Association of Metabolic Syndrome with Cardiovascular Mortality in The Elderly: A Meta-Analysis

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ABSTRACT
Metabolic syndrome should be considered an important issue in elderly individuals, as aging is a major contributor to the prevalence of the constellation of cardiovascular and metabolic risk factors that constitute the syndrome. However, recent studies that have investigated metabolic syndrome as a predictor of mortality in elderly shown conflicting results. The search was conducted using the PubMed, Cochrane library published in the last 20 years (January 2001 to January 2021). The search keywords were "Metabolic syndrome", "cardiovascular disease", "Mortality" and "Elderly". Data statistical analysis using *Review Manager* 5.3 (*RevMan Cochrane, London, UK*). Based on 6 prospective cohort studies, metabolic syndrome was associated with a higher risk of cardiovascular mortality when compared to non-cardiovascular mortality in the elderly (RR = 0,68; 95% CI=0,64-0,72; P=<0,00001), there was considerable heterogeneity in all studies used (I^2=98%; P=0,00001). Factor explaining heterogeneity between studies included sex, age, sample size, prevalence of metabolic syndrome, follow-up duration, and definition of syndrome metabolic. Cardiovascular mortality compared to those non-cardiovascular mortality, had a higher in elderly with metabolic syndrome. High blood glucose and hypertension were the main components of the cause of death from cardiovascular disease in the elderly. In addition, the combination of several symptoms of metabolic syndrome has a different risk of death and requires further research in the future.

Keywords: Metabolic syndrome, Cardiovascular disease, Mortality, Elderly.

1. INTRODUCTION

Metabolic syndrome (MetS) is a group of symptoms of impaired glucose metabolism, dyslipidemia, central obesity, and hypertension. The association of an increased risk of cardiovascular disease and mortality in patients with the metabolic syndrome is generally well known [1]. However, the association between an increased risk of cardiovascular disease and an increased risk of mortality in patients with the metabolic syndrome varies widely among populations based on race, sex, and age. Based on previous retrospective cohort studies showed that elderly individuals with metabolic syndrome are one of the risk factors for death from cardiovascular disease [2]. After the occurrence of insulin resistance syndrome, several organizations have developed criteria for the metabolic syndrome so that they can be applied in clinical practice. Based on epidemiological studies that compared several definitions used to diagnose the metabolic syndrome, the results showed different mortality rates. The criteria for diagnosis by the Joint Interim Statement (JIS) and the International Diabetes Federation (IDF) show an increase in mortality due to cardiovascular disease [3].

The increasing prevalence of the current metabolic syndrome is associated with environmental, genetic, and lifestyle changes. The increased incidence of the metabolic syndrome is associated with increased mortality from cardiovascular disease. In several studies, the high prevalence of the metabolic syndrome has a significant correlation with an increased incidence of coronary heart disease, myocardial infarction, and the development of heart failure in adults without a previous history of cardiovascular disease [4]. Components of the metabolic syndrome such as diabetes, obesity, hyperlipidemia, and hypertension are known to be cardiovascular factors that can increase the risk of heart failure. In patients with heart failure, diabetes is associated with an increased risk of mortality, whereas obesity, hyperlipidemia, and hypertension are relative risks associated with cardiovascular disease. These factors do not occur separately but tend to occur together in the same person, so the metabolic syndrome is associated with increased mortality from cardiovascular disease [5]. Therefore, the authors would like to discuss further about the impact of the metabolic syndrome on cardiovascular disease and the mortality rate due to cardiovascular disease caused by the metabolic syndrome. The author hopes that this research can help in the management of metabolic syndrome to prevent cardiovascular disease.

