

Zinc Deficiency as Severity Predictor in Pediatric Dengue Viral Infection : A Meta-Analysis

FIRYAL NADIAH RAHMAH¹, SALSABILA NABILAH RIFDAH², RICKY INDRA ALFARAY², ANDRY GONIUS¹, SUGENG SOEIJANTO³

¹Faculty of Medicine, Universitas Brawijaya. Veteran Street 5 Malang, Indonesia

²Faculty of Medicine, Airlangga University. Airlangga Street 4 Surabaya, Indonesia.

³Medical Faculty, Airlangga University, Tropic Medicine Department, Surabaya, Indonesia

Correspondence to Firyal Nadiyah Rahmah, Email: firyalnad@gmail.com

ABSTRACT

Background: Endothelial cells in dengue viral infection (DVI) produce Tumor Necrosis Factor (TNF- α) in abundant number from zinc deficient patients rather than non deficient. This finding suggest zinc is protective for maintenance of endothelial cell, thus decrease the severity of dengue viral infection.

Aim: In this meta-analysis, we will compare the zinc serum in deficient and non deficient patients from several studies as predictor in dengue viral infection.

Methods: We included all research articles in pediatric patients diagnosed with Dengue Fever or Dengue Hemorrhagic Fever with information on zinc serum available. Zinc deficiency is reported to be below 9,18 $\mu\text{mol/L}$. The severity is divided into dengue fever against dengue hemorrhagic fever.

Result: There were 217 patients included in this study. The meta-analysis showed that there are significant difference in both results (OR 6.32 [3.50 - 11.40], $p = 0.0003$; $I^2: 84\%$, $p < 0.00001$).

Conclusion: Zinc deficiency in pediatric dengue viral infection can be used for the predictor of severity in dengue viral infection. Zinc supplementation can be mandatory for dengue viral infection treatment

Keywords: Zinc deficiency, Dengue viral infection, dengue fever, dengue hemorrhagic fever

INTRODUCTION

Dengue is still become the most common viral infection related mosquito-borne in developing country such as Indonesia with more than 70% population may be affected¹. In Indonesia. Zinc deficiency is related with dysregulation of immune system and increase the susceptibility of infection. However the zinc deficiency role in dengue infection is not fully understood.² Endothelial cells in dengue viral infection (DVI) produce Tumor Necrosis Factor (TNF- α) in abundant number from zinc deficient patients rather than non deficient. This finding suggest zinc is protective for maintenance of endothelial cell, thus decrease the severity of dengue viral infection.³ In this meta-analysis, we will compare the zinc serum in deficient and non deficient patients from several studies as severity predictor in dengue viral infection.

METHODS

Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) were used to accomplish this meta-analysis.⁴ We systematically searched PubMed, SCOPUS, EuropePMC, ProQuest, and Cochrane Central Databases with the search terms "Dengue Infection" and "Zinc Deficiency" that were published within the year 2000 to 2020. Duplicate results were excluded. The remaining articles were independently screened for relevance by its abstracts with all authors. The full-text of the selected abstract then were thoroughly read, and those that fulfilled our criteria were included in the study. The final inclusion of studies was based on the agreements of all investigators. Any disagreement was resolved by consensus of all authors.

Study Selection: We included cross sectional, cohort prospective, retrospective study, and randomized

controlled trial study. We included all research articles in pediatric patients diagnosed with dengue viral infection with information on zinc serum available. The dengue viral infection is divided into dengue fever and dengue haemorrhagic fever. The outcome is defined in severity dengue infection. Study without zinc serum measurement were excluded from the selection.

Quality Assessment: The quality of the studies was appraised independently by two authors using the Modified Newcastle-Ottawa Scale (NOS). A score of 0–9 was allocated to each study, with studies having a total score of > 7 defined as high quality. Any disagreement in the quality assessment was resolved by discussion with both author.

