ traveling time to health facility[56]	
Unemployed [35, 36, 39]	Cost of treatment/ transport to health facilities[86]					Unemployed [101]	
Cost of treatment/ transport to health facilities[47]	No health insurance [68, 72, 73, 81]					Cost of health care incurred before diagnosis[101, 104]	
Behavioral							
Smoking[37]	Recreational drug use[61]		Smoking[77]		Poor TB knowledge [98]	Poor TB knowledge [46, 104]	Non-smoking[99]
Stigma[25, 40, 57]	Stigma[72, 83]					Stigma[100]	Recreational drug use[107]
Poor TB knowledge [26–28, 31, 38–40, 46–48, 53, 55]	Poor TB knowledge [64, 70, 75, 81, 82]					Alcohol use[102]	Alcohol use[85]
Poor perceived benefit that TB is incurable[24]	Alcohol use[85]						

ART, anti-retroviral therapy; DOTS, directly observed treatment, short course; HIV, human immunodeficiency virus; LIC; low-income countries; LMIC, low-middle-income countries; NTP, national TB program; TB, tuberculosis; UMIC, upper-middle-income countries;

Patient delay		Health system delay		Treatment delay		Total delay	
Poor perceived severity (perceived well and not sick) [36]							
Health-seeking							
Traditional/spiritual medicine[28, 38, 40]	Did not seek treatment because of first symptoms [60]	Non-hospital/ lower level facilities[30, 88]	Non-hospital/ lower level facilities[68, 71]	Traditional medicine[91]		Self-medication[23]	Non-NTP endorsed facilities[99]
Self-medication [20, 23, 27, 46, 59]	Self-medication[81]	Long waiting time in health facility[42]		Non-allopathic health provider[47]		Private health practitioner[46]	
Private health practitioner[28]		Non-DOTS center/facilities that do not provide TB services[42]		Private health practitioner[46]		Non-hospital/ lower level facilities[20]	
Pharmacy[28, 54]		Private health practitioner[30]		Multiple care seeking prior to diagnosis[46, 47]		Non-formal health provider[46, 101]	
Multiple care seeking prior to diagnosis[55]				Untraceable contact details (loss to follow-up post diagnosis)[93]		Non-NTP endorsed facilities[104]	
Non-formal health provider [20, 21, 26, 27, 29]						Multiple care seeking prior to diagnosis[21, 23, 46, 101, 104]	
Rural primary health facility/non-DOTS facility[42, 59]						Qualified health provider[23, 43]	
Clinical/Health services							
No chest pain[40]	Cough [65, 66, 70, 76, 84, 86]	TB-HIV co-infection/HIV positive[30, 88]	No cough[66]	No history of TB[97]	Smear positive [78, 99]	No history of TB in the family[101]	Chest pain[107]
No history of TB[32, 33, 35, 36]	Chest pain[66, 86]		No cavitary lesion[66]	Smear negative[44, 95]		Extrapulmonary TB[20, 23, 30]	HIV infection [85, 99]
Smear positive[28]	Cough without sputum[86]		History of TB[78]	Retreatment cases [92–96]		Smear negative[23]	Smear negative[107]
Smear negative[23]	Night sweats[70]		Smear negative [77, 78, 89]	Absence of TB diagnostic services in local health facility[94]		No HIV infection[21]	
Extrapulmonary TB[23, 30]	Fever[86]		Extrapulmonary TB[89]	HIV positive[96]			
Shorter duration of symptoms[35]	No hemoptysis [70, 74, 76]		Not on ART[90]	HIV status not known[94]			
Presence of more than 1 symptom[41]	No weight loss[60]		High HIV viral load[90]				
HIV negative[21]	Pulmonary cavities[69]						
Presence of other known medical conditions[38]	Hyperglycemia [69, 70]						
	No history of TB[67, 78]						
	Smear positive[69, 78]						

ART, anti-retroviral therapy; DOTS, directly observed treatment, short course; HIV, human immunodeficiency virus; LIC; low-income countries; LMIC, low-middle-income countries; NTP, national TB program; TB, tuberculosis; UMIC, upper-middle-income countries;

