Does Micronutrient Supplementation Reduce Tuberculosis Treatment Failure among Adult Tuberculosis Patients? A Systematic Review and Meta-Analysis of Randomized Clinical Trial

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Abstracts

Tuberculosis remains a major global public health challenge. However, the effectiveness of micronutrient supplementation on tuberculosis treatment outcomes has been debated for decades. Therefore, this systematic review and meta-analysis was aimed to summarize the large body of evidence from randomized controlled trials regarding the effectiveness of micronutrient supplementation on tuberculosis treatment outcomes. A systematic literature search for randomized controlled trials was performed in Psych-INFO, MEDLINE, Google Scholar, Web of science based on predefined criteria for inclusion of selected studies. The analysis was done using STATA se version 14, and a fixed-effects model was used to estimate risk ratios with 95% confidence intervals. The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. Seven studies, representing 2,666 participants, met the inclusion criteria. Although statistically non-significant, the overall Risk Ratio was 0.96 (95% CI: 0.86 to 1.07), suggesting 4% improvement of TB treatment outcomes up on micronutrient supplementation. Because of low heterogeneity with I^2=18.7%, p=0.29, we did not perform subgroup analysis. The risk of bias was not significant and the level of evidence quality was 'moderate'. The study indicates that micronutrient supplementation does not have a positive impact on tuberculosis treatment outcomes. However, further studies with well-controlled design are necessary before a clinically important effect can be excluded.

Keywords: Micronutrient supplementation, tuberculosis, treatment outcomes, systematic review, meta-analysis

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1. Introduction

1.1Statement of the Problem

Mycobacterium tuberculosis is one of the most common pathogens and the etiologic agent of tuberculosis (TB),which can infect and cause a clinically significant disease in human beings[1]. Although one-third of the global population is latently infected with *mycobacterium tuberculosis*, immuno-suppressed individuals have a 90% life time chance of reactivation to active TB[2]. Thus, TB remains a major global public health constraint, with 8.7 million new cases and 1.4 million deaths, annually[3]. About 6 in 10 of all TB cases are from Africa and South East Asia [2]. This event has been consistent with poverty, poor hygiene, under nutrition and immune-compromisation, especially in the context of higher rates of HIV infection [4]. Poor general nutritional status and food insecurity are significant contributors to the burden of TB because under-nutrition increases the risk of progression from latent TB to active TB disease [5-7]. Consequently, micronutrient deficiencies including Vitamin A and zinc deficiencies are common in pulmonary TB patients [8-10].

Tuberculosis treatment outcomes largely depend on a competent cell-mediated immune system, successful chemotherapy causing a rapid return to protective responses. This suggests that improving the micronutrient status of TB patients on chemotherapy patients may lead to faster bacterial clearance, and, thus, clinical recovery process by enhancing immune response [11]. In some trials, compared to the placebo group, consecutive receipt of micronutrient is helpful to sputum smear conversion, delay culture conversion rate, and death rate has significantly been improved[12, 13]. Indeed, although the mechanism remains unclear, vitamin A is crucial for the protection of mucosal immunity [14] as well as vitamins A, C, D and E have been described as immune boosters in different communicable diseases including TB, and supplementation of these vitamins has been shown to enhance immunity[15-17]. However, evidence from earlier trials were contradictory revealing non-therapeutic effects of micronutrient supplementation for TB treatment [18, 19]. Despite inconclusive remarks, the WHO generally recommends for nutritional care and support to improve TB treatment outcomes [20-22].

In general, the evidence base on the effect of micronutrient supplementation to reduce TB treatment failure remains inconclusive and inconsistence.

Moreover, the previous systematic review and Meta-analysis studies were more emphasized on the effect of micronutrient supplementations on sputum conversion, weight gain and chest X-ray absorption rate, rather than TB treatment outcomes. This systematic review and meta-analysis is therefore aimed to summarize the large body of evidence and contemporary evidence on the effect of micronutrient supplementation on TB treatment failure from Randomized Clinical Trial RCTs findings.

Methods and materials

Criteria for considering studies for this review, Participants, Interventions, Comparisons, and Outcomes, (PICO) were used to identify studies, extract and analyze the data.

