

Original Research Article

Effect of zinc on sputum conversion time of drug sensitive tuberculosis patients in Naypyitaw Union Territory: a quasi-experimental study

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ABSTRACT

Background: Tuberculosis (TB) remains a major global health problem, particularly in high-burden countries such as Myanmar. Malnutrition and zinc deficiency are common among TB patients and may impair immune response. Zinc supplementation has been proposed as an adjunct to standard anti-TB treatment to accelerate sputum conversion, but evidence remains inconsistent.

Methods: A quasi-experimental study was conducted from January 2024 to December 2025 in Naypyitaw territory, Myanmar, enrolling 310 newly diagnosed drug-sensitive tuberculosis patients. Participants in one district received standard anti-TB therapy plus zinc supplementation (20 mg daily), while those in another district received standard therapy alone. Data on socio-demographic, clinical, behavioral, and health belief variables were collected. Survival analysis and Cox proportional hazards regression with propensity score adjustment was used to compare sputum conversion times between groups.

Results: Zinc supplementation significantly improved sputum conversion time, with 72.9% reaching conversion earlier than 41.9% in the control group (adjusted hazard ratio [aHR]=1.93; 95% CI: 1.31–2.85; p=0.001). Additional factor positively influencing early sputum conversion was initial sputum grading. The findings indicated that zinc supplementation accelerates sputum smear conversion, likely by enhancing host immune defense.

Conclusions: The findings underscored the critical roles of nutritional support in influencing treatment outcomes. Integrating zinc into TB treatment protocols, particularly among malnourished populations, represented a cost-effective and feasible strategy to enhance early microbiological response, improve clinical recovery, and potentially reduce TB transmission risk.

Keywords: TB, Zinc supplementation, Sputum conversion, Naypyitaw

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a leading cause of global morbidity and mortality, especially in high-burden countries such as Myanmar. According to World Health Organization (WHO) estimates, Southeast Asia accounts for a substantial proportion of global TB cases and deaths, and Myanmar is categorized among the high-TB-burden countries facing challenges such as undernutrition, HIV co-infection, and drug resistance. Effective TB control

requires timely diagnosis and successful treatment to interrupt transmission and reduce mortality. Anyone anywhere can be affected by tuberculosis but about 90% of affected persons were adults, male: female ratio is 2:1, and case rates vary at the national level from fewer than 50 to over 5000 per 1 million population per year all over the world.¹ There are two types of TB infection known as active or latent stage. There will be the risk of tuberculosis in individuals who have latent *M. tuberculosis* infection (LTBI) is predicted to be 5–10% during their lifetime, with

around half of cases happening within the first 2 years after exposure.²

Malnutrition is a major risk factor in the pathogenesis and progression of TB, as it impairs the host's immune response. Zinc, an essential micronutrient involved in numerous biological functions including immune modulation, enzymatic activity, and cell-mediated immunity, is frequently deficient in TB patients. Zinc deficiency can result in the dysfunction of macrophages and T lymphocytes, increasing susceptibility to infections and potentially delaying sputum smear conversion during treatment. Early sputum conversion is a well-recognized biomarker of therapeutic response and lower infectiousness, it has been proposed that TB leads to malnutrition or 'wasting' while on the other, poor nutritional status has been postulated to be a risk factor for receiving TB.³ Malnutrition can cause a reduced immune system of the body, therefore the patient's ability to protect against mycobacteria becomes weakened.⁴ Among the micronutrients, vitamin A and zinc are common micronutrients that are deficient in people with TB.⁵ The killing of mycobacteria through the mechanism of metal poisoning in phagosomes is limited in zinc deficiency. Moreover, many biological functions, including immune responses, oxidative stress responses, DNA replication and damage repair, and apoptosis, are involved by zinc.⁶

The United Nations and WHO have committed to "ending the global TB epidemic" by 2030, adopting the end TB strategy in 2014. It was also found that the COVID-19 pandemic had a damaging impact on access to TB diagnosis and treatment and increased the burden of TB disease. Therefore, the progress made in the years up to 2019 has slowed, or reversed and global TB targets are off track.