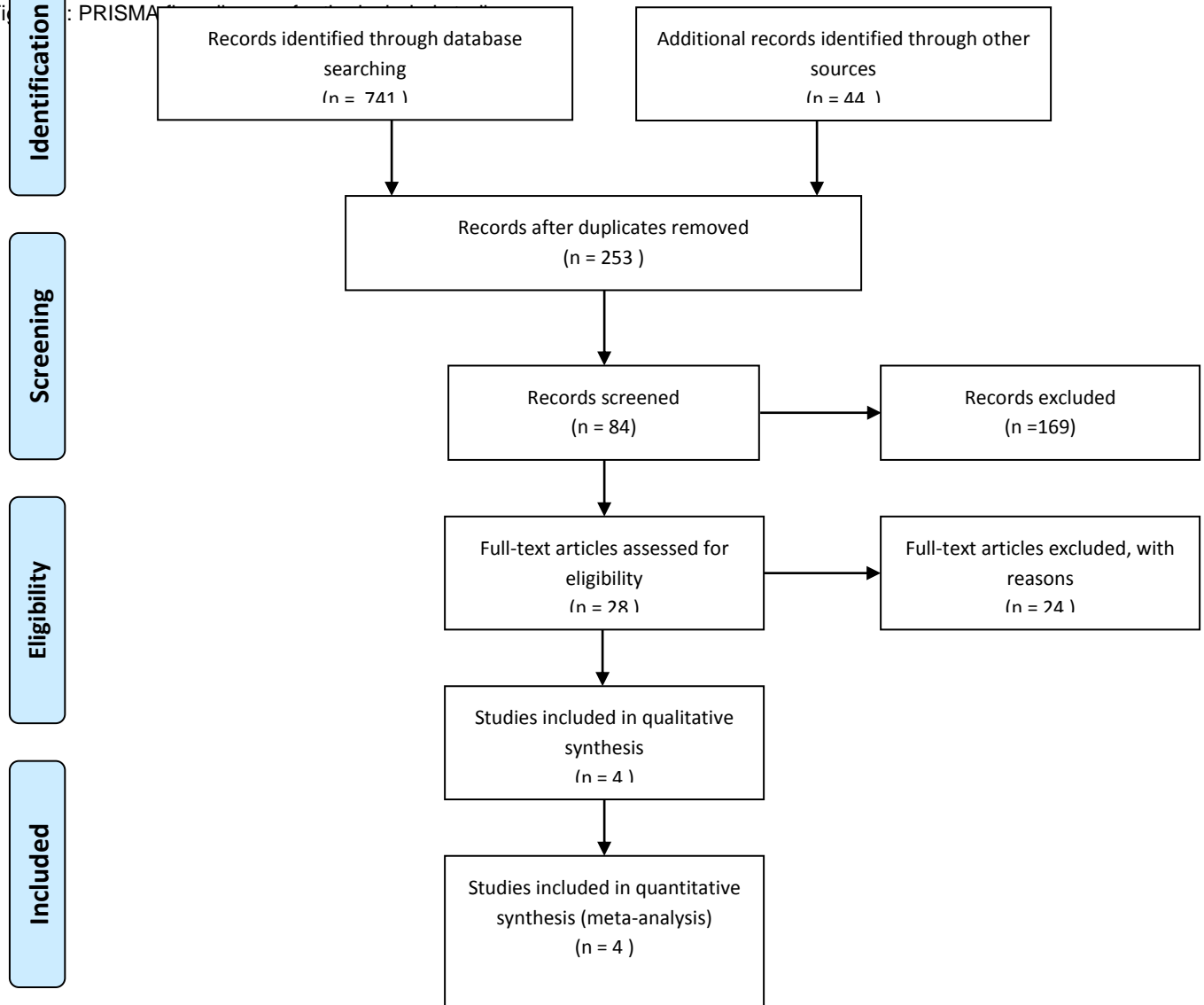
Statistical Analysis: To perform a meta-analysis, Review Manager (RevMan) 5.4 (Computer program, The Cochrane Collaboration, London, UK) and Comprehensive Meta-Analysis (CMA) 3.3 (Computer program, New Jersey, USA) were used to perform all statistical analysis. The heterogeneity was considered significant for a P-value less than 0.05, and its magnitude was substantial when I^2 was greater than 50%. A random-effects model was used to report the results of heterogeneous data, otherwise a fixed-effects model was used. Dichotomous variables were analyzed with the Mantel-Haenszel statistical method using Odds ratio (OR) as the summary statistic and reported with 95% confidence intervals (CI). Funnel Plot were used to screen for publication bias.

RESULTS

Characteristic of study included: The baseline characteristics of the included studies are presented in Table 1. A total of 3 publications were included, all of which are retrospective studies (evidence level II). There is one randomized-controlled trials (RCT) found on our search. There were 217 patients included in this study. The meta-

analysis showed that there are significant difference in both results (OR 6.32 [3.50 - 11.40], p = 0.0003; I²: 84%, p < 0.00001).