Types of study

All selected studies involve RCTs concerning micronutrient supplementation for adult TB patients on treatment (TB chemotherapy).

Types of Participants

All included studies recruited adult TB patients with acid-fast bacilli sputum smear-positive or culture positive for *M. tuberculosis*, with or without co-morbidity including HIV infection, diabetes mellitus and malnutrition; extra-pulmonary tuberculosis (EPTB), multidrug resistance tuberculosis (MDR-TB) patients, articles were not published in English and child patients (age <15 years old) were not eligible for this study.

Types of intervention

The types of interventions enclosed at least Vitamin A plus zinc or multi-micronutrient supplementation and follow-up at least for 5 months to evaluate TB treatment outcomes, and successful or unsuccessful TB treatment outcomes were recorded.

Comparison

Placebo or no intervention groups were considered as comparison groups.

The studies included: multi-vitamins vs. placebo group; micronutrient vs. placebo; and vitamin A plus Zinc vs. placebo. We excluded single micronutrient supplementation such as Vitamin A or Zinc supplementation either separately or placebo.

Outcomes

The outcomes were the micronutrient supplementation intervention effects on TB treatment, which were either successful or unsuccessful TB treatment (including patients who were lost to follow-up or death) considered as an event. home.llu.edu/files/docs/horvath-handout-cochrane

Table 4: The PICO (T) Question Format Using for Précising Statement of the Research Question

Problem, population	Intervention	Comparison	Outcome	Types of studies
adult TB patients smear-positive or culture positive, with or without co-morbidity	Multi-micronutrient supplementation	Placebo/no intervention	TB treatment failure(event)	RCTs

Search Strategy and Selection Criteria

We systematically searched reports of trials published in more via Google scholar, PubMed, and Web of Science, for retrieved studies or grey literature, up to August 2017. The PICO (Population, intervention, comparison and outcomes) search terms were used, entering the following key terms: "randomized," OR "blind," OR "clinical trial," OR "micronutrient" OR "vitamin A plus zinc" AND tuberculosis treatment outcome" OR"TB treatment outcome" AND "adult population". References lists and relevant articles were also retrieved. We included only full-text articles reported in English language. We made some efforts to communicate the authors whenever additional information was needed.

Measures of Treatment Effect

Interventions were compared using RR for dichotomous data. All results are presented with 95% CIs.

Data Synthesis and Analysis

Data were extracted and entered Microsoft Excel Spreadsheet and then exported to STATA version 14 for further analysis. The characteristics of the 7 included RCTs were summarized in a descriptive table and outcomes were presented in tables stratified by treatment failure and success. Heterogeneity between studies was assessed by calculating the I^2 statistic and its corresponding 95% confidence intervals (CIs) using STATA version 14[23]. In order to calculate risk ratios (RR), the Metan command was used,

specifying use of the fixed effect model was used (Mantel-Haenszel method). Fixed-effect model was demonstrated to pool the result of all trial studies. Meta-analysis was done using RR for dichotomous variables and their related 95% CIs and p-values. Funnel plot and Egger test ($p>0.05$) were used to test for possible risk of publication bias. Sensitivity analysis was employed to check for robustness of the results and evaluate the influence of single study by omitting (leave out one approach). To verify the results, two researchers independently computed main statistical analysis and checked for consistency.

Data Extraction and Quality Assessments

This systematic review and Meta-analysis study was demonstrated from July 01-September 30, 2017. Data extraction format was constructed and pilot-tested with a subset of eligible studies, and then summarized using table. Two reviewers independently extracted the required information from the relevant articles. The following study characteristics were extracted: country of study, year of publication, participant characteristics, study design, duration of follow-up, types of interventions and treatment outcomes. For dichotomous data, we extracted the number of participants with the outcome and the total number of sample size. Data were extracted independently by two investigators (FW, SE), and discrepancies resolved with a third reviewer (WW), whenever appropriate.