Patient delay	Health system delay	Treatment delay	Total delay
	Longer duration of suspicious symptoms[77]		
	Mild symptoms at onset[68]		
	Not aware of other TB patients around[76]		
ART, anti-retroviral therapy; DOTS, directly observed treatment, short course; HIV, human immunodeficiency virus; LIC, low-income countries; LMIC, low-middle-income countries; NTP, national TB program; TB, tuberculosis; UMIC, upper-middle-income countries;			

Table 3
Emergent themes and synthesized findings from qualitative studies

Country	Themes	Quotes
Patient delay		
Bangladesh[113, 114], Brazil[127, 128], Cambodia[115], China[133, 134], Ethiopia[108], India[113, 119], Nigeria[123], Philippines[124], Russia[135], South Africa[137–142], Tanzania[112], Zambia[125], Zimbabwe[126]	Perceived stigma and discrimination at workplace, within family and the community against women, and associating TB with HIV deterred presumptive TB cases from seeking TB diagnosis and care	<p>"When someone says, 'I have TB' others will say that the person has three words [HIV]."[141]</p> <p>"The person would be scared that she would lose her job and that people and friends would avoid her."[124]</p>
Brazil[129], Cambodia[44, 115], China[134], Ethiopia[109, 110], Philippines[124], Russia[135], South Africa[138, 140], Tanzania[112], Thailand[143]	Long distance to health facilities and language barrier led to delay in care seeking and TB diagnosis	<p>"Well, I didn't come to the health center early because it is far from my village."[109]</p> <p>"I don't understand the language, so I don't know what to do next after I finished the 15 days medication. The problem for me is the language because I can't speak Thai."[143]</p>
Bangladesh[113, 114], Brazil[129], Cambodia[115], China[132–134], Ethiopia[108–110], India[113, 116–120], Indonesia[121, 122], Mozambique[111], Nigeria[123], Philippines[124], Russia[135, 136], South Africa[137, 138, 140–142], Tanzania[112], Zambia[125], Zimbabwe[126]	Long chains of care seeking through multiple providers and the lack of trust in the health care system providing TB care led to delay in care seeking and TB diagnosis	<p>"Government doctor did not show any interest, neither he responded to my questions. They never spoke to me at all. We went there 1–3days and became fed-up. Even the 4th day they did not say anything. They asked me to go here and there. It was really a horrible experience to run around there. So, finally we decided and went to private"[120]</p> <p>"We usually try many other methods first and the hospital is the last choice."[115]</p>
Bangladesh[113, 114], India[113], Nigeria[123], Russia[135, 136], South Africa[142], Thailand[143], Zimbabwe[126]	Gender-specific factors such as men dominating and owning the decision-making power in family, more economic constraints for women to seek healthcare, and men concealing health issues or denying disease severity by substance (alcohol and nicotine) abuse led to delay in care seeking and TB diagnosis	<p>"There are very few women in my community who can afford the costs of transportation to the hospital and to pay the hospital fees."[123]</p> <p>"My husband told me to go to my parent's home. He refused to give me money for the cost of treatment. My neighbor did not help me that much either."[113]</p> <p>"When I drink, nothing is bad for me! Illness flies out with alcohol. You don't feel it. Alcohol softens everything, all diseases. When you drink you do not pay attention to illness. Well, today you sneeze, cough, but it will pass! In the morning you wake up, something squeaks, whistles; you groan but go anyway, then you forget about it during work."[136]</p>
Cambodia[44], China[132], Nigeria[123], Philippines[124], Russia[136], Thailand[143], Zambia[125]	Competing priorities of livelihood, work, and family led to delay in care seeking and TB diagnosis	<p>"They had to earn money for their families and had no time for illness and examinations."[136]</p> <p>"I work almost every day except on market days on the farm and Sundays or if there are special occasions. I usually return in the late afternoon to cook for my husband and children. So, if I should go to the hospital in the morning hours as I am told that is when they open and return in the afternoon, that whole day is gone."[123]</p>
Brazil[127], China[132, 133], Ethiopia[108, 110], India[119], Indonesia[121], Philippines[124], Russia[136], South Africa[138, 140], Tanzania[112], Zambia[125], Zimbabwe[126]	Poor knowledge regarding TB symptoms and treatment, and the availability of free treatment policy were barriers to early healthcare seeking	<p>"TB is not yet a disease that people recognize, then any respiratory problem is associated with virus diseases, flu, smoke, dust of the street, all but a disease like TB."[127]</p> <p>"Some participants in rural areas were skeptical whether free treatment actually existed"[121]</p>
Bangladesh[113], Cambodia[44, 115], Ethiopia[108], India[113, 117], Indonesia[122], Mozambique[111], Philippines[124], Russia[135], Tanzania[112]	Presumptive TB cases delayed care-seeking due to low perceived severity of symptoms, low perceived susceptibility to TB, believed that TB is hereditary or retribution for sinful behavior, blame others for delay and then overpowered by hopelessness	<p>"They also don't take the symptoms seriously, they just assume that is a flu."[140]</p> <p>"My uncle suspected that she [respondent's mother] had TB. But my mother said that in her family, no one had ever had TB ... She still rejected the idea and insisted that no one in her family ever had this TB. She asked us to stop referring her [to get medical help]"[115]</p> <p>"For all patients that had initially thought they were cursed, the fact that their disease was diagnosed in the hospital was perceived as a proof that TB is a punishment of God rather than caused by witchcraft forces. Now I realize it has nothing to do with witchcraft, like I thought in the past. It is a punishment of God. He pushes the wind that contains TB in the direction of the person that will subsequently develop TB."[112]</p>
DOTS, directly observed treatment, short course; HIV, human immunodeficiency virus; TB, tuberculosis		

