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Spatially varying associations between patient characteristics and mortality during tuberculosis treatment in Central Java, Indonesia: a spatial survival analysis

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Abstract

Background: Conventional Cox proportional hazards models assume that associations between patient characteristics and tuberculosis mortality are constant across geographic locations.

However, differences in healthcare access and local health systems may result in spatial variation. This study investigated spatial heterogeneity in associations with the hazard of death among tuberculosis patients in Central Java, Indonesia.

Methods: This retrospective observational study analyzed tuberculosis surveillance data from Central Java. A total of 52217 eligible tuberculosis patients were included. The primary outcome was all-cause mortality during tuberculosis treatment. Patients without recorded death were censored at their last treatment outcome or end of follow-up. Covariates included age, sex, occupation, residence, human immunodeficiency virus (HIV) status, diabetes mellitus, and tuberculosis site. Geographically weighted Cox regression (GWCR) was used to estimate local hazard ratios.

Results: GWCR revealed spatial heterogeneity in the associations between patient characteristics and mortality during tuberculosis treatment. HIV-positive showed a strong association, with local hazard ratios ranging from 4.38 to 6.23 across districts/cities. Higher hazards of death were observed among patients aged ≥ 60 years, males, unemployed individuals, and those with diabetes mellitus, whereas patients aged 6–17 years and those with extrapulmonary tuberculosis had lower hazards of death. GWCR provided a better model fit than the global Cox model, and exploratory analyses suggested that healthcare service burden may partly contribute to the observed spatial heterogeneity.

Conclusion: GWCR demonstrated that the associations between patient characteristics and tuberculosis mortality varied geographically across Central Java, indicating that a single global

hazard ratio may not adequately represent local mortality risk. These findings provide additional insight into the spatial epidemiology of tuberculosis mortality and may help inform geographically targeted tuberculosis control strategies.

Keywords: Cox proportional hazards, Geographically weighted Cox regression, Mortality, Spatial variation, Tuberculosis

Background

Tuberculosis (TB), an airborne infectious disease caused by *Mycobacterium tuberculosis*, remains the leading cause of death from a single infectious agent worldwide, accounting for more than one million deaths annually [1, 2]. According to the World Health Organization 2025 report, approximately 10 million people develop TB each year, with Indonesia ranking second among countries with the highest TB burden [1]. The Indonesian government's goal of reducing TB incidence from 319 cases per 100000 population in 2017 to 190 cases per 100000 population by 2024 was not achieved. Instead, the estimated incidence remained high at 382 cases per 100000 population in 2024 [1, 3, 4]. In Indonesia, Java Island, particularly Central Java, carries the country's TB burden. Previous studies have demonstrated that TB cases are not randomly distributed across districts and cities [5–8]. Furthermore, Indonesia's National Tuberculosis Control Strategy emphasizes district-level planning and local government involvement in TB prevention and programme implementation, making an understanding of local variation particularly relevant for public health decision-making [3].

Among TB treatment outcomes, mortality is particularly important because it reflects not only disease severity but also the effectiveness of diagnosis, treatment initiation, clinical monitoring, and health system responsiveness. Identifying factors associated with mortality is therefore essential for recognizing high-risk patient groups and geographic areas requiring additional

attention. Previous studies have shown that TB mortality is influenced by a wide range of demographic, socioeconomic, and clinical characteristics. Older age and male sex have consistently been associated with poorer treatment outcomes [9]. Socioeconomic factors, including employment status, may also influence survival through differences in healthcare access and financial resources [10, 11]. Human immunodeficiency virus (HIV) infection and diabetes mellitus (DM) are well-established comorbidities associated with increased mortality among TB patients [12–14], while disease presentation, such as pulmonary or extrapulmonary TB, has also been associated with prognosis [15, 16]. Collectively, these findings indicate that patient characteristics play an important role in determining survival outcomes during TB treatment.

The Cox proportional hazards model is one of the most widely used approaches for estimating the association between patient characteristics and mortality risk [17]. Machmud, et al. [18] have successfully applied the Cox model to identify determinants of TB mortality. However, conventional Cox models estimate a single global hazard ratio for each covariate, implicitly assuming that these associations are constant across all geographic locations. This assumption may not hold in practice because healthcare access, treatment monitoring, healthcare service capacity, social conditions, and environmental characteristics often differ substantially between districts.

Geographically weighted Cox regression (GWCR), introduced by Xue et al. [19], extends the conventional Cox model by allowing regression coefficients to vary across space through geographically weighted estimation. Rather than producing a single hazard ratio for the entire study area, GWCR estimates location-specific hazard ratios that can reveal geographic heterogeneity in the associations between patient characteristics and mortality risk. Such

information may provide additional insight into local patterns that are not captured by conventional global survival models. Therefore, this study aimed to investigate the spatial variation in the associations between patient-related risk factors and the hazard of death among TB patients in Central Java Province, Indonesia, using geographically weighted Cox regression.

Methods

Study design and data source

This retrospective observational study analyzed routinely collected individual-level tuberculosis surveillance data obtained from the Tuberculosis Information System (SITB). Access to the data was granted by the Provincial Health Office of Central Java through official administrative permission. The surveillance database comprised TB patients registered between 1 January and 31 December 2025. The dataset was provided to the research team by the Provincial Health Office of Central Java on 20 January 2026 and initially contained 85762 patient records before the application of the study eligibility criteria.

The dataset provided to the research team contained potentially identifying information, including patient's full names, SITB registration numbers, and detailed residential addresses. The research team had access to these variables during data preparation. Direct identifiers were not used as analytical variables. The patient's names, SITB registration numbers, and detailed residential addresses were not used as analytical variables. The district/city of residence recorded in the dataset was used to assign each patient to the corresponding administrative spatial unit and was matched with the official administrative spatial data to obtain the centroid coordinates for spatial analysis. Access to the dataset was restricted to authorized members of the research team, and the data was used solely for the purpose of this research.

Study population and eligibility criteria

The study population consisted of patients registered in SITB between 1 January and 31 December 2025. Patients were eligible for inclusion if they had drug-susceptible tuberculosis, were classified as new TB patients, received the Category I anti-tuberculosis treatment regimen, and resided in Central Java Province. Patients receiving Category II treatment or treatment for drug-resistant tuberculosis were excluded because their treatment pathways and prognosis differ substantially from those of patients with drug-susceptible TB treated under the Category I regimen.

Duplicate registration numbers were identified within the surveillance database. A review of duplicate records indicated that they primarily represented updated versions of the same TB episode rather than independent treatment episodes, as later records generally contained more complete clinical information (e.g., HIV status, diabetes mellitus status, laboratory results, treatment facility, and treatment dates). Therefore, the most recent record for each registration number was retained because it generally contained the most complete and updated information on the same TB episode. Finally, patients with missing treatment initiation dates or missing district/city information were excluded because their survival time and spatial location could not be determined.