Quality of Evidence

The quality of evidence was evaluated using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methods [24]. GRADE profiler was used to compute the evidence profile. The GRADE approach categorized and classified the quality of evidence based on GRADEpro approach (the quality of evidence was as follows: (1) high quality (further research is extremely unlikely to change the credibility of the pooled results); (2) moderate quality (further research is likely to influence the credibility of pooled results and may change the estimate); (3) low quality (further research is extremely likely to influence the credibility of pooled results and likely to change the estimate)' and (4) very low quality (the pooled results have extreme uncertainty).

Assessment of Risk of Bias

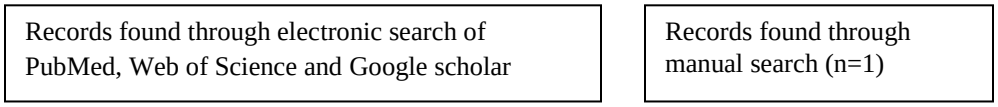
Methodological quality of each study was appraised by retrieving information on five components related to the design, execution and reporting of randomized trials: randomization technique, allocation concealment, blinding, manner of handling withdrawals and comparability of randomized groups, with respect to baseline characteristics[25].Any controversial ideas were settled by discussion, in case of dispute, the third reviewer acted as mediator. Studies were considered as a low risk of bias when all key aspects were assessed and found to be at low risk [25].

Assessment of Publication Bias

The funnel plots and egger test were used to assess publication bias. Sensitivity analysis was carried out to verify the robustness of our results.

Results Description of the Included Articles

Given the scarcity of existing articles, the systematic search yielded 192 articles; 20 duplicate and irrelevant articles were removed. Of these, 13



articles were excluded because of unfit outcome variables, controlled and experimental groups. Only 7 studies met eligible criteria and included for final pooled analysis. The included articles assessed the effectiveness of micronutrient supplementation, vitamin A plus zinc, among adults with TB (Figure 1).