Naypyitaw is the capital of Myanmar and most of the people who live in urban areas are government staff. In Naypyitaw, most of the people live in rural areas and have low levels of health education and health literacy status. On the other side, TB is one of the most contagious diseases and Naypyitaw stands at 8th place in case notification rate among 17 states and regions. If the TB cases are not properly controlled, it can elevate the latent TB infected (LTBI) cases which cause the public health burden of the country. In addition, it was found that zinc can increase the immune response of the human body support in early recovery of illness, and reduce the contingency of TB infection. But in active TB cases, serum zinc level is reduced and cause high grading of sputum positive smear. In this situation, zinc becomes the adjunctive therapy in combination with anti-TB treatment which can accelerate the reduction of sputum smear grading. There will be a gap about how much effect the adjunctive therapy of zinc has on sputum conversion time in the treatment of tuberculosis patients.

This study aimed to investigate the effect of zinc supplementation on sputum conversion time among drug-

sensitive TB patients receiving standard anti-TB therapy in Naypyitaw Union Territory, Myanmar, while addressing baseline confounders using propensity score adjustment and robust survival analysis methods.

METHODS

Study design, setting and population

This study employed a quasi-experimental design conducted from January 2024 to December 2025 in Naypyitaw Union Territory, Myanmar, targeting newly diagnosed pulmonary drug-sensitive tuberculosis (DSTB) patients aged 15 years and above receiving standard anti-TB treatment. Two districts were selected, with one serving as the intervention site where patients received adjunctive zinc supplementation (20 mg elemental zinc daily) alongside standard treatment, and the other as the control site receiving only standard anti-TB therapy. Naypyitaw is the capital of Myanmar and most of the people who live in urban areas are government staff. In Naypyitaw, most of the people live in rural areas and have low levels of health education and health literacy status. On the other side, TB is one of the most contagious diseases and Naypyitaw stands at 8th place in case notification rate among 17 states and regions.

Sample size and sampling procedure

The sample size was each 155 DSTB patients for intervention and control group. Total sample size was 310 DSTB patients. The two districts from Naypyitaw were selected purposively based on criteria of closely comparable socio-economic and demographic factors and were randomly assigned to intervention and control groups. Participants were recruited consecutively upon confirmation of DSTB diagnosis via sputum smear microscopy. Baseline data included socio-demographic characteristics, clinical variables, behavioral factors, anthropometric measurements (including BMI), and health belief model constructs gathered through structured interviews. Sputum smear microscopy was performed at baseline and regularly during treatment to monitor conversion status.

Data collection tools and methods

Data collection was conducted by face-to-face interview with structured questionnaires to collect background characteristics, disease related factors, access to health care and perception on TB by the patients. Anthropometric measurements (weight and height) were conducted by seca weighing scale and stadiometer at the start of enrollment to assess their nutritional status. Sputum smear examination was included to evaluate sputum conversion. Zinc capsules were administered daily throughout the intensive phase of anti-TB treatment, adhering to WHO dosing recommendations to intervention group for two months. Adherence was monitored by healthcare staff and patient family members.

Data analysis

Data entry and data analysis was done using STATA (version 14, Stata Corporation, and College Station TX) software. Data analysis comprised descriptive and inferential statistics. To detect the baseline differences of characteristics of the tuberculosis patients between intervention and control groups, Chi-square test was used. The variables that are associated with outcome (gender, age, occupational status, educational level, expenditure, perception on frequency of meal, perception on expenditure of food, smoking, accessibility) were selected for calculating propensity score. These scores were used as covariates in adjusted Cox proportional hazards models to reduce confounding bias.