Variables and spatial unit

The primary outcome was death recorded during the TB treatment episode. Survival time was defined as the number of days from TB treatment initiation to the recorded date of death. As the surveillance database did not distinguish the underlying cause of death, all deaths recorded during treatment were considered events. Patients without a recorded death during treatment

were treated as censored observations at the date of treatment completion, treatment failure, loss to follow-up, transfer out, or the end of the observation period, whichever occurred first. The independent variables included age (≤ 5 , 6–17, 18–59, and ≥ 60 years), sex (male/female), occupation (formal employed, informal employed, self-employed, and unemployed), place of residence (urban/rural), HIV status (positive/negative), diabetes mellitus status (positive/negative), and anatomical site of TB (pulmonary/extrapulmonary). These variables were selected based on previous evidence demonstrating their association with TB mortality and treatment outcomes.

The spatial unit of analysis was defined as the district/city where the patients lived, as it reflects the geographic context in which patients resided and captures potential variations in healthcare access and other local contextual factors associated with TB outcomes. Geographic locations were represented by the latitude and longitude of the administrative centroid of each district/city, derived from the official administrative boundary shapefile of Central Java Province.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the study population according to treatment outcome. Patient characteristics were summarized using frequencies and percentages. Kaplan-Meier survival curves were constructed to describe survival probabilities during the TB treatment period.

A multivariable Cox proportional hazards model was first fitted to estimate adjusted hazard ratios (HRs) and 95% confidence intervals for death during TB treatment. The hazard function for individual i at time t is expressed as

$$h_i(t) = h_0(t) \exp(\mathbf{X}_i^T \boldsymbol{\beta}) \quad (1)$$

158 where $h_0(t)$ is the unspecified baseline hazard function, $\mathbf{X}_i$ is the vector of covariates for
 159 individual i , and $\boldsymbol{\beta}$ is the corresponding vector of regression coefficients. Parameter estimation
 160 was performed using the Cox partial likelihood

$$161 \quad PL(\boldsymbol{\beta}) = \prod_{i=1}^n \prod_{t \geq 0} \left[\frac{Y_i(t) \exp\{\mathbf{X}_i^T \boldsymbol{\beta}\}}{\sum_j Y_j(t) \exp\{\mathbf{X}_j^T \boldsymbol{\beta}\}} \right]^{dN_i(t)} \quad (2)$$

162 where $Y_i(t)$ denotes the at-risk indicator and $dN_i(t)$ indicates whether subject i experienced the
 163 event at time t .

164 The proportional hazards assumption was assessed using Schoenfeld residuals. Spatial
 165 autocorrelation remaining after the global Cox model was evaluated by applying Moran's I
 166 statistic to district-level mean deviance residuals. To account for possible spatial non-stationarity,
 167 a geographically weighted Cox regression (GWCR) model was subsequently fitted following the
 168 approach proposed by Xue et al. [19]. Unlike the global Cox model, GWCR allows the
 169 regression coefficients to vary by geographic location. For a location $\mathbf{s}$, the local partial
 170 likelihood is defined as

$$171 \quad PL(\boldsymbol{\beta}(\mathbf{s})) = \prod_{i=1}^n \prod_{t \geq 0} \left[\frac{w_i(\mathbf{s}) Y_i(t) \exp\{\mathbf{X}_i^T \boldsymbol{\beta}(\mathbf{s})\}}{\sum_j w_j(\mathbf{s}) Y_j(t) \exp\{\mathbf{X}_j^T \boldsymbol{\beta}(\mathbf{s})\}} \right]^{dN_i(t)} \quad (3)$$

172 where $w_i(\mathbf{s})$ represents the geographical weight assigned to observation i according to its graph
 173 distance from location $\mathbf{s}$, and $\boldsymbol{\beta}(\mathbf{s})$ is the vector of location-specific regression coefficients.

174 Regression coefficients were estimated by maximizing the local partial likelihood using Newton-
 175 Raphson algorithm. Spatial weights were constructed using graph distances between district/city
 176 centroids derived from a queen contiguity neighborhood structure. The optimal bandwidth was
 177 selected by minimizing the Takeuchi Information Criterion (TIC). The GWCR model generated
 178 district-specific regression coefficients and corresponding local hazard ratios for each covariate.

Local parameter estimates and hazard ratios were visualized using choropleth maps based on the official administrative boundary shapefile of Central Java Province.

Statistical analyses were performed using R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a two-sided p-value < 0.05.

Results

Characteristics of study population

A total of 52217 eligible TB patients registered between 1 January and 31 December 2025 were included in the analysis, of whom 2336 (4.47%) died during treatment and 49881 (95.53%) were censored (Table 1). Patients who died were generally older than censored patients, with more than half (53.04%) aged ≥ 60 years, whereas patients aged 18–59 years comprised the largest proportion of the censored group (66.96%). Male patients predominated in both groups but represented a larger proportion among those who died (64.08% vs. 55.51%). Patients who died also had higher proportions of HIV-positive status (6.59% vs. 1.62%), DM-positive status (18.41% vs. 12.76%), and pulmonary TB (93.11% vs. 88.50%) than censored patients. In contrast, the distributions of occupation and place of residence were broadly similar between the two groups.

Fig 1 presents the district-level mortality proportion during TB treatment along with HIV-positive proportion, DM-positive proportion, and proportion of TB patient aged ≥ 60 years across Central Java. Mortality proportion varied geographically, with the highest rates approaching 7% in some districts. Deaths during treatment were recorded in all districts or cities, although the magnitude of the mortality proportion differed across locations, indicating geographic variation in TB mortality during treatment. Variation in percentage was also observed in the selected characteristics.

Table 1. Baseline characteristics of the study population by survival status during TB treatment.

Variable	Category	Censored (n = 49881)	Death (n = 2336)	All (n = 52217)
Age (years), n (%)	≤5	127 (0.25)	3 (0.13)	130 (0.25)
	6–17	2498 (5.01)	33 (1.41)	2531 (4.85)
	18–59	33400 (66.96)	1061 (45.42)	34461 (66.00)
	≥60	13856 (27.78)	1239 (53.04)	15095 (28.91)
Sex, n (%)	Male	27691 (55.51)	1497 (64.08)	29188 (55.90)
Occupation, n (%)	Formal employed	3811 (7.64)	149 (6.38)	3960 (7.58)
	Informal employed	12178 (24.41)	660 (28.25)	12838 (24.59)
	Self-employed	5475 (10.98)	198 (8.48)	5673 (10.86)
	Unemployed	15914 (31.90)	745 (31.89)	16659 (31.90)
	Other	1141 (2.29)	559 (23.93)	1166 (2.23)
	Unknown	11362 (22.78)	25 (1.07)	11921 (22.83)
Place of residence, n (%)	Rural	10555 (21.16)	519 (22.22)	11074 (21.21)
	Urban	39326 (78.84)	1817 (77.78)	41143 (78.79)
HIV Status, n (%)	HIV Negative	43692 (87.59)	1989 (85.15)	45681 (87.48)
	HIV Positive	809 (1.62)	154 (6.59)	963 (1.84)
	Unknown	5380 (10.79)	193 (8.26)	5573 (10.67)
DM Status, n (%)	DM Negative	37983 (76.15)	1647 (70.51)	39630 (75.89)
	DM Positive	6364 (12.76)	430 (18.41)	6794 (13.01)
	Unknown	5534 (11.09)	259 (11.09)	5793 (11.09)
Site of Bacterial, n (%)	Pulmonary	44144 (88.50)	2175 (93.11)	46319 (88.70)
	Extrapulmonary	5737 (11.50)	161 (6.89)	5898 (11.30)

HIV, human immunodeficiency virus; DM, diabetes mellitus.