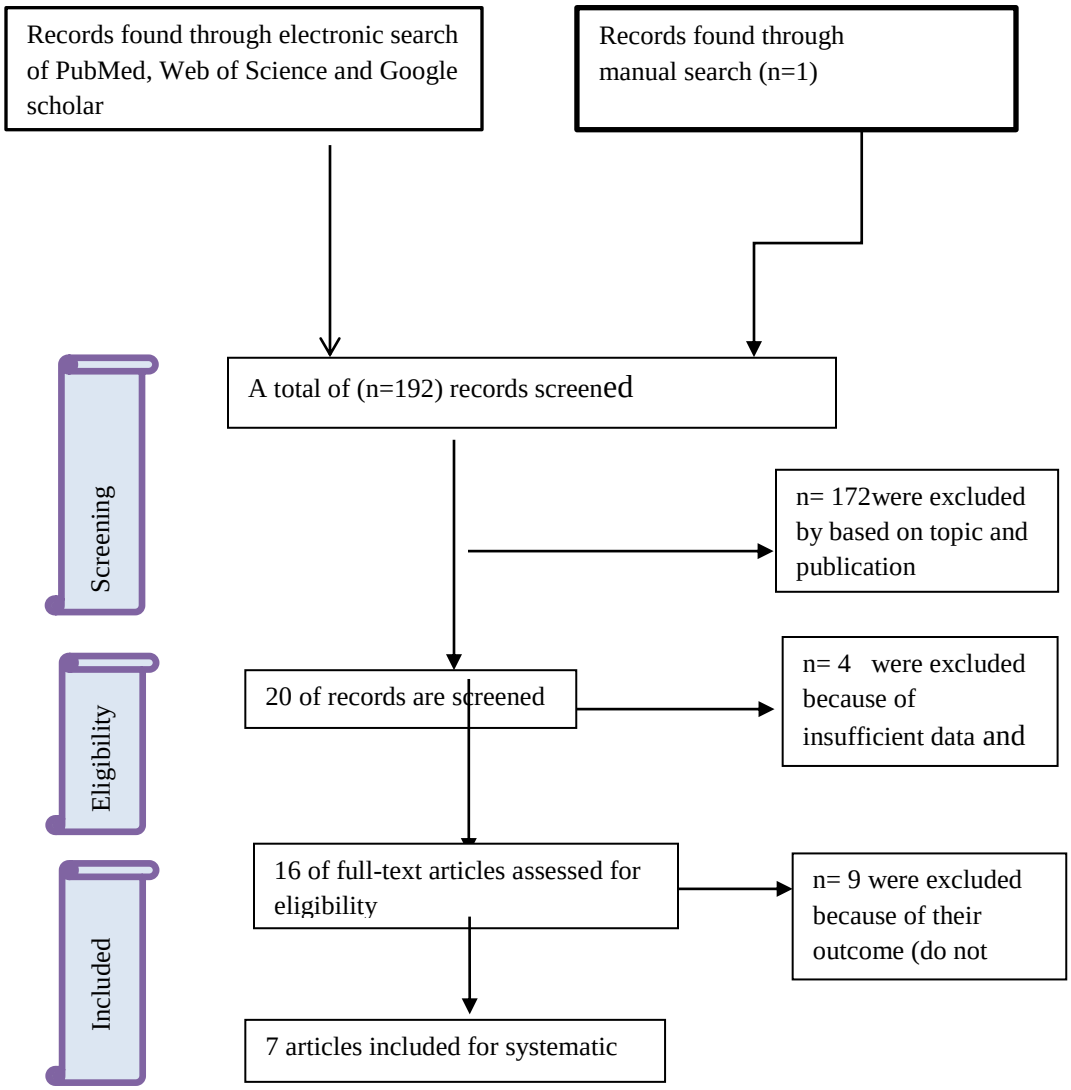


Figure 1: Flow Chart Describing the Selection of Studies for a Systematic Review and Meta-Analysis of the Effect of Micronutrient Supplementation on TB Treatment Outcomes among Adult TB Patients, 2017

Study Characteristics

Of the included studies, 3(43%)[26-28] were published in 2010 and 4 studies were conducted in Indonesia [27, 29] and Tanzania [30, 31]. Sample size of the included studies ranged from 39 [26] to 1002 [32] participants with the total sample size of 2,666 participants, The largest sample size of 1002

participants was obtained from one study [32].The trials focused on an adult population with age range between 15-78 years. The follow-up duration for outcome evaluation ranged from 5 to 8 months. All included studies did not distinguish patient appearance and biochemical profile (Table 2).

Table 5: Summery of Systematic Reviewed Studies

N. Range et al.	L. Lawson et al.	Karyadi ET AL 2002	Authors	Armijos RX			
2005	2010	Indonesia	Year of study	2010			
Tanzania	Nigeria	110	Country	Mexico			
265	233	Each micronutrient capsule contained 1500 retinol equivalents (5000 IU) vitamin A (asretinyl acetate) and 15 mg Zn (as zinc sulfate) in a lactose matrix. The placebo consisted of lactose alone. Plus Anti-TB drugs 6months 14 54 16 56 [29]	participants	39			
Micronutrient (vitamin A(1·5mg), vitamin B1 (20 mg), vitamin B2 (20 mg), vitamin B6 (25 mg), vitamin B12 (50mg), folic acid (0·8 mg), niacin (40 mg), vitamin C (200 mg), vitamin E (60 mg), vitamin D3 (5mg), selenium (0·2 mg) and copper (5 mg), and Zn tablets)	Five times the daily dose of zinc and the daily dose of vitamin A plus anti TB		Interventions	Experimental group	Four months of supplementation with 5000IU/day of vitamin A as retinal acetate and 50 mg/day elemental zinc as zinc chelate; plus standard Anti-TB drugs		
Placebo Plus Anti-TB drugs	Placebo Plus Anti-TB drugs			Control Group	Placebo group subjects received organoleptic ally identical		
8months	6 months		Follow-up months	6 months			
20	36		Events	3		Experimental	
133	117		Total	20			
28	26		Event	3		Control	
132	116		Total	19			
[30]	[28]		Reference	[26]			