2. METHOD

2.1. Inclusion Criteria, Data Sources, and Study Search Protocol

The method in compiling this systematic review and meta-analysis uses the PRISMA (Preferred Reporting, Items for Systematic Reviews and Meta-Analysis) method. The search was conducted using the PubMed and Medline databases published from January 2001 to December 2020. The search strategies were "metabolic syndrome" and "cardiovascular disease" and "mortality" and "elderly". The articles obtained were 77 articles and then an assessment was carried out referring to the inclusion and exclusion criteria. We included RCTs that met the following inclusion criteria: elderly participants (≥65 years), using a prospective cohort study design, death from cardiovascular disease as a result, published in English, and available in full text. Based on these inclusion criteria, there were 6 main articles used in the review shown in Figure 1.
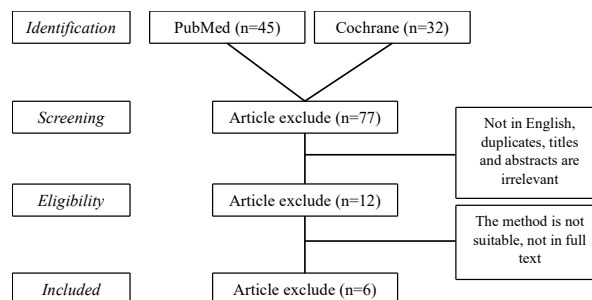

Figure 1. PRISMA Method in Article Selection

2.2. Exclusion criteria, extraction, and quality assessment

The exclusion criteria we used in this meta-analysis were a specific condition or risk factor for metabolic disease and non-elderly (<60 years) participants. Article reviews, meta-analyses, and abstracts were also included in the exclusion criteria. The authors of this study independently screened articles based on titles and abstracts and then reviewed the methods and results of full-text research articles. The information reviewed in the article is first author, year of publication, age, gender, sample size, definition of metabolic syndrome used, mortality rate, death from cardiovascular disease caused by the metabolic syndrome, and other risk factors that influence mortality. Articles that met the inclusion and exclusion criteria were included in this meta-analysis.

2.3. Data synthesis and analysis

The synthesized results are presented as RRs with 95% confidence intervals (95% CI). We used Q and I^2 statistics to analyze heterogeneity among the included trials. The Q statistic shows heterogeneity when the P value < 0.10, while I^2 < 50% indicates that the heterogeneity is moderate. If the value of I^2>50% or P<0.10, the random effects model was adopted. We also performed a sensitivity analysis by excluding each study sequentially if the I^2 value was >50% or P<0.10 and calculated the meta-analysis. Results were considered statistically significant at P < 0.05. Funnel plots were examined visually, Egger's test was used to test for publication bias, and P < 0.05 was considered significant for publication bias. All analyzes in our study were performed using Review Manager version 5.3 (RevMan Cochrane, London, UK).

3. RESULT

3.1. Study Selection and Characteristics of the Trials Included

We identified 77 studies using keywords and obtained 12 potentially relevant studies. We found 6 RCTs with a total of 1,145 elderly patients with the metabolic syndrome who died from cardiovascular disease with a duration of follow-up varying from 4 to 9 years. The characteristics used in each study are summarized in table 1.

Table 1. Demographic characteristics of eligible studies

	Number of patients	Age (years old)	Average age (years old)	Follow-up (years)	Sex	Metabolic syndrome definition	Metabolic syndrome prevalence (%)	Number of CVD mortality	Number of Non-CVD mortality
Mozaffary et al. (2014) [8]	922	≥ 65	73	9.9	M and F	WHO	40.6	82	111
Akbaraly et al. (2010) [10]	7.118	≥ 65	73	7	M and F	NCEP	21.2	133	442
Salminen et al. (2010) [9]	1260	≥ 65	73.5	9	M and F	IDF Modification	19	181	241
Hildrum et al. (2009) [7]	1973	60-74	77	7.9	M and F	IDF	47	219	364
Zambon et al. (2008) [4]	2910	≥ 65	74	4.4	M and F	NCEP	39	96	134
Wen et al. (2008) [6]	10547	≥ 65	70	8	M and F	AHA/ NHLBI	50.1	300	182