Country	Themes	Quotes
		<p>"I had been sick for two years. I went to a traditional healer, but he suggested to me to go to the hospital. Before that, my friend who also had got TB suggested to me to check my sputum because he thought I might have got TB as well. I insisted that it was not TB because I have never lived with TB patients... I have heard about TB, but I did not think I would get TB." [122]</p> <p>"Patients referred to impoverished living conditions, unclean water and insufficient food as the reasons for their TB. These causes were linked to a sense of hopelessness and an inability to improve conditions of one's life." [113]</p>
Health system delay		
Bangladesh[114], Brazil[127, 130], China[131, 133], Ethiopia[108, 109], India[116, 120], Indonesia[121, 122], Tanzania[112]	Poor practice at the health facilities and ignorance of TB led to a delay in TB diagnosis	<p>"He had told me to take injections daily and I was taking it as advised. But he did not tell me anything. He kept on saying it is typhoid. We told him that sputum is coming while coughing. But he said, it will happen like this even for typhoid also." [120]</p> <p>"There was poor adherence of the doctors to the recommended algorithm for investigating a patient suspected to have TB." [116]</p>
Brazil[128, 130], China[131], India[94, 117], Philippines[124], South Africa[142]	Complicated procedures at the health facilities to reach TB diagnosis	"Referrals from public day or tertiary hospitals to clinics were not managed smoothly and receiving clinics frequently seemed to question the referral and/or diagnosis, sending the patient away without treatment or referring the patient on to another service provider." [142]
Brazil[127, 128, 130], India[94], Russia[136], South Africa[142]	Lack of resources and materials in the health facilities led to a delay in TB diagnosis	<p>"Very often we do not have enough doctors or nurses in the medical sites. Our doctor is absent very often. Then we go to another one. But she might not know my situation and prescribes something at random." [136]</p> <p>"Where the patient was diagnosed at a center without microscopy or had to be referred for treatment to a local DOTS center, delay was more likely to occur." [94]</p>
Treatment delay		
Cambodia[44], India[94, 117], South Africa[139]	Self-perception of health, and unconvinced of the diagnosis and the effectiveness of TB treatment led to a delay in TB treatment initiation	<p>"Sometimes they argued and denied (their condition). They would say they are healthy. Why did we think they had the disease? They didn't trust us because they were still feeling strong." [44]</p> <p>"Some people distrust that the medication would not be effective. Some commented on such cases where the treatment did not work or where people repeatedly kept getting TB." [139]</p>
India[117]	Diagnosis and treatment initiated in different facilities caused a delay in TB treatment initiation	"Active referrals by the diagnosing provider to another provider for treatment initiation constituted the major reason for delay." [117]
South Africa[139]	Geographical distance to health facilities and other competing priorities delayed TB treatment initiation	"Sometimes respondents were referred for treatment, but because of work related issues, particularly work hours and the place of work, they could not access care." [139]
India[94], South Africa[139]	Health system factors such as lack of organization at the facilities to manage patients, poor staff attitude, and logistic issues caused a delay in TB treatment initiation	<p>"A lack of organization at the facilities causing delays in service and queues." [139]</p> <p>"Complaints included that staff sent a patient away when they assumed that he was not taking treatment, treat patients like children and in a derogatory manner, blame patients for problems for which they are not responsible and for shouting and swearing at patients. These raised anger and irritation at the services. While the fear may motivate patients to remain on treatment, it can make it difficult for them to return if they did not initiate treatment." [139]</p> <p>"Delay in transport of drugs from the Peripheral Health Institution to the DOTS centers where the patient is supposed to start his DOTS." [94]</p>
Zambia[125]	Women experienced stigma due to TB diagnosis resulting in concealment of diagnosis or being isolated	"A TB patient described that she was sent away and that in rural areas TB treatment was not easily accessible or available. This contributed to her treatment disruption and aggravation of TB." [125]
DOTS, directly observed treatment, short course; HIV, human immunodeficiency virus; TB, tuberculosis		