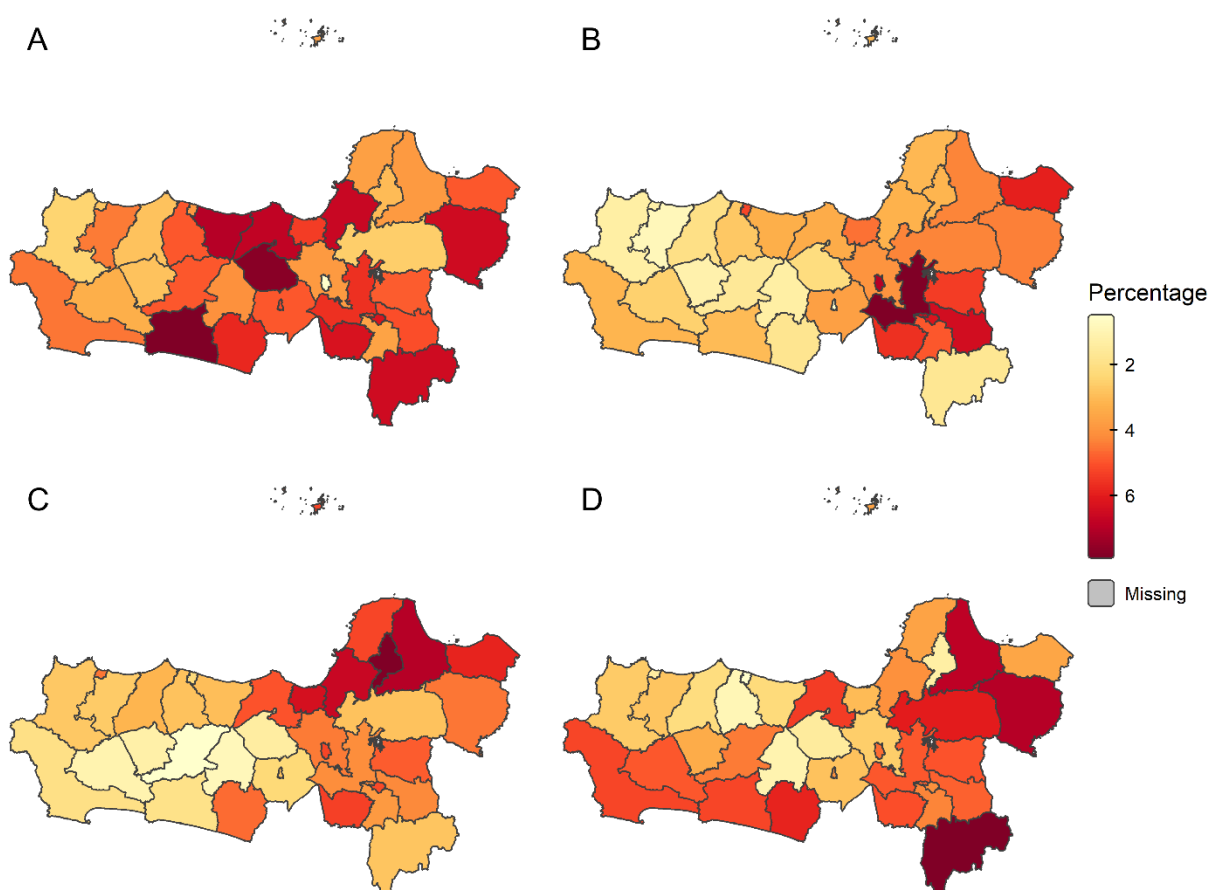


Fig 1. District-level mortality among tuberculosis patients and selected patient characteristics in Central Java, Indonesia.

Panels show (A) mortality proportion during TB treatment, (B) HIV-positive proportion among TB patients with known HIV status, (C) diabetes mellitus (DM)-positive proportion among TB patients with known DM status, and (D) proportion of TB patients aged ≥ 60 years.

Fig 2 presents the overall Kaplan-Meier survival curve together with Kaplan-Meier survival curves stratified by HIV status, DM status, and sex. Median survival time was not reached as the estimated survival probability remained above 50% throughout the follow-up period, remaining approximately 93% at the end of follow-up (Fig 2A). The survival probability was consistently lowest among patients with HIV-positive status, declining to approximately 80% after 200 days of follow-up (Fig 2B). Patients with DM also had lower survival probabilities than those without

DM, although the separation between the survival curves was less pronounced than that observed for HIV status (Fig 2C). Male patients consistently exhibited lower survival probabilities than female patients throughout follow-up (Fig 2D).