3.2. Correlation of metabolic syndrome with cardiovascular death in the elderly

The forest plot provided in Figure 2 shows a statistically significant finding for cardiovascular mortality in adults over 60 years of age who have the metabolic syndrome (RR = 0.68; 95% CI = 0.64-0.72; P = < 0.00001). Based on the statistical results, it was found that there was considerable heterogeneity in all studies used (I2=98%; P=0.00001). The forest plot of the statistical calculation results is shown in Figure 2 below
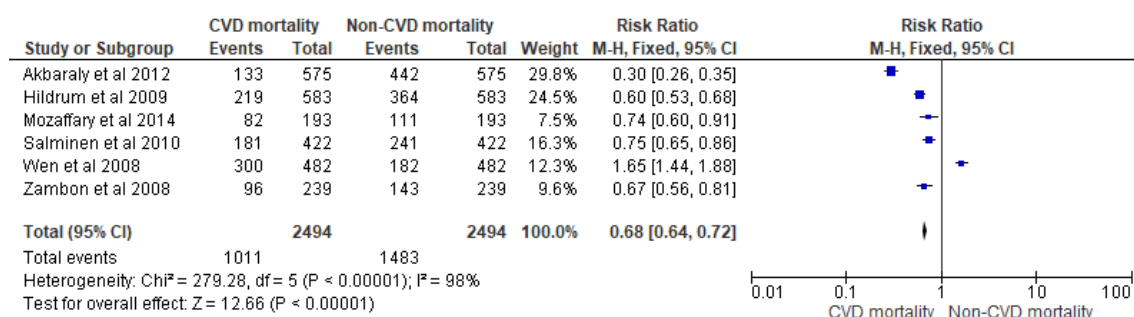

Figure 2. Forest plot of the number of deaths from cardiovascular and non-cardiovascular diseases in the elderly with metabolic syndrome

In this study, funnel plots were assessed to exclude the risk of publication bias. Based on the results of the funnel plot, symmetrical results were obtained based on the 6 different studies included in this study, this shows that the results of the study have a low publication bias. The funnel plot of statistical calculation results is shown in Figure 3 below.
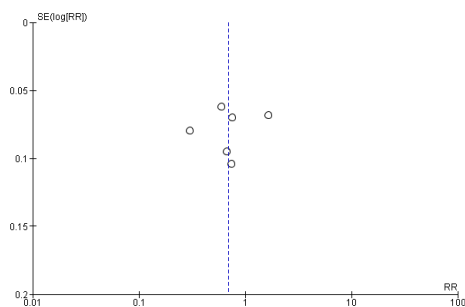
Figure 3. Funnel plot of the number of deaths from cardiovascular and non-cardiovascular diseases in the elderly with metabolic syndrome.

4. DISCUSSION

In this meta-analysis, there were 6 RCT studies published in 2001-2021 on mortality from cardiovascular disease in the elderly with metabolic syndrome. Based on the results of this meta-analysis showed an increased risk of death from cardiovascular disease in the elderly population with metabolic syndrome. The estimated risk of death from cardiovascular disease in the elderly with metabolic syndrome was 0.68 (0.64-0.72). Correlation of metabolic syndrome with cardiovascular causes of death in the elderly can be influenced by geographic location, sample size, and the definition of metabolic syndrome used in the study which is a weakness in the meta-analysis adjustment.

A study by Hildrum et al. examined the risk of death from cardiovascular disease in adults and the elderly with metabolic syndrome, which found an increased risk of death from cardiovascular disease in the elderly with metabolic syndrome with the general adult population (14.2% and 20.7%, respectively) [8]. This difference may occur due to factors related to the aging process such as weakness, malnutrition, and an immunocompromised state where in this situation the elderly has a greater risk of contracting infectious diseases so that they can increase the risk of death due to a decrease in physiological functions needed by the body in overcoming the metabolic syndrome experienced.[6]

In the study of Mozaffary et al., there was an increased risk of death from cardiovascular disease in the elderly with metabolic syndrome by 60% who were diagnosed using the JIS and WHO definitions [8]. Based on the definition of metabolic syndrome by the IDF, central obesity is a core component of the metabolic syndrome, but this component does not show a significant relationship with mortality from cardiovascular disease. This is different from the definition of metabolic syndrome by WHO and JIS which uses body mass index (BMI) or waist circumference (WC), where this value shows a 10 times greater risk increase when accompanied by impaired glucose metabolism and hypertension which is associated with death from cardiovascular disease [8]. The results of this study have different results from those of Salminen et al., where the IDF's definition of metabolic syndrome can predict higher mortality from cardiovascular disease when accompanied by impaired glucose metabolism and hypertension [9]. This is because the obesity component of the metabolic syndrome as measured by BMI can reduce the prevalence of metabolic syndrome in this study when compared to WC measurements (WC > 94 cm in men and WC > 80 cm in women. BMI is associated with fat mass, in the elderly body fat mass is replaced by fat due to aging which is clearly visible in women. In both studies, the components of blood glucose and hypertension were the main components of the cause of death from cardiovascular disease in the elderly with hypertension regardless of the definition used in the diagnosis of the metabolic syndrome [9].

