Underweight Nutritional Status as a Predictor of Mortality in Alzheimer’s Disease: A Systematic Review and Meta-Analysis of Prospective Cohort Study

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ABSTRACT

Purpose: The research was conducted to determine the risk of mortality in underweight Alzheimer’s patients and consider nutritional maintenance as an important management approach in Alzheimer’s patients. Methods: This review used publications found in Pubmed, Scopus, Cochrane, and ScienceDirect. The keywords were “[(Alzheimer’s Disease) AND (Underweight) AND (Mortality)]”. A meta-analysis review with Revman 5 software calculated the average relative risk from all selected cohort studies. Result: The process identified 230 articles; only three studies with 1423 patients were included. The meta-analysis result showed that underweight patients have a higher risk of mortality than normal weight patients based on their BMI status. (RR: 1.65, 95% CI: 1.32-2.06). Conclusion: Underweight nutritional status in Alzheimer’s patients increases the risk of mortality compared to the individuals with normal nutritional status.

Keywords: Alzheimer’s disease, nutritional, underweight

INTRODUCTION

The United Nations reported 703 million people aged sixty-five years or over in the world in 2019, which is nine percent of the global population. Ageing is a predisposing factor for several diseases such as arthritis, heart disease, and Alzheimer’s. Alzheimer’s disease is the most common type of dementia. WHO data (2017) showed 30-35 million Alzheimer’s cases globally. In Indonesia, current statistics suggest there are 1.2 million cases across the nations, and a projection of a 400% case increase within the next 30 years if no serious prevention measures are taken.

Currently, no proven drugs are available for treating Alzheimer’s disease completely. The general approaches help patients to maintain their physical function and wellbeing. Drugs containing cholinesterase inhibitors, commonly prescribed for mild to moderate cases, act as a temporary reliever in controlling and reducing symptoms. Other activities such as memory training, social and mental stimulation, and physical exercises are suggested to maintain independence and cognitive performance.

Kivimaki, et al. (2018) mentioned an association between dementia, including Alzheimer’s, and BMI. Its incidence is higher among people with high BMI levels, considered overweight and obese. Several publications suggest that underweight condition also contributes to Alzheimer’s progression. This research will analyze the impact of underweight nutritional status on Alzheimer’s mortality.

METHOD

This systematic review and meta-analysis were conducted by searching through online journal databases: PubMed, Scopus, Cochrane, and ScienceDirect with the keywords “[Alzheimer’s Disease) AND (Underweight) AND (Mortality)].” The inclusion criteria consisted of suitability with PICO, type of research (systematic review and meta-analysis, cohort study, and case control study), and research conducted on humans. The exclusion criteria consisted of no available article’s full text, use of languages other than Indonesian or English, and publications over ten years. A duplication check was conducted, followed by selection according to inclusion and
exclusion criteria. From those four databases, 228 articles related to our topic (PubMed (9), Cochrane (1), Scopus (13), ScienceDirect (205)) were found. Title and abstract screening were conducted, resulting in 6 articles in total. A flowchart of the literature search strategy can be seen in Figure 1. A meta-analysis review was done with Revman 5 software to calculate the average relative risk from all selected cohort studies.

RESULT
Based on the criteria, three case-control studies from 4 journal databases (228 subjects) were selected. Two studies showed a significant risk ratio on the increased mortality risk of Alzheimer’s patients with underweight status compared to normal weight. In contrast, one study doesn’t indicate any significant risk ratio. De Sousa, et al, (2020) and Jang, et al, (2015) showed significant results with RR>1 with the precision limit below 1. However, Chen, et al, (2019) show an insignificant result.

All subjects included subjects aged 65 or above. Follow-ups were between 25 months and 60 months. All studies used the same BMI’s underweight cut-off value, which is below 18.5. Specific detail on the selected studies can be seen in Table.

DISCUSSION
Chen, et al, (2019) involved 14 subjects with underweight and 53 subjects with normal weight, of 14 underweight subjects (50%) died, and 22 of 53 normoweight subjects (41.5%) died. The risk ratio is not insignificant with wide precision (RR 1.20, 95% confidence interval 0.65-2.22). de Sousa, et al, (2020) is a novel study with 13 underweight subjects and 35 normal weight subjects. After follow-up, there were 77% deaths in underweight subjects and 22.8% deaths in normal weight subjects. There is a significant risk ratio (RR 3.37, 95% confidence interval 1.71-6.63) with a wide precision range due to relatively few subjects.10

Jang, et al, (2015) study involved more subjects. There are 181 underweight subjects with a 29.2% death rate compared to 1127 normal weight subjects with an 18.4% death rate. The study shows a more significant percentage of underweight death than normal weight (RR 1.65, 95% confidence interval 1.32-2.06) categorized as narrow precision.9

We combined outcomes from three studies based on the total death among underweight and normal weight patients as the output. The calculation and analysis with Revman 5 Software resulted in RR 1.65 with 95% CI 1.32-2.06. The measures mean that patients with underweight nutritional status have a 1.65 x mortality risk; chi2 P value in this study was 0.07, indicating no significant (>0.05) heterogeneity in the studies included in this meta-analysis.

Several scientific reasons may explain the increased mortality risk in underweight Alzheimer’s patients. Patients with lower BMI tend to have small muscle mass, known as sarcopenia. Patients with sarcopenia possess limited training capacity and mobility, which correlates to the total mortality rate increase.12,13 The second reason is that lower BMI is an indirect biomarker for malnutrition.14,15

CONCLUSION
The underweight condition increases mortality risk among Alzheimer’s patients.

| Author and Year | Study Design | Location | Sample Size | Age | Intervention | Duration of Follow Up | Risk Ratio |
|-----------------|--------------|----------|-------------|-----|-------------|----------------------|------------|
| Chen, et al, 2019 | Prospective cohort | Taiwan | 84 | 86.6 | Underweight BMI ≤18.5 | 2.1 years | 1.20 [0.65, 2.22] |
| de Sousa, et al, 2020 | Prospective cohort | Portugal | 79 | 65-93 | Underweight BMI ≤18.5 | 60 months | 3.37 [1.31, 6.63] |
| Jang, et al, 2015 | Prospective cohort | South Korea | 2,490 | 73.4 | Underweight BMI ≤18.5 | 43.7 months | 1.59 [1.23, 2.05] |

Table. Details of the selected studies

Figure 1. Search strategy flowchart

Figure 2. Forest plot of three studies
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