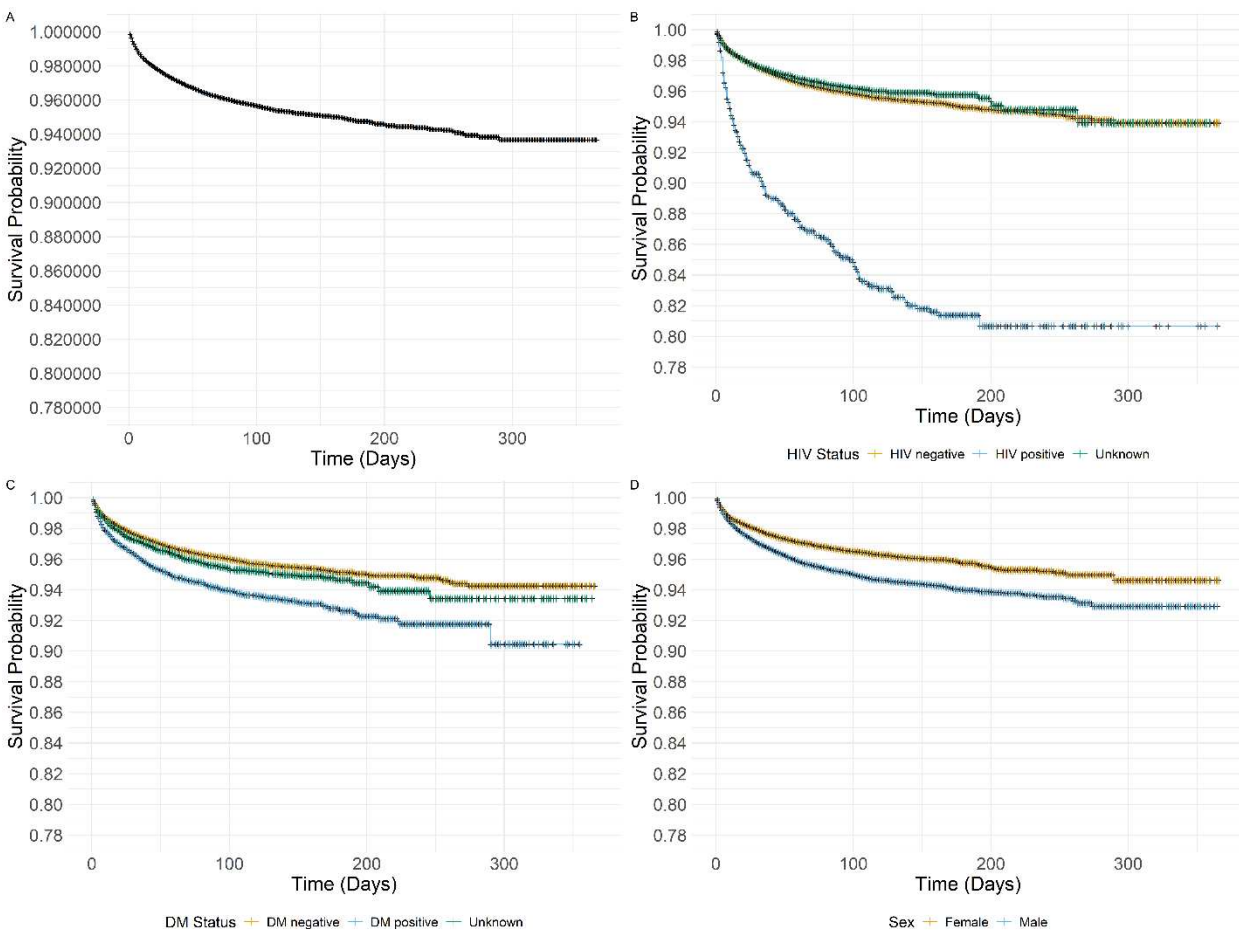


Fig 2. Kaplan-Meier survival curves for TB patients in Central Java, Indonesia.

Panels show (A) overall survival and stratified by (B) HIV status, (C) diabetes mellitus status, and (D) sex.

Abbreviations: HIV, human immunodeficiency virus; DM, diabetes mellitus.

Cox proportional hazards model

Table 2 presents the results of the multivariable Cox proportional hazards model. After adjustment for all covariates, age, sex, occupation, HIV status, diabetes mellitus status, and anatomical site of TB were significantly associated with the hazard of death during TB treatment,

whereas place of residence was not. Hazard ratios and 95% confidence intervals are presented in Table 2. HIV-positive status showed the strongest association with mortality, while older age, male sex, diabetes mellitus, and unemployment were also associated with an increased hazard of death. In contrast, patients aged 6–17 years and those with extrapulmonary TB had lower hazards of death than the respective reference groups.

Table 2. Global Cox proportional hazards model results.

Variable	$\hat{\beta}$	P-value	HR	95% CI of HR
Place of residence				
Urban (ref)				
Rural	0.0319	0.5243	1.0324	0.9359–1.1387
Age (years)				
≤5	−0.2791	0.6285	0.7559	0.2432–2.3487
6–17	−0.8220	<0.0001	0.4396	0.3096–0.6241
18–59 (ref)				
≥60	1.0303	<0.0001	2.8019	2.5719–3.0525
Sex				
Female (ref)				
Male	0.3160	<0.0001	1.3717	1.2420–3.1053
Occupation				
Formal employed (ref)				
Informal employed	0.0411	0.6563	1.0419	0.8695–1.2485
Self-employed	−0.2033	0.0618	0.8160	0.6592–1.0101
Unemployed	0.2553	0.0068	1.2908	1.0730–1.5528
Other	−0.4589	0.2680	1.1086	0.4134–0.9662
Unknown	0.1031	0.0341	0.6320	0.9238–1.3304
HIV Status				
HIV Negative (ref)				
HIV Positive	1.6472	<0.0001	5.1925	4.3885–6.1437
Unknown	−0.1490	0.0576	0.8616	0.7388–1.0048
DM Status				
DM Negative (ref)				
DM Positive	0.3217	<0.0001	1.3795	1.2392–1.5357
Unknown	0.1518	0.0288	1.1639	1.0159–1.3334
Site of Bacterial				
Pulmonary (ref)				
Extrapulmonary	−0.2393	0.0040	0.7872	0.6688–0.9264

HR, hazard ratio; CI, confidence interval; HIV, human immunodeficiency virus; DM, diabetes mellitus; ref, reference category.

Categories as “ref” were used as reference groups in the global Cox proportional hazards model.

This preliminary examination explores the link between individual-level factors and the risk of death among TB patients in Central Java. The subsequent analysis will begin with an assessment of the proportional hazard assumption, followed by Moran's I test to determine the presence of spatial correlation in the aggregated residuals of the global Cox model.

Proportional hazards assumption

The proportional hazards assumption was assessed using Schoenfeld residuals. All covariates satisfied the proportional hazards assumption except occupation ($p = 0.0013$). Because the primary objective of this study was to investigate spatial variation in regression coefficients rather than to estimate time-varying effects, occupation was retained in the subsequent analysis. This potential limitation is acknowledged in the Discussion. The complete results of the proportional hazards assumption test are presented in Additional file 1.

Moran's I

Moran's I was calculated using the district-level mean deviance residuals from the global Cox proportional hazards model to assess whether residual spatial autocorrelation remained after adjustment for the observed patient characteristics. As shown in Fig 3, the positive slope of the regression line (Moran's $I = 0.163$) indicates weak positive spatial autocorrelation, with districts exhibiting relatively high (or low) residuals tending to be located near neighboring districts with similarly high (or low) residuals. Together with the significant Moran's I test ($p = 0.046$), these findings suggest that the global Cox model did not fully account for the spatial structure in the data, supporting the subsequent application of geographically weighted Cox regression.