Furthermore, poor TB knowledge (Fig. 6), unawareness of free TB treatment policies [26], low perceived susceptibility, and severity of TB was associated with patient delay [36, 44, 108, 111–113, 115, 117, 122, 124, 135]. Perceived stigma and discrimination (Fig. 6) at the workplace, within the family, and community and associating TB with HIV deterred presumptive TB patients from care-seeking [108, 112–115, 119, 123–128, 133–135, 137–142]. From the qualitative data, we found alcohol consumption and smoking to be associated with patient delay, especially among men where these substances were used to conceal

health issues [114, 126, 135, 136, 142, 143]. However, these lifestyle behaviors were not statistically significant in the meta-analysis where the estimates from both sexes were pooled (Fig. 6).

Long chains of care-seeking through multiple non-formal or private health providers was also identified as a determinant of patient delay [108–126, 132, 133, 135, 136, 138, 140–142]. Qualitative data also suggested that the lack of trust in the public health care system perpetuated delays in care-seeking [120, 129, 134–137, 141, 142]. Unlike hemoptysis and weight loss, the presence of cough [65, 66, 70, 76, 84, 86] was associated with patient delay (Fig. 7).

Health system delay

The pooled median health system delay (Fig. 3) in LIC and LMIC was 14 days (95%CI 7–27). The pooled median health system delay in UMIC was 9.8 days (95%CI 1–95.9). The overall median health system delay in high TB-burden countries was 11.5 days (95%CI 3.9–24.7). In the meta-analysis, rural residence in LIC and LMIC was associated with longer health system delay (Fig. 4). Twelve qualitative studies reported that poor practices and ignorance of TB among health providers at health facilities led to a delay in TB diagnosis [108, 109, 112, 114, 116, 120–122, 127, 130, 131, 133]. Seven qualitative studies identified that complicated administrative procedures at the health facilities [94, 117, 124, 128, 130, 131, 142], which could have resulted in longer waiting time [42], and complex referral system [142] that eventually prolonged health system delay. This review identified that visiting lower-level facilities and those that did not provide TB services [30, 42, 68, 71, 88] was associated with health system delay. Six qualitative studies mentioned inadequate resources and supplies in health facilities as such could have delayed TB diagnosis [94, 127, 128, 130, 136, 142]. We also found that people with smear-negative TB were more likely to experience health system delay [77, 78, 89].

Treatment delay

The pooled median treatment delay (Fig. 3) in LIC and LMIC was 13 days (95%CI 2.3–35.5). The pooled median treatment delay in UMIC was 0 days (95%CI 0–1). The overall median treatment delay in high TB burden countries was 6 days (95%CI 1–28.4). One qualitative study noted that the geographical distance to health facilities, especially when diagnosis and treatment were initiated in separate institutions delayed TB treatment initiation [139]. This could be exacerbated by residing in areas without health centers nearby [95]. Health system factors such as logistical issues in drug transportation [94, 139] and the absence of TB diagnostic services in local health facilities [94, 117] compounded delay in treatment initiation. Similar to patient delay, women experienced the stigma of TB diagnosis resulting in its concealment or isolation; thus, delaying treatment initiation [125]. Four qualitative studies mentioned self-perception of health, and unconvinced of the diagnosis and the need for TB treatment, and the perceived low effectiveness of TB treatment led to a delay in TB treatment initiation [44, 94, 117, 139]. We also found that retreatment cases were more likely to delay TB treatment initiation [92–96].