Survival analysis was used to compare the time to sputum conversion and symptom relief between the intervention and control groups. The outcome of interest in this study was time to early sputum conversion. Sputum conversion time was defined as the interval from treatment initiation to the first negative sputum result, with conversion categorized as early conversion (<30 days) and late conversion (≥ 30 days).⁷ Symptom relief time was also categorized into early symptom relief (<14 days) and late symptom relief (≥ 14 days).⁸

Kaplan-Meier survival curves were plotted to visualize the differences in time to sputum conversion between the groups. The Cox proportional hazards model was used to assess the effect of zinc supplementation on sputum conversion time. Statistical significance was defined as a 2-sided p value < 0.05 . The proportional hazards assumption was tested using Schoenfeld residuals, ensuring no violation for key covariates including the intervention. Model selection and comparison were guided using Akaike information criterion (AIC) and Bayesian information criterion (BIC), favoring models with better parsimony and fit. Likelihood ratio tests (LR tests) compared nested models to evaluate the significance of adding zinc supplementation in explaining sputum conversion time variation.

Potential ethical issues

The purpose of the study was explained thoroughly to the participants with a detailed information sheet before the data collection. Only after they had fully understood the nature of the study, they were invited to take part in the study. To ensure the safety of enumerators, they were provided with appropriate training for infection prevention and control measures according to WHO guidelines. Additionally, personal protective equipment such as gowns, face masks, face shields, gloves, and hand sanitizer was provided. Well-ventilated working environment was set to minimize the dispersion of infectious particles. For intervention group, zinc 20 mg (as zinc sulphate) tablet was given daily and, in this case, zinc tablets were bought from most reliable brand with same batch number which had been approved from Myanmar FDA.

RESULTS

In alignment with the general and specific objectives of the study, the collected data were systematically organized and subjected to detailed statistical analysis to assess the effect of zinc supplementation on sputum conversion time among drug-sensitive tuberculosis patients. A total of 319 participants were enrolled from four selected townships within Naypyitaw Union Territory, Myanmar (Figure 1).

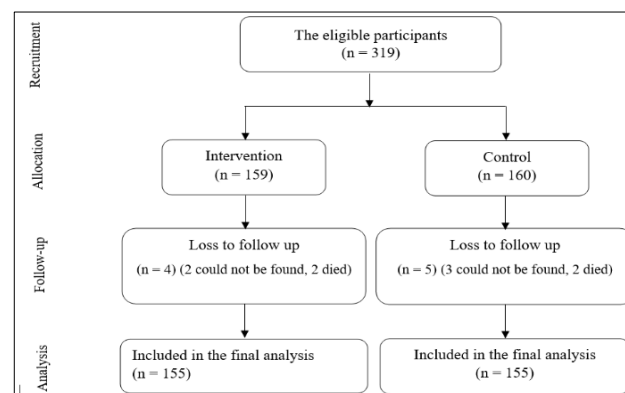


Figure 1: CONSORT flow diagram of the study.

A total of 310 newly diagnosed drug-sensitive tuberculosis patients were enrolled, with 155 patients in the intervention group (receiving zinc supplementation plus standard therapy) and 155 patients in the control group (standard therapy only). Baseline comparison showed significant differences between groups in several socio-demographic variables including gender distribution, age, education, occupation, and monthly family income, which were accounted for in propensity score modeling (Table 1).

The bar chart compared early and late sputum conversion rates between intervention and control groups in tuberculosis treatment which clearly demonstrated the effectiveness of the intervention, with nearly three-quarters of intervention group patients achieving early sputum conversion compared to less than half in the control group (Figure 2).

Figure 3 illustrated the proportion of early relief (within 14 days) and late relief (14 days or more) among participants in both the intervention and no-intervention groups. In the Intervention group, all participants (100.00%) experienced early relief, defined as relief occurring in less than 14 days. Notably, there were no cases (0.00%) of late relief (≥ 14 days) in this group. In contrast, within the no-intervention group, the vast majority (96.13%) also experienced early relief. However, a small proportion (3.87%) reported late relief, with symptom improvement occurring after 14 days. After adjusting for other variables in the model, those who received zinc supplementation had a significantly higher early conversion rate of 72.90% compared to 41.94% in the no-intervention group. The zinc supplementation group had an adjusted hazard ratio (aHR) of 1.93 (95% CI: 1.31–2.85, $p=0.001$), indicating nearly double the likelihood of

early conversion relative to those without intervention. Propensity score adjustment showed a strong association with early conversion as well, with an aHR of 2.50 (95%

CI: 1.09–5.75, $p=0.031$), supporting the robustness of the intervention effect.