George PrayGod	2011	Tanzania	865	Micronutrient (vitamin A (retinal palmitate), 1.5 mg; thiamin (thiamine hydrochloride), 20 mg; riboflavin, 20 mg; vitamin B-6 (pyridoxine hydrochloride), 25 mg; vitamin B-12 (cyanocobalamin), 50copper (copper gluconate), 5 mg; and zinc (zinc acetate),	The control biscuit weighed 30 g and contained 4.5 g of protein, 70 mg sodium, 150	>5months	82	433	73	432	[31]
Semba RD	2007	Malawi	1002	Micronutrient (vitamins A (8000 IU), C (500 mg), D (400 IU), E (200 IU), B6 (2 mg), B12 (6 _g), riboflavin (1.7 mg), thiamin (1.5 mg), niacin (20 mg), folate (0.4 mg), zinc (10	Placebo plus anti-TB	8months	242	519	253	483	[32]
Pakasi et al.	2010	Indonesia	152	micronutrient capsule contained 1500 retinol equivalents (5000 IU) vitamin A (as retinyl acetate) and/or 15 mg zinc (as zinc sulfate) in a lactose matrix.	Placebo Plus anti-TB drugs	6months	10	66	9	86	[27]

Pooled Effect of Micronutrient Supplementation on TB Treatment Outcomes

Although micronutrient supplementation for adult TB patients reduced, TB treatment failure rate by 4%. It did not reached statistically significant level (RR=0.96:95% CI: 0.86-1.07) (Figure 2).

Moreover, there was no evidence for heterogeneity of the included studies (Figure 2). Subjective assessment of funnel plot suggested symmetric distribution, and that there was no evidence for publication bias on Egger's test (Figures 3 and 4).

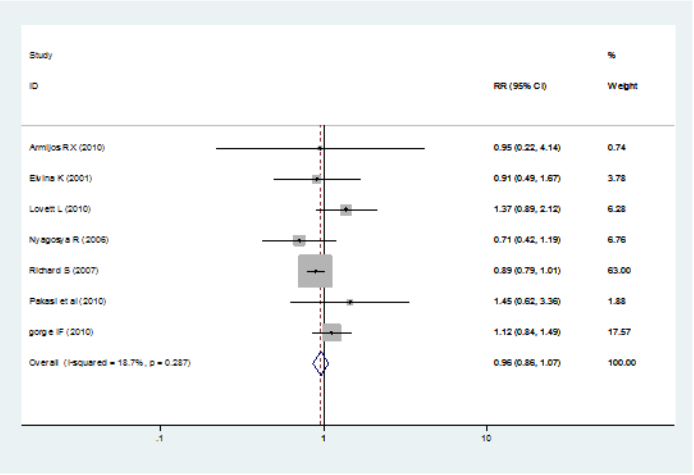


Figure 2: Forest Plot of the 7 RCT Studies That Quantitatively Assessed the Effect of Micronutrient Supplementation on TB Treatment Outcome among TB Patients, 2017.

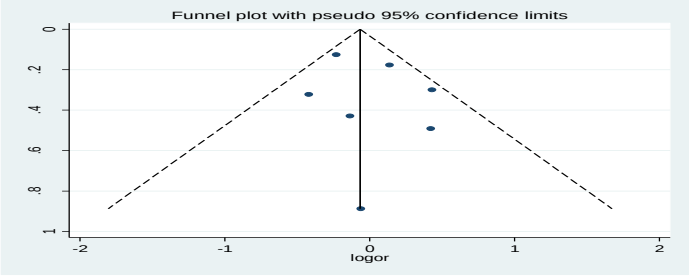


Figure 3: Funnel Plot Elaborated 7 Studies to Show the Effect of Micronutrient on TB Treatment Outcome among TB Patients.