The results of a study conducted by Zambon et al. showed that 41% of deaths due to cardiovascular disease in the elderly with metabolic syndrome, where in this study components of the metabolic syndrome in the form of high blood glucose, hypertension and low HDL were significantly associated with death from cardiovascular disease. Research conducted by Akbaraly et al. showed an increased risk of death from cardiovascular disease in the elderly with metabolic syndrome with an RR of 2.21 (95% CI 1.07-4.55) where this increased risk of death was associated with a component of the metabolic syndrome in the form of glucose levels [10]. Blood pressure, HDL cholesterol and hypertension are the main contributors to death in the elderly with metabolic syndrome [4].

This meta-analysis study has limitations as in some RCTs it has different variations regarding the definition in diagnosing the metabolic syndrome used. The population included in the RCT case study is still in a relatively small area. However, based on the funnel plot, there is no significant bias between each study. Several studies in this meta-analysis showed that the hypertension component was an independent risk factor for death from cardiovascular disease in the elderly with metabolic syndrome. Of each component of the metabolic syndrome, elevated blood glucose and low HDL cholesterol were significantly associated with increased mortality in the elderly. Thus, the findings of this meta-analysis raise questions about the definition of the metabolic syndrome that can be used to predict the cause of death from cardiovascular disease in the elderly.

5. CONCLUSION

Metabolic syndrome is a group of symptoms of impaired glucose metabolism, dyslipidemia, central obesity, and hypertension. Cardiovascular mortality

compared to those non-cardiovascular mortality, had a higher in elderly with metabolic syndrome. High blood glucose and hypertension were the main components of the cause of death from cardiovascular disease in the elderly. In addition, the combination of several symptoms of metabolic syndrome has a different risk of death and requires further research in the future.

REFERENCES

[1]   Wu SH, Liu Z, Ho SC. Metabolic syndrome and all-cause mortality: a meta-analysis of prospective cohort studies. Eur J Epidemiol 2010; 25:375–84.

[2]   Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007; 49: 403–414.

[3]   Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120: 1640–1645

[4]   Zambon, Sabina, et al. Metabolic syndrome and all-cause and cardiovascular mortality in an Italian elderly population: the Progetto Veneto Anziani (Pro. VA) Study. *Diabetes care*, 2009, 32.1: 153-159.

[5]   Ju, Sang-Yhun; LEE, June-Young; KIM, Do-Hoon. Association of metabolic syndrome and its components with all-cause and cardiovascular mortality in the elderly: a meta-analysis of prospective cohort studies. *Medicine*, 2017, 96.45.

[6]   Wen, C. J., et al. The metabolic syndrome increases cardiovascular mortality in Taiwanese elderly. *European journal of clinical investigation*, 2008, 38.7: 469-475

[7]   Hildrum, B., et al. Metabolic syndrome and risk of mortality in middle-aged versus elderly individuals: the Nord-Trøndelag Health Study (HUNT). *Diabetologia*, 2009, 52.4: 583-590.

[8]   Mozaffary, A., et al. Added value of different metabolic syndrome definitions for predicting cardiovascular disease and mortality events among elderly population: Tehran Lipid and Glucose Study. *European journal of clinical nutrition*, 2014, 68.7: 853-858.

[9]   Salminen, M., et al. The metabolic syndrome defined by modified International Diabetes Federation criteria and mortality: a 9-year follow-up of the aged in Finland. *Diabetes & metabolism*, 2010, 36.6: 437-442.

[10]   Akbaraly, Tasnime N., Mika Kivimaki, Marie-Laure Ancelin, Pascale Barberger-Gateau, Thibault Mura, Christophe Tzourio, Jacques Touchon, Karen Ritchie, and Claudine Berr. "Metabolic syndrome, its components, and mortality in the elderly." *The Journal of Clinical Endocrinology & Metabolism* 95, no. 11 (2010): E327-E332.