Table 1: Baseline characteristic of the respondents (n=310).

Characteristic	Intervention		Control		P value*
	Number	Percent	Number	Percent	
Gender					<0.001
Male	103	66.45	130	83.87	
Female	52	33.55	25	16.13	
Age (completed year)					<0.001
15-25	25	16.13	21	13.55	
26-40	58	37.42	31	20	
41-60	52	33.55	62	40	
>60	20	12.9	41	26.45	
Education					<0.001
No formal education	8	4.52	12	7.74	
Primary school	32	20.65	42	27.1	
Secondary school	42	27.1	60	38.71	
High school or equivalence	54	34.84	28	18.06	
Bachelor degree or higher	20	12.9	13	8.39	
Occupation					0.007
Dependent	31	20	18	11.61	
Manual worker	39	25.16	29	18.71	
Government staff	8	5.16	6	3.87	
Private employee	35	22.58	69	44.52	
Other (specify)	42	27.1	33	21.29	
Family income (MMK)					0.229
<150,000 (low)	3	1.94	6	3.87	
150,000 to <400,000 (medium)	95	61.29	102	65.81	
≥400,000 (high)	57	36.77	47	30.32	
Family expenditure for food (MMK)					<0.001
<100,000 (low)	9	5.81	3	1.94	
100,000to<300,000 (medium)	66	42.58	103	66.45	
≥300,000 (high)	80	51.61	49	31.61	
Sputum result					0.568
Scanty	26	16.77	9	5.81	
1+	41	26.45	63	40.65	
2+	47	30.32	35	22.58	
3+	41	26.45	48	30.97	
Perception on frequency of meals					0.018
Not enough	50	32.26	27	17.42	
Average	6	3.87	10	6.45	
Enough	99	63.87	118	76.13	
Perception on expenditure on food					<0.001
Not enough	51	32.9	36	23.23	
Average	45	29.03	20	12.9	
Enough	59	38.06	99	63.87	
Smoking					<0.001
Never	97	62.58	49	31.61	
Ex-smoker	51	32.9	75	48.39	
Current smoking	7	4.52	31	20	
BMI					0.099
≤18.5 (underweight)	105	67.74	118	76.13	
>18.5 to ≤25 (normal)	50	32.26	37	23.87	

*Chi-square test

Sputum result indicated that participants with scanty and 1+ results had a significantly higher chance of early conversion compared to those with 2+ and 3+ results (aHR=1.62; 95% CI: 1.19–2.19; p=0.002).

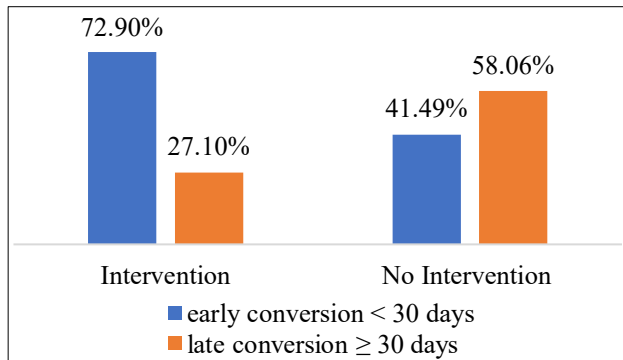


Figure 2: Sputum conversion between two groups.