Fig 1: PRISMA



Zinc Deficiency related Dengue Viral Infection

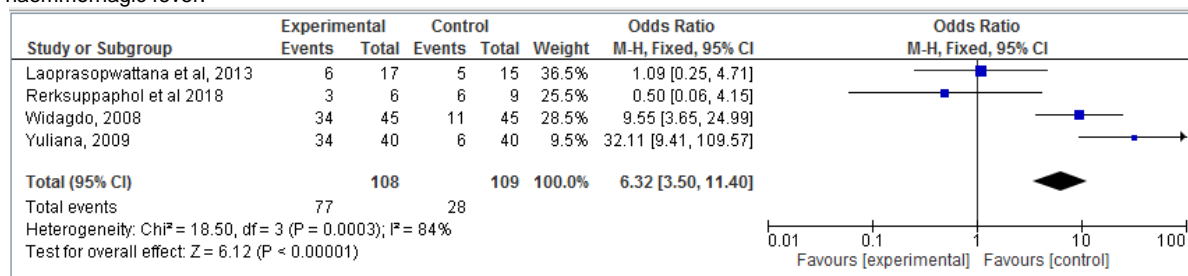
Table 1: Characteristics of the included studies

Author and Year	Study Design	Country	Quality Score	Characteristic of Participant	Zink deficiency	Comment on Outcome
Laoprasopwattana <i>et al</i> , 2013 ⁵	Cohort prospective	Thailand	8	39 patients 15 patients with Dengue Shock Syndrome	6 deficiency in DHF all grades 5 deficiency in DF	Children who had higher dengue severity associated with low zinc serum
Widagdo, 2008 ⁶	Cross Sectional	Indonesia	7	51 patients enrolled	34 deficiency in DHF 11 deficiency in DF	There are no association between zinc level and dengue severity
Yuliana <i>et al</i> , 2009 ⁷	Cross sectional	Indonesia	7	60 patients DF 20 patients DHF 20 patients DSS 20 patients	34 deficiency in DHF 6 deficiency in DF	Low zinc serum was not a risk factor for the development of severe dengue infection in pediatric
Rerksuppaphol <i>et al</i> , 2018 ³	Randomized Controlled Trial	Thailand	9	195 patients with critically ill COVID-19	3 deficiency in DHF 6 deficiency in DF	Zinc supplementation reduce dengue duration and limit hospitalization

Table 2. Newcastle-Ottawa Scale

Study	Selection				Comparability of cases and controls on the basis of the design analysis or	Exposure			Total Stars
	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Laoprasopwattana <i>et al</i> , 2013	1	1	1	1	2	0	1	1	8
Widagdo, 2008	1	1	1	1	1	0	1	1	7
Yuliana <i>et al</i> , 2009	1	1	1	1	1	1	1	0	7
Rerksuppaphol <i>et al</i> , 2018	1	1	1	1	2	1	1	1	9

Figure 2. The metaanalysis of zinc deficiency on the dengue infectionseverity. Comparison severity between dengue fever against dengue haemorrhagic fever.



DISCUSSION

In many reports, zinc deficiency in children shows increase severity from dengue hemorrhagic fever and prolonged duration hospitalization.^{3,4} Zinc is an essential micronutrient for innate and adaptive immunity which affect CD8+ CD73+ in human model experimental.⁸ Study from Yauch *et al* shows CD8+ T cells are important against flavivirus to decrease the viral load from dengue infection.⁹ From meta-analysis, we found significant finding in zinc deficiency as a predictor of severity for dengue viral infection of terms dengue fever against dengue hemorrhagic fever.

Endothelial cells in human with dengue viral infection (DVI) produce Tumor Necrosis Factor (TNF-α) in abundant number from zinc deficient patients rather than non deficient. When zinc supplementation is given, the inflammatory cytokine such as TNF-α is significantly decrease.¹⁰ This may associate with our finding which decrease of severity is where the reduction in severity is proportional to the clinical outcome of the patient through decreased duration of hospital stay and speed of recovery.³

This study has some limitations. There are only few studies related to measure zinc serum before admission. There is only one RCT study included and only 4 studies were analyzed. Further study and strong design are needed to prove this finding.

CONCLUSION

Zinc deficiency in pediatric dengue viral infection can be used for the predictor of severity in dengue viral infection. Zinc supplementation can be mandatory for dengue viral infection treatment

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