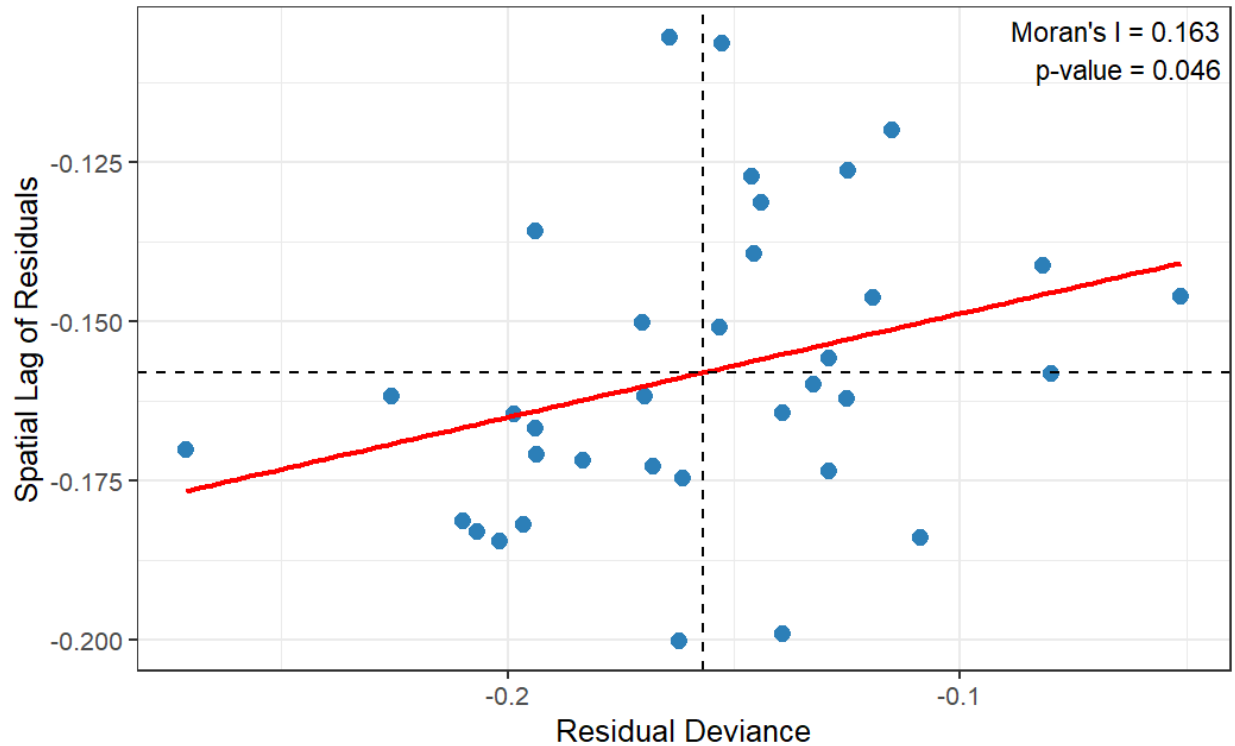


Fig 3. Moran's I scatterplot of district-level mean deviance residuals from the global Cox model.

The scatterplot illustrates the spatial autocorrelation of district-level residuals. The red line represents the fitted regression line, and the dashed lines indicate the mean values of residual deviance and spatial lag of residuals.

Moran's I is a measure of global spatial autocorrelation.

Based on the queen contiguity neighborhood structure, graph distances among districts/cities were used to determine the optimal bandwidth for the GWCR model. Candidate bandwidths were evaluated using the TIC, and the optimal bandwidth was selected by minimizing the TIC as shown in Additional file 2. A bandwidth of three was subsequently used for the GWCR analysis.

Geographically weighted Cox regression

The GWCR model revealed substantial spatial heterogeneity in the associations between several patient characteristics and the hazard of death across the 35 districts/cities of Central Java (Fig

4). The magnitude of the local parameter estimates varied geographically, indicating that the effects of several covariates were not spatially uniform.

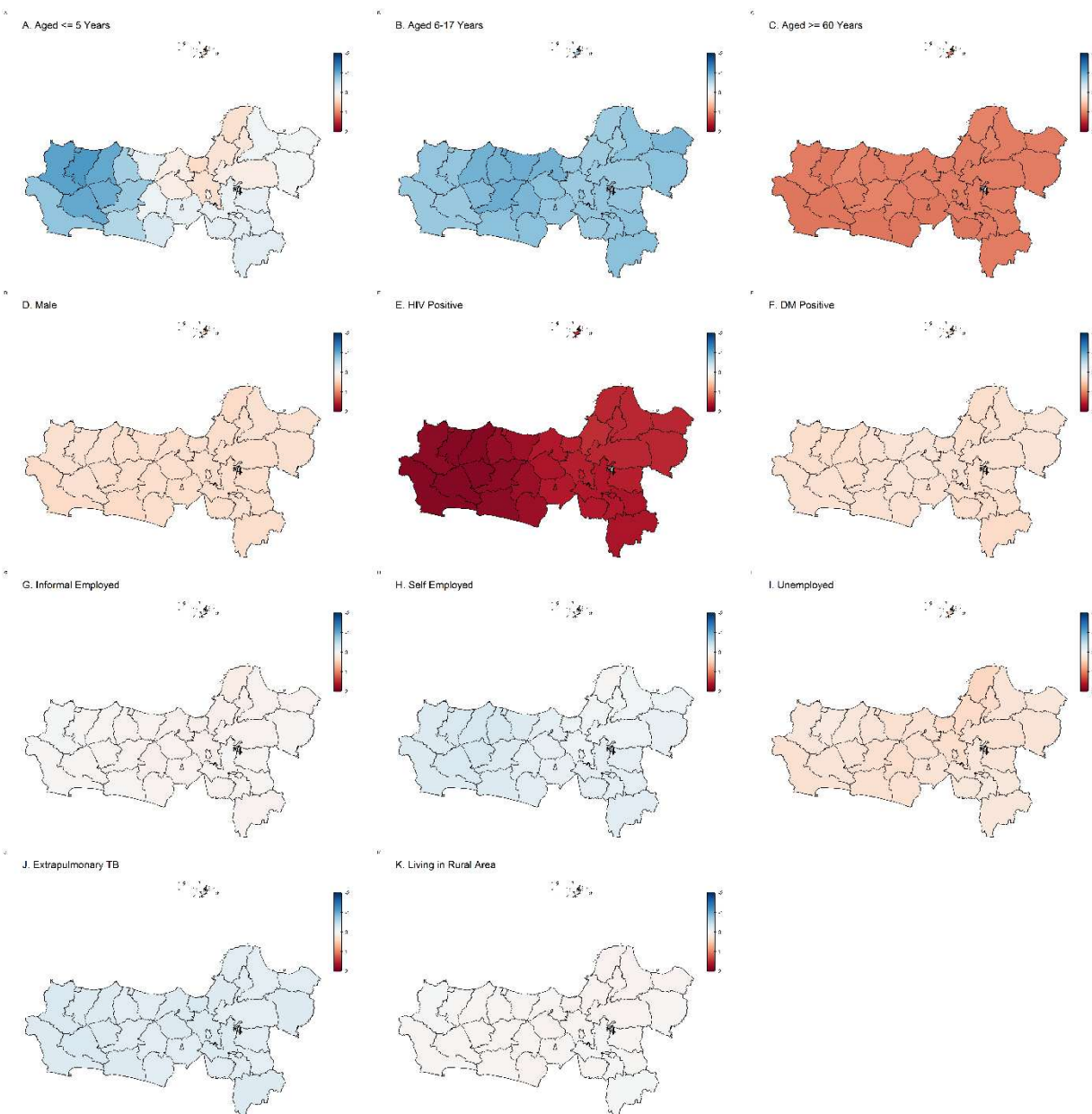


Fig 4. Spatial distribution of district-specific parameter estimates from GWCR model.

Panels show local parameter estimates for (A) age ≤ 5 years, (B) age 6–17 years, (C) age ≥ 60 years, (D) male sex, (E) HIV-positive status, (F) diabetes mellitus-positive status, (G) informal employment, (H) self-employment, (I) unemployment, (J) extrapulmonary TB, and (K) rural residence. Warmer colors indicate larger positive parameter

estimates (higher hazard of death), whereas cooler colors indicate more negative parameter estimates (lower hazard of death). Abbreviations: HIV, human immunodeficiency virus; DM, diabetes mellitus.