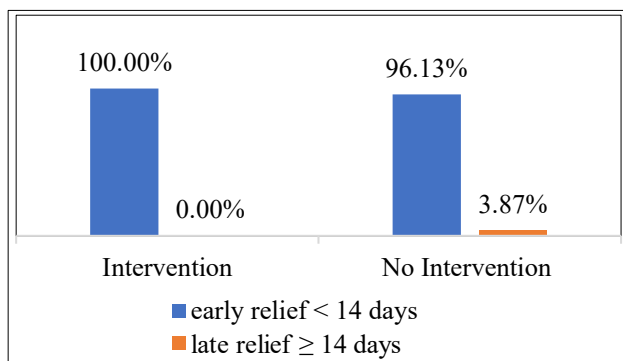


Figure 3: Symptom relief time between two groups.

In summary, zinc supplementation and sputum results were significant predictors of early conversion. Propensity score adjustment further confirmed the effect of zinc intervention. Other socio-demographic and behavioral factors showed no significant association in this analysis (Table 2).

The survival probability for remaining sputum-positive decreased more rapidly in the intervention group compared to the control group throughout the analysis period, indicating earlier sputum conversion among those receiving the intervention. By day 20, the probability of remaining sputum-positive had declined steeply in the intervention group, with a visible separation between the two survival curves becoming apparent from approximately day 15 onward. At the end of the observation period (day 54), the proportion of patients who remained sputum-positive was markedly lower in the intervention group than in the control group. These findings suggested that the intervention was associated with a faster rate of sputum conversion compared to standard care alone. The separation of the survival curves and the non-overlapping confidence intervals indicate a potentially meaningful effect of the intervention on accelerating culture conversion in patients with tuberculosis (Figure 4).

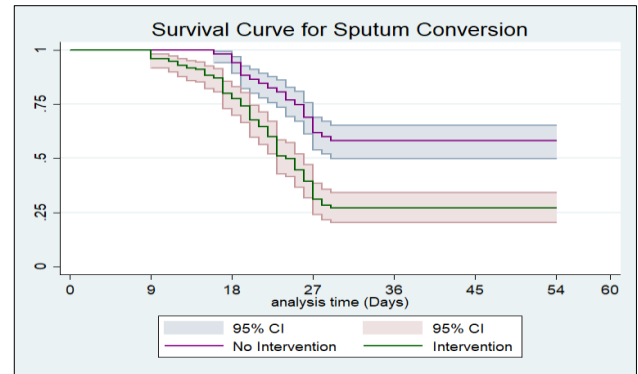


Figure 4: Kaplan-Meier survival curve for sputum conversion.

Kaplan-Meier survival curves comparing the time to symptom relief between two groups: the survival probability decreases over time for both groups, indicating that more participants experience symptom relief as time progresses. The curves for the intervention and control groups are closely aligned, suggesting similar rates of symptom relief between the two groups throughout the follow-up period. The overlap between the CIs for both groups further indicates no statistically significant difference in time to symptom relief. By the end of the analysis period, nearly all participants in both groups have achieved symptom relief, as the survival probability approaches zero (Figure 5).

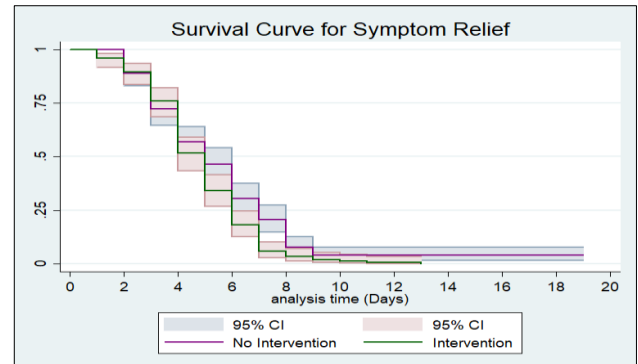


Figure 5: Kaplan-Meier survival curve for symptom relief.

The interaction between zinc supplementation and normal BMI did not reach statistical significance (aHR=1.43; 95% CI: 0.70–2.93; p=0.326), suggesting that BMI does not modify the effect of zinc on sputum conversion substantially. The above data did not support that the effect of zinc supplementation on the sputum conversion time differed by BMI category. It means, the impact of zinc supplementation on the sputum conversion time appeared consistent regardless of BMI status.