Discussion

Our review is the first to focus on determinants of delayed TB diagnosis and treatment among high TB burden countries using evidence-based quantitative and qualitative information. Overall, the median patient delay among high TB burden countries was 28 days, and the delay in LIC/LMIC (30 days) and UMIC (24.5 days) were not significantly different. Our findings were consistent with previous systematic reviews conducted in countries of different income levels [5, 8]. However, the median patient delay among UMIC in this review was shorter than the findings from observational studies conducted in other high-income countries [145, 146]. TB burden in high-income countries has been progressively reduced through improvements in socio-economic conditions, strong health systems components such as the delivery of TB services and universal health coverage, and social protection schemes [147]. Notwithstanding, TB remains an issue in such settings [148], especially among hard-to-reach populations like migrants [149], who face challenges in accessing healthcare due to stigma, language barriers, and cost of testing and treatment [6]. For the natives, the high standards of living and wellbeing shaped the notion that TB is not a significant concern, rendering a lower index of suspicion of TB and thus delaying TB care-seeking [150].

The median health system delay in this review (11.5 days) was found to be shorter than previous systematic reviews conducted among countries of similar economies [5, 8]. As this review included studies conducted in the last decade, the improvement in health system delay may be attributed to the enhancements of healthcare systems [151], and the quality of TB laboratories [152]. The ability of clinicians to consider TB as a differential diagnosis in high burden settings is also essential for early diagnosis and treatment [153]. However, there remains a paucity of data in several high TB burden countries, including seven in Africa (Central African Republic, Congo, Democratic Republic of Congo, Lesotho, Liberia, Namibia, and Sierra Leone) and four in Asia (Democratic People's Republic of Korea, Myanmar, Papua New Guinea, and Vietnam), potentially due to logistical challenges in conducting such studies. Therefore, this review could allow countries that have yet to collect empirical evidence on delayed TB diagnosis and treatment initiation to infer potential barriers that people with TB in those settings might face.

Patient delay

While TB is a disease affecting mostly men [154], in our review, we found that women still faced challenges in accessing TB care promptly in some settings. In the Philippines, Hu and colleagues [124] described the struggles of women with TB juggling with their responsibility as a caretaker of their children and their wellbeing. Lorent and colleagues also reported competing priorities among Cambodian women who shouldered familial and financial responsibilities [44]. Likewise, men were found to conceal health issues using substances such as alcohol and nicotine. High doses of alcoholism were related to oblivion to one's condition, poor social and financial status, and low motivation to seek treatment [135]. In another study in Russia by Kuznetsov and colleagues [136], the influence of alcohol is further reiterated on participants being in denial and ignoring their symptoms. Globally, men are more likely to smoke, consume alcohol, and drink in high volume compared to women [155, 156]. Therefore, the correlates for alcohol consumption and smoking and patient delay in the meta-analysis were possibly biased towards null because the estimates were pooled from both sexes. Nevertheless, it is imperative to recognize sex disparities in TB care-seeking, and women with TB in high burden countries experienced delays in diagnosis and treatment because of barriers to TB services. Investment cases for programming and interventions should be tailored to address sex-specific vulnerabilities and needs to improve access to TB services among men and women.

Despite wide coverage of free TB diagnostic and treatment services in high burden countries [157], people with TB and their families, especially the poor, bear the impact of significant economic costs [158]. High indirect medical costs [44, 124], productivity, time, and income loss [44, 123, 125, 132, 136, 143] as a result of disease suffering further worsen household vulnerabilities and contribute to a delay in TB diagnosis and poor health outcomes [159]. Our review identified livelihood, work, and family were prioritized and led to a delay in care-seeking. These factors, coupled with the physical environments and impoverished living conditions [125, 136] plunged low-income households into a vicious cycle of impoverishments [160, 161], making the elimination of TB overtly challenging. Gosoni and colleagues reported that people with TB living in poor conditions felt hopeless and blamed poverty for their TB diagnosis [113]. A similar report in Russia [135] mentioned that poor participants were overwhelmed by their day-to-day struggles and had little hope to overcome their conditions, thus delaying TB care-seeking. To seek care, people affected by TB suffer income loss and incur catastrophic costs [162]. Aside from the broad expansion of TB services – improved access to services, treatment, and case-finding strategies – that has been shown to reduce financial burden on TB affected households [163], it is also essential to ensure that financial and social protection policies are in place to protect those at risk of catastrophic TB costs and poverty.