Table 3 summarizes the distribution of the district-specific parameter estimates and corresponding hazard ratios obtained from the GWCR model. Patients aged 6–17 years consistently showed lower hazards of death than patients aged 18–59 years, with local HRs remaining below one across districts. In contrast, the local HRs for patients aged ≤ 5 years showed greater geographic variability, with the observed range crossing one, indicating that the association varied both in magnitude and, in some districts, in direction relative to the reference age group.

Table 3. Summary statistics of local parameter estimates and corresponding hazard ratios.

Variable	Category	Mean $\hat{\beta}$	Median $\hat{\beta}$	SE $\hat{\beta}$	Min $\hat{\beta}$	Max $\hat{\beta}$	Median HR	HR range
Age	≤ 5 years	-0.270	-0.129	0.448	-1.124	0.386	0.879	0.325–1.471
	6–17 years	-0.818	-0.798	0.086	-1.049	-0.685	0.450	0.350–0.504
	≥ 60 years	1.023	1.016	0.019	0.993	1.061	2.761	2.700–2.890
Sex	Male	0.333	0.338	0.026	0.241	0.368	1.403	1.272–1.444
Occupation	Informal employed	0.051	0.047	0.037	-0.021	0.142	1.048	0.979–1.153
	Self-employed	-0.187	-0.176	0.090	-0.353	0.005	0.838	0.702–1.005
	Unemployed	0.277	0.278	0.062	0.132	0.432	1.321	1.142–1.541
	Other	0.122	0.118	0.053	0.004	0.222	1.125	1.004–1.249
	Unknown	-0.438	-0.426	0.087	-0.689	-0.262	0.653	0.502–0.770
Place of residence	Rural	0.026	0.025	0.025	-0.037	0.078	1.026	0.964–1.081
HIV status	HIV Positive	1.636	1.604	0.113	1.477	1.829	4.974	4.379–6.227
	Unknown	-0.134	-0.097	0.109	-0.364	0.049	0.908	0.695–1.050
DM status	DM positive	0.310	0.308	0.028	0.264	0.361	1.361	1.303–1.435
	Unknown	0.141	0.144	0.039	0.071	0.249	1.155	1.073–1.283
Site of Bacterial	Extrapulmonary	-0.239	-0.241	0.033	-0.301	-0.175	0.786	0.740–0.839

$\hat{\beta}$, estimated log hazard coefficient; SE, standard error; HR, hazard ratio; HIV, human immunodeficiency virus; DM, diabetes mellitus.

Male patients also showed a consistently higher hazard of death across districts. Among the occupational categories, unemployment was consistently associated with an increased hazard of death compared with formal employment, whereas self-employment tended to be associated with

lower hazards. Informal employment showed relatively little spatial variation. HIV-positive status exhibited the strongest association with mortality among all covariates, with local HRs ranging from 4.38 to 6.23. Although the magnitude of the association varied geographically, HIV-positive status remained associated with substantially higher hazards of death across all districts/cities. In comparison, DM-positive status was associated with a more modest increase in mortality hazard (median HR = 1.36) and showed considerably less geographic variation than that of HIV. Rural residence showed local HRs close to one across districts, suggesting little spatial variation in its association with mortality.

Overall, the GWCR model indicated that geographic heterogeneity was greatest for patients aged ≤ 5 years and those who were HIV-positive, whereas the effects of diabetes mellitus, extrapulmonary TB, and rural residence were comparatively homogeneous across districts. Compared with the global Cox proportional hazards model, the GWCR model yielded a substantially lower TIC value (32963.48 vs. 48778.06), representing a reduction of 15814.58 (Table 4). This indicates a better overall model fit for the GWCR model.

Table 4. Model comparison based on Takeuchi Information Criterion.

Methods	TIC
Cox proportional hazards model	48778.06
Geographically weighted Cox regression	32963.48

TIC, Takeuchi information criterion.

District-level caseload patterns and local heterogeneity of hazard ratios

To explore whether the spatial heterogeneity identified by the GWCR model was associated with district-level healthcare service burden, correlations between clinic caseload indicators and district-specific local hazard ratios were examined.

Spearman correlation analysis identified significant positive associations between both the mean TB caseload per clinic and the variation in clinic caseload across districts and the local HR for HIV-positive status (Figs 5A–5B). Districts with higher average clinic caseloads and greater variation in patient workload across clinics tended to exhibit stronger local associations between HIV-positive status and the hazard of death.

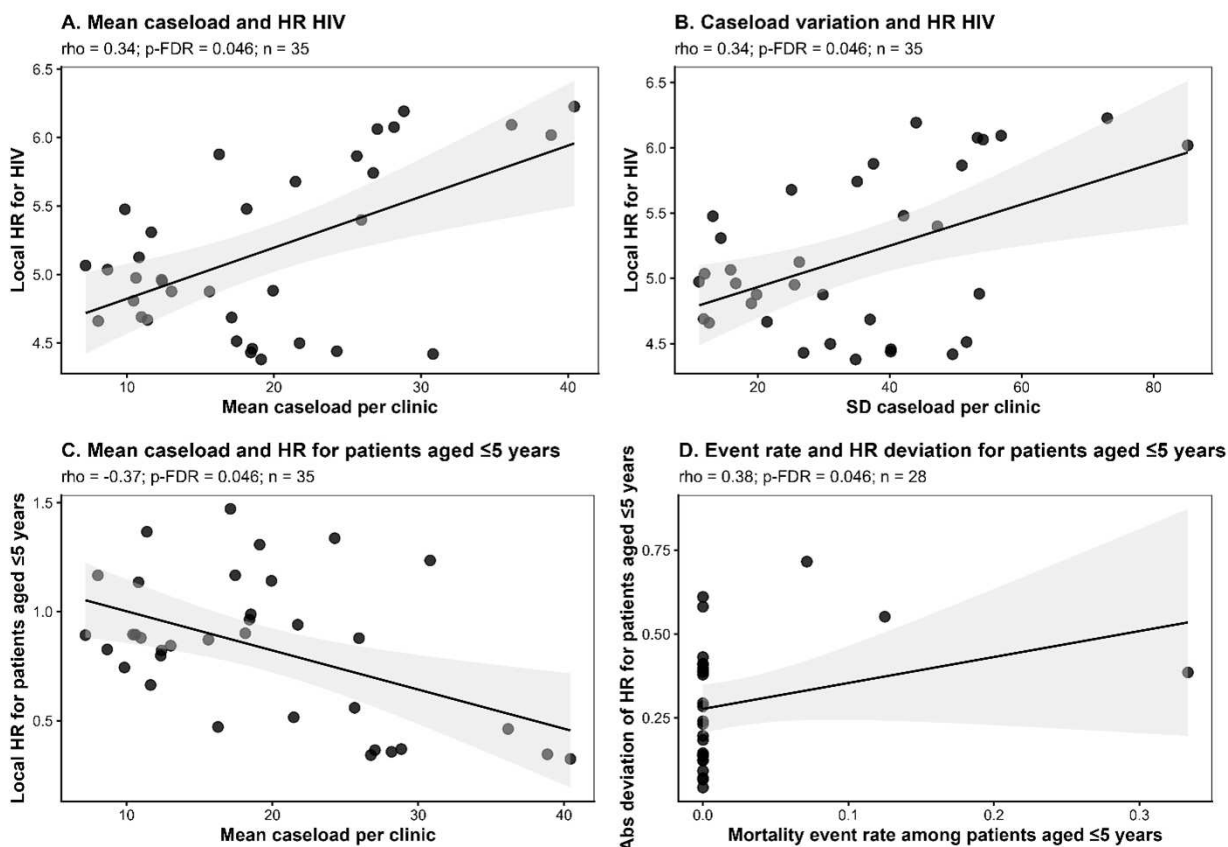


Fig 5. District-level caseload patterns and local heterogeneity of hazard ratios.