The lack of significance suggested that BMI did not modify the relationship between zinc supplementation and the sputum conversion time of the respondents (Table 2).

Table 2: Multivariate cox-regression for early sputum conversion time (n=310).

Characteristic	Number	% Early conversion	Crude HR (95% CI)	Adjusted HR (95% CI)
Zinc supplementation				
Control	65	41.94	1	1
Intervention	113	72.90	2.44*** (1.79-3.31)	1.93*** (1.31-2.85)
Family income (MMK)				
<400,000	107	51.94	1	1
≥400,000	71	68.27	1.44* (1.07-1.95)	1.29 (0.95-1.75)
Sputum result				
2+ and 3+	86	50.29	1	1
Scanty and 1+	92	66.19	1.53** (1.14-2.06)	1.62** (1.19-2.19)
BCG scar				
Absent	21	52.50	1	1
Present	157	58.15	1.11 (0.70-1.74)	1.39 (0.87-2.20)
Alcohol consumption				
Drink	85	53.13	1	1
Never drink	93	62	1.29 (0.96-1.73)	0.95 (0.69-1.32)
BMI				
Under weight	126	56.5	1	1
Normal	52	59.77	1.06 (0.77-1.47)	0.97 (0.70-1.32)
HBM (perception on tuberculosis)				
Moderate	110	50.46	1	1
High	68	73.91	1.83*** (1.35-2.48)	1.23 (0.88-1.71)

Adjusted with p score, *p value <0.05, **p value <0.01, ***p value <0.001

DISCUSSION

This quasi-experimental study demonstrated that adjunctive zinc supplementation significantly accelerates sputum smear conversion among pulmonary TB patients receiving standard anti-tuberculosis therapy in Naypyitaw, Myanmar. These findings aligned with mechanistic evidence on zinc's critical role in immune function and prior clinical studies suggesting beneficial effects of zinc micronutrients on TB treatment outcomes.

This study provided strong evidence that zinc supplementation significantly accelerated sputum smear conversion and symptom relief among DSTB patients receiving standard anti-TB therapy. The findings were consistent with previous research demonstrating that zinc plays a crucial role in enhancing host immune function, particularly in T-cell mediated immunity and macrophage activity, which are vital for controlling *Mycobacterium tuberculosis* infection.^{6,9} The accelerated sputum conversion observed in the zinc-supplemented group aligns with findings from randomized controlled trials and meta-analyses showing that micronutrient supplementation, especially zinc, improves early microbiological response during TB treatment.^{10,11}

Sociodemographic factors such as gender and socioeconomic status also influenced sputum conversion, highlighting the importance of considering multiple social determinants in TB management strategies. The accelerated sputum conversion observed could translate

into lower infectivity periods, potentially reducing transmission and improving community-level control. Socioeconomic status and nutritional factors also significantly affected treatment outcomes, consistent with prior findings that malnutrition and poverty worsen TB prognosis and response to therapy.¹² Addressing these determinants through integrated health interventions is essential in high-burden, resource-limited settings.

Interestingly, higher initial sputum bacterial load (2+ or 3+) was expected to delay sputum conversion; however, this study found that other clinical or immunological factors may have played a more prominent role in influencing conversion time. This observation reflects the complex host-pathogen interaction and suggests that zinc's immunomodulatory effects could overcome some of the disadvantages conferred by higher bacillary burden.¹³ The association of better patient perception of TB severity and treatment benefits with earlier sputum conversion underscores the importance of behavioral interventions alongside nutritional support to improve adherence and outcomes.¹⁴ Improving knowledge and beliefs about TB promotes adherence and engagement with treatment, which are essential for successful outcomes.

This quasi-experimental study incorporated rigorous methods such as propensity score adjustment and proportional hazards assumption testing to strengthen causal inference, but limitations such as nonrandomized design and residual confounding remain. Future randomized controlled trials with larger samples and

longer follow-up are needed to confirm optimal zinc supplementation strategies.