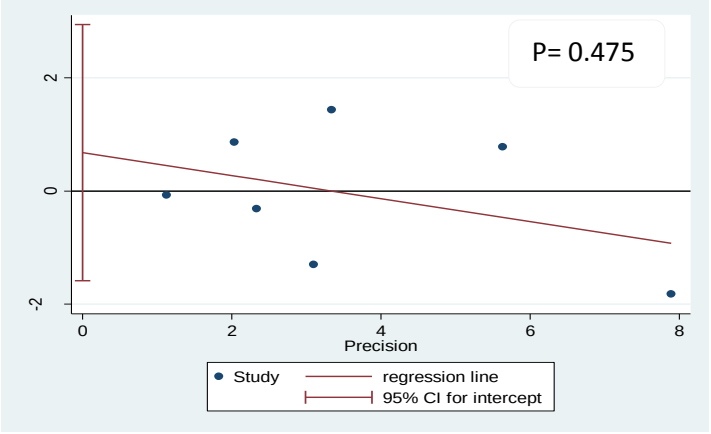


Figure 4: Egger Test Shows That the Possible Publication Bias of the Included Studies

Sensitivity Analysis

The sensitivity analysis reported that no study was overly influential in these findings. In our studies, the effect of micronutrient supplementation on TB treatment outcome, after taking away one study, [32] the result of *RR* was 1.08 (95% *CI*: 0.89–1.37). Although exclusion of study done by Richard.S et al.[32] pooled RR increased from 0.96 to 1.08. This finding still did not have statistical significance difference between two groups. As a result, whether this study included or excluded the result of *P* value, there was no statistical different between two groups. For that reason, the results of the sensitivity analysis demonstrated that our study results were sound as

well as believable. Overall the results indicate that the studies have low risk of bias in general) (Figure 5&6).

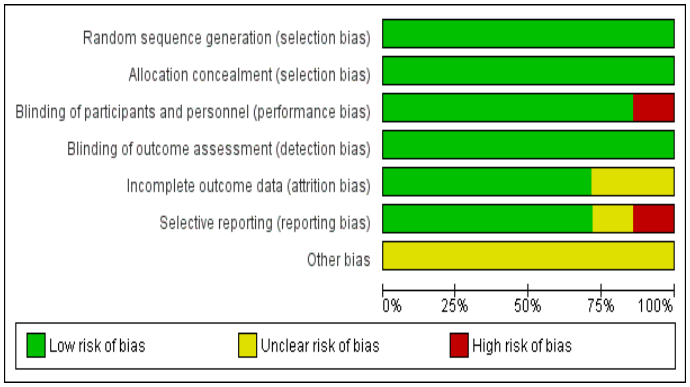


Figure 5: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

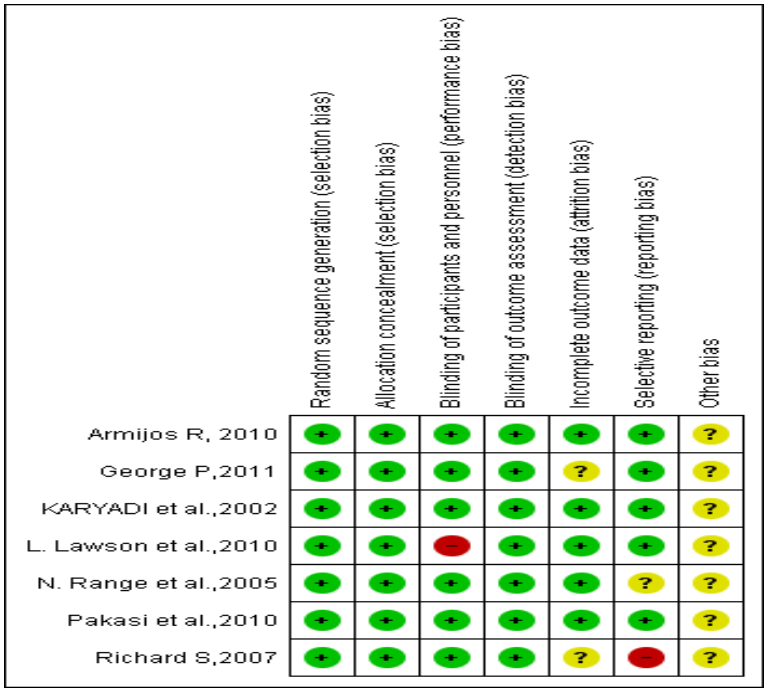


Figure 6: Risk of Bias Summary: Review Authors' Judgments about Each Risk of Bias Item for Each Included Study

Quality of Evidence

The level of quality evidence was evaluated by using GRADE pro criteria's, which gave a moderate level of quality evidence (Table 3).