In countries where TB diagnostic and treatment services are provided for free, access to TB care is further challenged by poor knowledge and awareness regarding such policies, making presumptive TB not seek treatment early. In China [133] and Indonesia [121], two separate studies reported that even though public health care centers offered free health care treatment, participants were skeptical regarding the availability of free treatment. A few others also assumed that the TB drugs offered in free treatment would be of poor quality. In addition to poor awareness about free TB treatment policy, we also found poor knowledge regarding TB symptoms to be associated with a delay in TB care-seeking. The inability of people with TB to recognize symptoms such as fever and cough that were not ascribed to TB intrinsically leads to self-medication and treatment or waiting for symptoms to self-resolve due to low perceived disease severity [108, 117, 124, 126, 127, 132, 135, 138, 140]. Therefore, people with TB would delay care-seeking until only when their illness compromised their ability to work and earn for livelihoods [113]. Contrarily, a study in Cambodia [44] found instances where people with TB did not feel ill prior to diagnosis, thus not prompting healthcare seeking. The Cambodia National TB Prevalence Survey in 2011 also revealed that 56% of smear-positive TB and 77% of smear-negative TB cases identified did not exhibit any symptoms [164]. Conventionally, symptomatic individuals are linked to TB transmission, and they are regarded as the target group for TB case-finding activities using the TB symptoms screening approach [165]. However, TB transmission could also occur during the subclinical (asymptomatic) phase, particularly heightened during episodes of symptoms exhibition unrelated to TB pathologies, such as bouts of either acute or chronic cough [166]. As people with subclinical TB might not report any symptoms, they have lower awareness and motivation to seek care; thus, leading to a delay in TB diagnosis and treatment and potentially sustaining TB transmission [167] in the household and community. Therefore, a better understanding of subclinical TB, its transmission dynamics, and the implications for TB control efforts are needed. Also, the duration of TB diagnosis and treatment delay was predominantly quantified using the self-reported date of onset of symptoms; standardizing the ways of measuring delay in care-seeking should be reconsidered.

Furthermore, misperception regarding the causes of TB was also found to delay TB care-seeking. Several studies in Africa [108, 111, 112] highlighted superstitious beliefs that TB is caused by divine retributions of past misdeeds, sinful behaviors, and curses; thus, help is first sought from traditional or spiritual healers instead of a health provider. Besides, studies in Asia reported the misconception that TB is hereditary [115, 124]. Therefore, when no one in the family is ever diagnosed with TB, presumptive TB did not self-initiate care-seeking or is specifically discouraged by family members to seek TB diagnosis and treatment [115]. Other misconceptions, such as low perceived susceptibility to TB due to a healthy lifestyle, also led to a delay in TB care-seeking [114, 122]. Therefore, it is imperative first to measure the level of knowledge, awareness, and practices regarding TB in settings where studies as such have yet to be conducted. The gaps identified could then be used to develop health education programs and interventions about TB. Studies have shown that health education programs and dissemination of TB information are effective in improving TB knowledge and awareness [168], enabling care-seeking and increasing identification of TB cases [169]. Furthermore, understanding of the knowledge and practices of health professionals could be done in parallel to improve care and facilitate early identification of TB [170].

Evident in this review, TB stigma was associated with TB diagnosis and treatment delay. TB stigma continues to be a major barrier for people to access TB diagnosis and complete treatment [10, 141], and the delay in diagnosis not only affects the health and undermines the wellbeing of people with TB but also sustains TB transmission in the community. Moreover, stigma could also reduce the use of face mask [6, 171], further contributing to the transmission of the infection. Despite being an increasingly important agenda of TB programs worldwide, there is a paucity of data on stigma [172], in particular, information from the perpetrators of stigma [173]. There is also limited evidence on effective interventions that can reduce TB-related stigma [174]. Considering the importance of stigma reduction in TB control and elimination efforts, TB de-stigmatization must include approaches that address all socio-ecological levels through education, awareness-raising activities, community mobilization and activism, institutional practices that enhance patient-provider partnerships, and national policies for a more inclusive care plan.