Panels A and B show the associations of district-level mean caseload per clinic and caseload variation with the local HR for HIV. Panel C shows the association between district-level mean caseload per clinic and the local HR for patients aged ≤5 years. Panel D shows the association between the mortality event rate among patients aged ≤5 years and the absolute deviation of the local HR for patients aged ≤5 years from the global HR. The fitted lines represent linear trends with 95% confidence intervals. Correlation coefficients are Spearman rho values. p-FDR values were adjusted using the Benjamini-Hochberg method. Panel D included only districts with data on patients aged ≤5 years.

Abbreviations: HR, hazard ratio; HIV, human immunodeficiency virus; SD, standard deviation; FDR, false discovery rate; ρ , Spearman's rank correlation.

In contrast, a significant negative correlation was observed between the mean TB caseload per clinic and the local HR for patients aged ≤ 5 years (Fig 5C). Districts with higher average clinic caseloads tended to have lower local HR estimates for this age group relative to patients aged 18–59 years.

To assess whether this finding could be influenced by sparse outcome data, a diagnostic analysis was performed (Fig 5D). As summarized in Table 5, among the 27 districts with TB cases in patients aged ≤ 5 years, only three districts recorded a mortality event (one death in each district), whereas the remaining 24 districts recorded no deaths in this age group.

Table 5. Sparse-event diagnostics for TB mortality among patients aged ≤ 5 years.

A. Overall sparse-event summary			
Indicator			Value
Districts with TB cases aged ≤ 5 years			27
Districts with ≥ 1 mortality event aged ≤ 5 years			3
Districts with zero mortality event aged ≤ 5 years			24
Total TB cases aged ≤ 5 years			130
Total mortality events aged ≤ 5 years			3
Mortality event rate in aged ≤ 5 years			2.31%
B. Districts with mortality events among patients aged ≤ 5 years			
District	TB cases aged ≤ 5 years	Mortality events	Event rate (%)
Demak	8	1	12.50
Kendal	3	1	33.33
Semarang City	14	1	7.14

TB, tuberculosis. Mortality event rate (%), number of mortality events divided by the total number of TB cases among patients aged ≤ 5 years $\times 100$. Panel A presents the overall sparse-event summary, while Panel B presents districts with mortality events among patients aged ≤ 5 years.

Discussion

This study demonstrated that the associations between patient characteristics and mortality during TB treatment were not spatially uniform across Central Java. Compared with the conventional Cox proportional hazards model, geographically weighted Cox regression revealed

geographic variation in the effects of several patient characteristics while providing a better overall fit to the observed survival data. HIV-positive status remained the strongest predictor of mortality across districts and the magnitude of its association varied geographically, indicating that a single global hazard ratio may not adequately characterize local mortality risk. The effect of HIV co-infection on the hazard of death was positive across regions, indicating that TB patients with HIV co-infection had a higher hazard of death than those without HIV co-infection. Stronger positive estimates were observed in the western part of Central Java than in the eastern part. This suggests that the mortality hazard associated with TB-HIV co-infection may be more pronounced in western districts or cities. In contrast, the local parameter estimates for DM-positive status compared with DM-negative status showed less spatial variation. The estimates were positive across districts or cities but relatively similar in magnitude, indicating that DM-positive status was consistently associated with an increased hazard of death among TB patients, with a more homogeneous effect across Central Java. These findings are consistent with previous studies identifying HIV infection and diabetes mellitus as important comorbidities associated with poor outcomes among TB patients. TB patients living with HIV have weakened immune systems and experience reciprocal interaction between the two diseases, making them more vulnerable to disease progression and mortality than patients without HIV [9, 12, 20]. Similarly, among patients with diabetes mellitus, impaired glucose control may affect the body's response to infection as well as the effectiveness of TB treatment [10, 21]. The age group of ≤ 5 years showed a pronounced geographic variation in its association with the hazard of death, indicating that the effect of very young age was not uniform across locations.

Prior studies have emphasized that TB in children under 5 years remains clinically important because diagnosis is challenging and vulnerability is shaped by factors such as household exposure, HIV infection, malnutrition, and access to pediatric TB services [22, 23]. In a low-burden setting, Pasqualini et al. [22] showed that TB risk among children aged 0–5 years was strongly related to exposure intensity, particularly household or close contact. Evidence from Ethiopia and Indonesia also highlights the role of nutritional vulnerability, as TB among children under five years has been linked to severe acute malnutrition and stunting-related factors [24, 25]. Therefore, the wide spatial variation observed in the ≤ 5 years age group in this study may reflect differences in local case detection, contact investigation, nutritional status, referral pathways, and access to pediatric TB services across districts or cities.

For the other age groups, patients aged 6–17 years consistently had a lower hazard of death than patients aged 18–59 years, whereas patients aged ≥ 60 years had a higher hazard of death. This result is consistent with the study conducted by Osman et al. [9] in South Africa, which demonstrated that the risk of unsuccessful treatment outcomes differs across age groups and tends to increase among older individuals. In addition, several studies have reported that the working-age population remains at considerable risk due to higher mobility, social activity, and exposure to various risk factors that may worsen health conditions [26, 27]. On the other hand, elderly individuals are more vulnerable due to declining immune function, the presence of comorbidities, and delays in diagnosis that occur more frequently within this age group [28].

The local parameter estimates showed that extrapulmonary TB was consistently associated with a lower hazard of death compared with pulmonary TB but with limited spatial variation (Fig 4J). This indicates that the effect of extrapulmonary TB on mortality hazard was relatively homogeneous across districts. This finding is consistent with the studies by Asgedom et al. [29]

and Siamisang et al. [30], although contrasting results have also been reported, such as by Carter et al. [15].

Male patients showed a consistently higher hazard of death than female patients. This finding aligns with studies by Nordholm et al. [10] and Osman et al. [9], which reported poorer TB treatment outcomes among male patients. This pattern may reflect differences in health-seeking behavior, treatment adherence, comorbidity profiles, occupational exposure, or delayed access to care.

Occupational effects (Figs 4G–4I) showed some geographic variation, although the clearest and most consistent pattern was observed for unemployment. Across districts, unemployed TB patients generally exhibited higher hazards of death than formally employed patients, consistent with previous studies linking socioeconomic disadvantage to poorer TB outcomes [10, 31].