The survival curve for sputum conversion demonstrated a clear, statistically supported difference between patients receiving the intervention and those without the intervention, emphasizing the intervention was substantial impact in accelerating sputum conversion among TB patients. The early separation of curves, particularly within the first 18 to 27 days, was critical as it reflected crucial treatment dynamics during the intensive phase of TB therapy when bacterial load was highest and transmission risk greatest. Moreover, the divergence between the curves demonstrated a consistent benefit of zinc supplementation in reducing the time to sputum conversion. The narrowing of the 95% confidence intervals around the intervention curve also reflected the precision and reliability of this finding. The intervention's association with an adjusted hazard ratio of 1.93 in the multivariate Cox regression further verified the survival analysis, indicating a 93% increase in the hazard (rate) of early sputum conversion when adjusting for confounders. This finding aligned with various studies showing adjunctive zinc supplementation improved immune responsiveness through modulation of macrophage and T-cell activities, thereby promoting *Mycobacterium tuberculosis* clearance from sputum.¹⁵ It was consistent with clinical trials reporting that micronutrient interventions enhanced sputum smear conversion rates, especially in malnourished or immunocompromised populations.¹⁶ The research done in Spain observed as there were difference between time of sputum conversion among the tuberculosis patients depended on severity of disease, health behaviour and association of co-morbid infection.¹⁷ However, most of the published article proved that zinc enhance the immune response, supporting antimicrobial activity and contribute to improved treatment outcomes for drug-sensitive tuberculosis.

The survival curve for symptom relief, the intervention group, exhibited a rapid decline to near-zero symptoms within the first few days, indicating swift and consistent symptom relief. This suggested that the intervention was highly effective in providing relief early on. In contrast, the control group showed a slower decline in symptom relief, with individuals continuing to report symptoms well beyond the 10-day mark. Both curves showed a sharp decline in symptom presence during the first 7–10 days, with the intervention group reaching near complete symptom relief slightly earlier. The confidence intervals overlapped but the trend suggested a potential benefit from zinc in reducing symptom duration. This suggested that the intervention accelerated symptom relief, while the absence of intervention lead to prolonged symptoms. This finding was consistent with evidence indicating zinc's critical role in enhancing immune function and modulating inflammatory responses, which were vital in combating *Mycobacterium tuberculosis* infection.¹⁸ One of the systematic review and meta-analysis with Twenty-eight RCTs with 5446 participants revealed zinc could

significantly reduce the symptoms resolved 2 days earlier with sublingual or intranasal zinc compared with placebo (95% CI 0.61 to 3.50) and 19 more adults per 100 were likely to remain symptomatic on day 7 without zinc (95% CI 2 to 38). There were clinically significant reductions in day 3 symptom severity scores (mean difference, MD –1.20 points, 95% CI –0.66 to –1.74).¹⁹

The above data did not support that the effect of zinc supplementation on the sputum conversion time differed by BMI category. It means, the impact of zinc supplementation on the sputum conversion time appeared consistent regardless of BMI status and BMI did not modify the effect of zinc on sputum conversion substantially. The lack of significance suggested that BMI did not modify the relationship between zinc supplementation and the sputum conversion time of the respondents.

CONCLUSION

This study provided valuable insights into the factors influencing sputum conversion, symptom relief, and survival outcomes in TB patients. Zinc supplementation significantly accelerated sputum conversion time in drug-sensitive tuberculosis patients, improving early microbiological response alongside standard anti-TB treatment. This suggested that nutritional support might enhance TB treatment outcomes and highlighted the importance of addressing nutritional status and socioeconomic factors to optimize treatment outcomes. While higher sputum bacterial load (2+ or 3+) was expected to delay conversion but other clinical or immune-related factors might play a more significant role. Incorporating zinc into TB treatment protocols, especially in malnourished populations, represented a cost-effective strategy to improve TB control and reduce transmission risk. In addition to that, the study would like to recommend to conduct randomized controlled trials to confirm the effect of zinc supplementation on sputum conversion and TB treatment outcomes. And longitudinal studies can provide more insight into the long-term effects of supplementation on relapse rates and resistance development.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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