In high TB-burden countries, we found that people who presented with cough, fever, and night sweats were more likely to delay TB care-seeking. This is consistent with another systematic review conducted among low and middle-income countries [5]. A study conducted in Russia [136] elaborated that cough symptoms are very common and can be attributed to numerous conditions such as bronchitis, pneumonia, and smoking. The inability to link these symptoms to TB was claimed as one of the major reasons causing a delay in seeking care [136]. Contrarily, more severe symptoms such as hemoptysis were more likely to reduce delay in care-seeking. Therefore, education and awareness-raising activities could be recalibrated to specifically highlight the possibility of TB besides other respiratory illnesses in the event of more general symptoms such as cough and fever. Simultaneously, the awareness of health workers on this matter in high-burden settings should be raised to improve TB case finding.

Health system and treatment delay

In this review, we found that patient delay was mostly associated with individual, interpersonal, and community risk factors. On the contrary, health system and treatment delay were mostly associated with organizational and policy-related risk factors. Health system delay was more pronounced in LIC and LMIC

compared to UMIC, likely due to the standard of health care, the strength of the national health systems, and the availability of resources. Among LIC and LMIC, a systematic review reported that the quality of health care in public and private sectors was poor, of which the private sectors relatively outperformed the public sector with regards to the delivery of care and medicines availability [175]. The discrepancies in effectiveness and efficiency were highlighted as a facilitator to seek private healthcare, which eventually leads to a delay in TB diagnosis in a high TB burden setting like Cambodia [176]. Narrowing down to high TB-burden countries, quality of both public and private healthcare were also found to be below par, and systematic evaluations are needed to identify gaps in the TB care pathway [157]. Likewise, treatment delay was longer in LIC and LMIC compared to UMIC, and the delay was due to logistic factors such as long distance to treatment centers, availability of anti-TB drugs, and the absence of TB diagnostic services in local health facilities [94, 95]. Beyond systemic factors, individual and interpersonal risk factors like low perceived susceptibility, and TB stigma could delay an individual's decision to initiate TB treatment [44, 125]. To encourage prompt initiation of TB treatment, interventions to decrease isolation post-diagnosis, and social support should be provided [177]. Health providers also play a vital role in assisting people with TB to internalize the diagnosis and supporting them in the decision-making process [178].

Strengths and limitations

To our knowledge, this systematic review will be the first to focus on countries with a high TB burden, where most of the TB cases in the world [2] are found. As the list consisted of countries from LIC, LMIC, and UMIC, we attempted to discern the differences in the determinants of delayed TB diagnosis and treatment between these countries. Moreover, we strived to be comprehensive by systematically assessing and reviewing quantitative and qualitative studies using validated tools and processes. We also found high levels of heterogeneity amongst the studies, which is well within the expectations of the review team as we retained the definitions of delays as to how they were defined in individual studies for comprehensiveness. We incorporated heterogeneity into random-effects models with the inclusion of confidence intervals for the pooled odds ratio for pragmatic interpretations in the real-world settings [179].

Nevertheless, as most of the independent variables were grouped differently using varied cut-offs, we were not able to standardize them all, and therefore, meta-analyses were only performed for selected variables. However, we strived to maintain the comprehensiveness of this review through the triangulation of findings from narrative synthesis and thematic analyses of qualitative studies. This review did not include data from all 30 high TB-burden countries due to the absence of key outcome data and research activities. Notwithstanding the potential lack of representativeness due to scarcity of data from several countries, we believe that this review highlights the gaps in knowledge and provides insights into the determinants of TB diagnosis and treatment delay in high-burden countries, and these findings will inform future interventions to reach these undiagnosed cases effectively.

Conclusions

Our analyses revealed a substantial delay between the onset of TB symptoms and TB care-seeking among high burden countries, highlighting the need to continue to shape knowledge, change attitude, and raise awareness of the community, people at risk of TB, and the health providers. To improve access to TB services and early diagnosis, specific vulnerabilities such as sex disparities in care-seeking, being older, and geographic isolation should be recognized and addressed through tailored approaches [180]. It is also crucial to improve consciousness of the society regarding TB to battle stigma, and networks [181] of support from within the families, the grassroots, and institutions could create an enabling environment for early care-seeking, treatment adherence and success. In contrast to patient delay, the shorter health system and treatment delay were encouraging. Nonetheless, TB programs should strive to test and treat TB through the adoption of WHO recommendations for same-day TB diagnosis [182] to further reduce TB transmission and mortality [183]. Higher-level policies and interventions such as health system strengthening, universal health coverage, and the provision of sustainable social welfare schemes are important to reduce delays, improve access to TB care, and ultimately achieve the global TB targets [184].