Table 6: GRADE pro level of quality evidences assessment

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**micronutrient**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
TB treatment outcome											
7	Randomized trials	not serious	not serious	serious	not serious	none	407/1342 (30.3%)	408/1324 (30.8%)	**RR** -- (0.86 to 1.07)	**-- per 1,000** (from 22 more to 43 fewer)	⊕⊕⊕◯ **MODERATE**
								10.0%			
								50.0%		**-- per 1,000** (from 35 more to 70 fewer)	

CI: Confidence Interval; **RR:** Risk Ratio

Discussion

Food supplementation may be provided to people with TB in order to promote treatment adherence, to improve treatment outcome, or to mitigate the financial cost of prolonged disease [33]. In cognizant, the WHO guideline recommends that all individuals with active TB should be evaluated of their nutritional status counseling based on their nutritional status at the beginning of diagnosis and throughout the course of treatment[34]. Micronutrient such as vitamins A,C, D and E have been found to be immune system boosters, and supplemented in different infectious disease conditions including TB[17].

Based on the present evidence, the effect of micronutrient supplementation on TB treatment outcome (failure) among adult TB patients is not statistically significant. That is, there is no evidence for differences between the micronutrient supplement group and placebo group. This finding is in concordance with a meta-analysis that reveals non-significant effect for nutritional supplements for people on treatment for active TB and subsequent TB case mortality after 6–8 months of micronutrient supplementation [35]. Similar the study also reveals that the benefit of micro-nutrient supplementation is not accompanied any significant effect difference on mortality among tuberculosis patients [36]. In addition, the meta-analysis of TB score, hemoglobin, and albumin with micronutrient supplement did not

explain any statistical significance during anti-TB treatment period[37]. Various factors might have accounted for this non-significant finding. Moreover, majority of patients were under-nutrition and being in a catabolic state, especially receiving anti-TB drug treatment, which may be an issue that associated to the enormously high dose requirement in comparison with well-nourished people, especially combined with HIV and diabetes. The concentration of albumin has a pivotal role in diagnosis and prognosis of TB disease though the presence of liver disease and under-nutrition can lead to low concentration of albumin [38].

Some trials on pediatrics tuberculosis also showed that micronutrient supplementation was not significant effect. For instance, study done in Tanzania reported that there is significant effect of multivitamin supplementation on child weight gain after initial phase of tuberculosis treatment[39]. Concordantly, another systematic review and meta-analysis study done by Ramakrishnan et al reveals that the effect of micronutrient supplementation doesn't have statistically significant difference between intervention and placebo groups on child growth and weight gain [40].

However, another review done by ZhuangLi Si et al. indicates that nutritional support has significant speed up positive treatment outcomes as evidenced by negative sputum conversion for continuous nutritional support (e.g., protein, energy and micronutrient intake) as compared to the control group[41]. The possible explanation for this variation might be because of the different types of interventions given to each population. For example, our review focused on only micronutrient supplementation, rather than any nutritional support including protein, fat, energy and so on.

Furthermore, the primary outcomes of the studies may vary. That said, this review largely focused on primary outcomes and didn't consider sputum conversion or weight gain. Similarly, RCT with shorter follow-up were unlikely to demonstrate the effect of micronutrient supplementation on TB treatment outcome.

However, the sensitivity analysis report has different results, implying that the evidence was reliable. This may mean that the quality of evidence was moderate, suggesting the observed effect was close to true effect. Some of important limitations included the inclusion of studies published only in

English might have been done to compromise representativeness (language bias) and our manuscript did not have a pre-published protocol. Although we preferred the end of the follow-up period, it was not applied to some trials which might report only intensive phase. Finally, the doses of micronutrient may not be standardized in different countries.

Conclusion

The effect of micronutrient supplementation on TB treatment outcomes in adult TB patients is not significant. We strongly recommend up to date robust findings are necessary to incorporate whether micronutrient supplementation is needed to improve clinical outcomes of TB treatment in adult patients.

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