Economic instability, limited access to healthcare services, and difficulties in maintaining treatment adherence may partly explain this relationship [11].

On the other hand, rural residence showed local hazard ratios close to 1, suggesting limited spatially varying association with the hazard of death after accounting for other patient-related factors.

To further understand the geographic variation identified by GWCR, we conducted an exploratory analysis to examine whether district-level healthcare service burden was associated with the local hazard ratio estimates. We found that districts with higher mean TB caseload per clinic and greater variation in clinic caseload across facilities tended to exhibit stronger local hazard ratios for HIV-positive status (Figs 5A–5B). These findings suggest that variation in healthcare service burden may contribute to the spatial heterogeneity in the estimated association of HIV and TB mortality.

412 One possible explanation is that TB-HIV management is operationally more complex than
413 routine TB care because it requires coordinated delivery of HIV testing, timely initiation of
414 antiretroviral therapy, clinical monitoring, and continued follow-up through integrated TB-HIV
415 services, as recommended in international TB-HIV care guidance [32, 33]. Districts with higher
416 clinic workloads or more uneven distributions of TB patients across healthcare facilities may
417 therefore experience greater challenges in delivering these services consistently. Consequently,
418 the observed geographic variation in the effect of HIV may partly reflect differences in
419 healthcare service capacity and organization across districts.

420 This interpretation is consistent with evidence from Indonesia, indicating that TB service
421 delivery at primary healthcare facilities is frequently constrained by shortages of trained
422 personnel, competing clinical responsibilities, limited infrastructure, and reporting requirements
423 that increase staff workload [34]. Such operational constraints may disproportionately affect the
424 management of TB-HIV co-infection because integrated care requires coordination between
425 multiple healthcare programmes and sustained patient monitoring. Nevertheless, this exploratory
426 analysis was ecological and correlational. Therefore, the observed associations should not be
427 interpreted as evidence that higher clinic caseload directly causes poorer outcomes among HIV-
428 positive TB patients. Rather, they suggest that healthcare service burden may partly contribute to
429 the spatial heterogeneity captured by GWCR.

430 In contrast, district-level mean clinic caseload was negatively associated with the local hazard
431 ratio for patients aged ≤ 5 years. This finding should be interpreted with caution because
432 mortality events in this subgroup were extremely sparse. Among the 27 districts with TB cases in
433 children aged ≤ 5 years, only three districts recorded a single death, whereas the remaining
434 districts had no mortality events. With such limited outcome information, district-specific hazard

ratio estimates are based on very few events and are therefore more susceptible to random variation than estimates derived from subgroups with larger numbers of events [35, 36]. Consequently, the observed negative association is unlikely to indicate that higher clinic workload is associated with a lower mortality risk among young children. Rather, it more plausibly reflects the limited precision of local estimates arising from the sparse distribution of mortality events. Future studies with larger pediatric TB cohorts, longer follow-up periods, or statistical approaches designed for sparse-event survival data are needed to determine whether geographic variation in the effect of young age persists in larger populations.

Several limitations should be considered when interpreting these findings. First, this study was based on routinely collected surveillance data, which limited the availability of several potentially important clinical and health system variables, including treatment adherence, antiretroviral therapy status, nutritional status, and facility-level resources. Second, although the proportional hazards assumption was satisfied for most covariates, occupation showed evidence of non-proportional hazards. Because the primary objective of this study was to investigate spatial heterogeneity using the same covariate structure across the global Cox model and the GWCR model, occupation was retained in the analyses. Therefore, the estimated effects of occupation should be interpreted with caution, as the corresponding hazard ratios may represent average effects over the follow-up period rather than constant effects over time. Third, the exploratory analysis of district-level healthcare service burden was ecological and correlational, precluding causal inference. Finally, sparse mortality events among patients aged ≤ 5 years limited the precision of district-specific hazard ratio estimates for this subgroup, and these findings should therefore be considered exploratory.

Taken together, these findings suggest that the determinants of TB mortality cannot always be adequately characterized by a single global hazard ratio. Incorporating geographic variation into survival analysis provides additional insight into local differences in mortality risk and may help identify areas where the effects of patient characteristics differ from the provincial average. Such information could support more geographically responsive TB control strategies and guide future investigations of healthcare system factors underlying spatial variation in TB outcomes.

Conclusions

This study demonstrates the applicability of geographically weighted Cox regression (GWCR) for examining spatial heterogeneity in tuberculosis mortality. Whereas the conventional Cox proportional hazards model assumes that covariate effects are constant across locations, GWCR revealed that the associations between several patient characteristics and the hazard of death varied across districts/cities, indicating spatially heterogeneous effects. Although some covariates exhibited relatively consistent associations across the study area, others showed substantial geographic variation, suggesting that global hazard ratios may mask important local differences in TB mortality risk. Exploratory analyses further suggested that part of this spatial heterogeneity may be associated with differences in healthcare service burden across districts, in addition to underlying epidemiological variation. Together, these findings highlight the importance of incorporating spatial context into survival analyses to improve understanding of local TB mortality patterns and to inform geographically tailored TB control strategies and future research.

List of abbreviations

HIV	Human Immunodeficiency Virus
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479	GWCR	Geographically Weighted Cox Regression
480	TB	Tuberculosis
481	SITB	Tuberculosis Information System
482	DM	Diabetes Mellitus
483	HR	Hazard Ratio
484	TIC	Takeuchi Information Criterion

485 **Declarations**

486 **Ethics approval and consent to participate**

487 The individual-level tuberculosis surveillance data used in this study were obtained from the
488 Provincial Health Office of Central Java under official administrative permission. The study
489 protocol was reviewed by the Health Research Ethics Committee (HREC) of Politeknik
490 Kesehatan Kemenkes Jakarta II, which determined that the study was eligible for exemption
491 from ethical review (Reference Number: DP.04.03/I/KE/L/635/2026). As part of this
492 determination, The HREC granted a waiver of informed consent because the study involved the
493 retrospective use of anonymized and unlinked data, in accordance with the National Research
494 Ethics Guidelines (2021) and the Committee's standard operating procedures. The waiver
495 applied to all participants, including those younger than 16 years. Therefore, individual informed
496 consent and separate parental or legal guardian consent for participants younger than 16 years
497 were not required for this secondary analysis. No participants were directly recruited or
498 contacted for this study, and no personally identifiable information was included in the analysis
499 or presented in the manuscript. All patient information was handled confidentially.

500 **Consent for publication**

501 Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the Provincial Health Office of Central Java, but restrictions apply to the availability of these data, which were used under official administrative permission for the current study. The authors do not have the authority to distribute the individual-level dataset publicly. Data may be available from the authors upon reasonable request and with permission from the Provincial Health Office of Central Java.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HY, MJ, and LMP conceptualized the study. LMP conducted the formal analysis. MJ reviewed and interpreted the results and drafted the manuscript. HY supervised the analysis and the manuscript preparation process. PPI contributed to the review and editing of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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Additional files

Additional file 1. Proportional hazard assumption test.

Additional file 2. Bandwidth selection based on minimum Takeuchi Information Criterion.

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