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

AKJT, SY, LYH, and SRS conceptualized and designed the study. AKJT and SRS developed the search terms. AKJT conducted the searches. AKJT and STS screened, extracted, and verified the data. AKJT, SRS, and KP analyzed the data. KP and AKJT performed the meta-analysis. AKJT and SRS performed the

systematic review and analyzed the qualitative data. AKJT, KP, and SRS prepared the tables and figures. AKJT, KP, and SRS wrote the initial draft of the manuscript. All authors reviewed, revised, and approved the final manuscript.

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Abbreviations

CASP	Critical Appraisal Skills Program
CI	Confidence interval
HIV	Human immunodeficiency virus
HQ	High quality
LIC	Low-income countries
LMIC	Lower-middle-income countries
LQ	Low quality
MQ	Medium quality
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	International Prospective Register of Systematic Reviews
TB	Tuberculosis
UMIC	Upper-middle-income countries
USA	Unites States of America
WHO	World Health Organization

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Figures

Figure 1

PRISMA flow diagram for articles identification, screening, and selection

Figure 2

Geographical coverage of studies published between 2008–2018 included in this systematic review of delayed diagnosis and treatment of pulmonary tuberculosis. The 30 high tuberculosis (TB) burden countries which have been designated by the World Health Organization are outlined in black. Of them, countries with studies presenting various types of delay are categorized by the various colors. For example, countries shaded in green had studies presenting both patient and health system delay, and those with diagonal strips presented total delay too. Some of the high TB burden countries shaded in grey had no studies identified here, or lacked key outcome data. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Figure 3

Duration of delay of diagnosis and treatment of pulmonary tuberculosis by regions and types of delay reported in high tuberculosis burden countries. Countries were grouped by WHO region and categorized as (i) LIC/LMIC (low- or lower-middle income countries), or (ii) UMIC (upper-middle income countries) as designated by the World Bank in 2019. The median delay—patient (in blue), health system (in yellow), treatment (in pink)—were pooled by the countries’ economic status using Medians of Medians methods by McGrath (2019). Duration of delay in days are presented in the log scale.

Figure 4

Association of sociodemographic and socioeconomic variables on delayed diagnosis and treatment of pulmonary tuberculosis by regions and types of delay reported in high tuberculosis burden countries. Countries were grouped by WHO region and categorized as (i) LIC/LMIC (low- or lower-middle income countries), or (ii) UMIC (upper-middle income countries) as designated by the World Bank in 2019. The association between sociodemographic and socioeconomic variables—sex, marital status, urbanicity—and patient (in blue), health system (in yellow), and treatment (in pink) delay were pooled by the countries' economic status using Bayesian normal random-effects meta-analysis. Odds ratios are presented in the log scale.

Figure 5

Subgroup analysis of patient delay and selected covariates by sex of the individual. Tamhane and colleagues (2012), represented as square points, and Mfinanga and colleagues (2008), represented as round points, provided sex-specific association of patient delay and three covariates; i.e., being unemployed, having to travel long distances or long travelling time, and having poor TB knowledge. The sex-specific odds ratio, in the log scale, for males are presented in hues of blues and for females in hues of reds.

Figure 6

Association of behavioral variables on patient delay of pulmonary tuberculosis by regions in high tuberculosis burden countries. Countries were grouped by WHO region and categorized as (i) LIC/LMIC (low- or lower-middle income countries), or (ii) UMIC (upper-middle income countries) as designated by the World Bank in 2019. The association between behavioral variables—smoking, alcohol consumption, stigma, TB knowledge—and patient delay were pooled by the countries’ economic status using Bayesian normal random-effects meta-analysis. Odd ratios are presented in the log scale.

Figure 7

Association of clinical variables on patient delay of pulmonary tuberculosis by regions in high tuberculosis burden countries. Countries were grouped by WHO region and categorized as (i) LIC/LMIC (low- or lower-middle income countries), or (ii) UMIC (upper-middle income countries) as designated by the World Bank in 2019. The association between clinical variables—cough, hemoptysis, weight loss, fever, chest pain, and night sweats—and patient delay were pooled by the countries' economic status using Bayesian normal random-effects meta-analysis. Odds ratios are presented in the log scale.

Supplementary Files

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