Obesity and Diabetes Mellitus as Predictors of Mortality in Patients with Stroke: A Meta Analysis

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ABSTRACT

Background: Stroke is the leading cause of death and disability throughout the world. Based on studies in the United States (US), a person experiences a stroke every 40 seconds and every 4 minutes someone dies. The problem of comorbidity or the presence of more than one disease is the risk of stroke. This causes a person with comorbidities to have a higher risk of mortality than stroke patients without comorbidities. This study aims to examine the effect of obesity and diabetes mellitus as predictors of mortality in stroke patients.
Subjects and Method: This was a meta-analysis and systematic review. The articles were obtained from Google Scholar, PubMed, Springer Link, Clinical key, and ProQuest databases. The articles have been published from 2010-2019. Keywords to search for articles are as follows: "comorbidity and stroke", "comorbidity and mortality and stroke and cross sectional study", "comorbidity and mortality and stroke and adjusted odd ratio", "comorbidity or stroke", "comorbidity or mortality or stroke or cross sectional study ", "comorbidity or mortality or stroke or adjusted odd ratio". The articles studied are full text articles with observational study design. Articles are collected using PRISMA diagram, and analyzed using the Review Manager application 5.3.
Results: Obesity (aOR = 1.51; 95% CI = 1.03 to 2.21; p = 0.030) and diabetes mellitus (aOR = 1.75; 95% CI = 1.33 to 2.29; p <0.001) are predictors of mortality in stroke patients.
Conclusion: Obesity and diabetes mellitus are predictors of mortality in stroke patients.

Keywords: obesity, diabetes mellitus, *stroke*

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BACKGROUND

WHO data (2016) reports that one of the non-communicable diseases which causes the highest mortality is stroke. Stroke is the leading cause of death and disability throughout the world (GBD DALYS and Hale Collaborators, 2015). Stroke is responsible for every 20 deaths, totaling ≥ 130,000 cases annually in the United States and incurs direct and indirect costs of $ 33-$ 34 billion annually (CDC, 2017; Mozaffarian et al., 2016).

Strokes kill about 140,000 people in America every year. Someone in the United States has a stroke every 40 seconds and every 4 minutes someone dies of a stroke (CDC, 2017).

The problem of comorbidity, or the presence of more than one disease, is the risk associated with non-communicable diseases including stroke. In general, people with stroke have one or more chronic comorbid conditions (NCDA, 2019; WSO, 2019). Less than 6% do not have a predictor of stroke (Nelson et al., 2017). In an adult population of around 10,000 people, there may be 500 to 2,000 people with diabetes, 3 to 8 people have an acute heart attack, and 4 to 16 have an acute stroke (WHO, 2014; Feigin et al., 2014; GBD Mortality, 2014; WHO , 2016).

Previous researchers have projected an increase in the prevalence of stroke by 22 per 100,000 population in 2020 to 27 per 100,000 population in 2025 due to obesity (Keaver et al., 2013).

A study by Zhao et al. (2014) stated that stroke patients who are obese have a 2.01 times greater risk of dying compared to stroke patients without comorbid obesity. However, other studies have shown that obesity is a protective factor (OR= 0.56 to 0.84) to the incidence of stroke mortality (Doehner et al., 2013; Hernandez et al., 2013).

Stroke patients with diabetes mellitus have a risk of 1.31 to 3.19 times more death than without predictors of diabetes mellitus (Fischer et al., 2006; Donnell et al., 2010; Price et al., 2018). However, other studies have shown that predictors of diabetes mellitus have no relationship with mortality in stroke patients and are only a protective factor (Barba et al., 2015).

Various studies have been conducted to see the effect of obesity and diabetes mellitus as a predictor of mortality in stroke patients but the results of the study still have not shown consistent results. Further analysis is needed to get conclusive conclusions about the effect of obesity and diabetes mellitus as predictors of mortality in stroke patients.

SUBJECTS AND METHOD

1. Study Design

This study is a systematic study and meta-analysis. The articles used in this study are articles that have been published from 2010-2019 and were obtained from Google Scholar, PubMed, Springer Link, Clinical key, and ProQuest databases.

Keywords used in finding articles are "comorbidity and stroke", "comorbidity and mortality and stroke and cross sectional study", "comorbidity and mortality and stroke and adjusted odd ratio", "comorbidity or stroke", "comorbidity or mortality or stroke or cross sectional study", "comorbidity or mortality or stroke or adjusted odd ratio".

2. Population and Sample

The articles included in this study are article texts with observational studies that have been published from 2010-2019. The article chosen discusses the influence of obesity and diabetes mellitus as predictors of mortality in stroke patients. The article used is an article published in English. The study sample was hospital patients. Study data are multivariate. The final results of the study were reported using the adjusted odds ratio (aOR).

3. Inclusion and Exclusion Criteria

The exclusion criteria in this study were articles with RCT, case control, quasi-experiments, and protocol studies. Article not published in English. The statistical results reported are not AOR.

4. Operational Definition of Variables

Obesity was excessive fat accumulation due to imbalance of energy intake (energy intake) with the energy used (energy expenditure) for a long time.

Diabetes mellitus was a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces.

Mortality was the permanent loss of all signs of life at any time after live birth, namely the disappearance of the functions of life after birth, without the possibility of resuscitation.

5. Data Analysis

Data processing is performed using Review Manager (RevMan 5.3) by calculating the value of effect sizes and heterogeneity to determine the combined study model and form the final result of a forest plot meta-analysis (Wijiwinarsih et al., 2019).

RESULTS

The process of finding articles using a journal database is shown in Figure 1. Figure 2 shows the area where the article was published according to inclusion criteria. The articles in this study came from 5 continents, namely Asia, Africa, Europe, North America and South America.

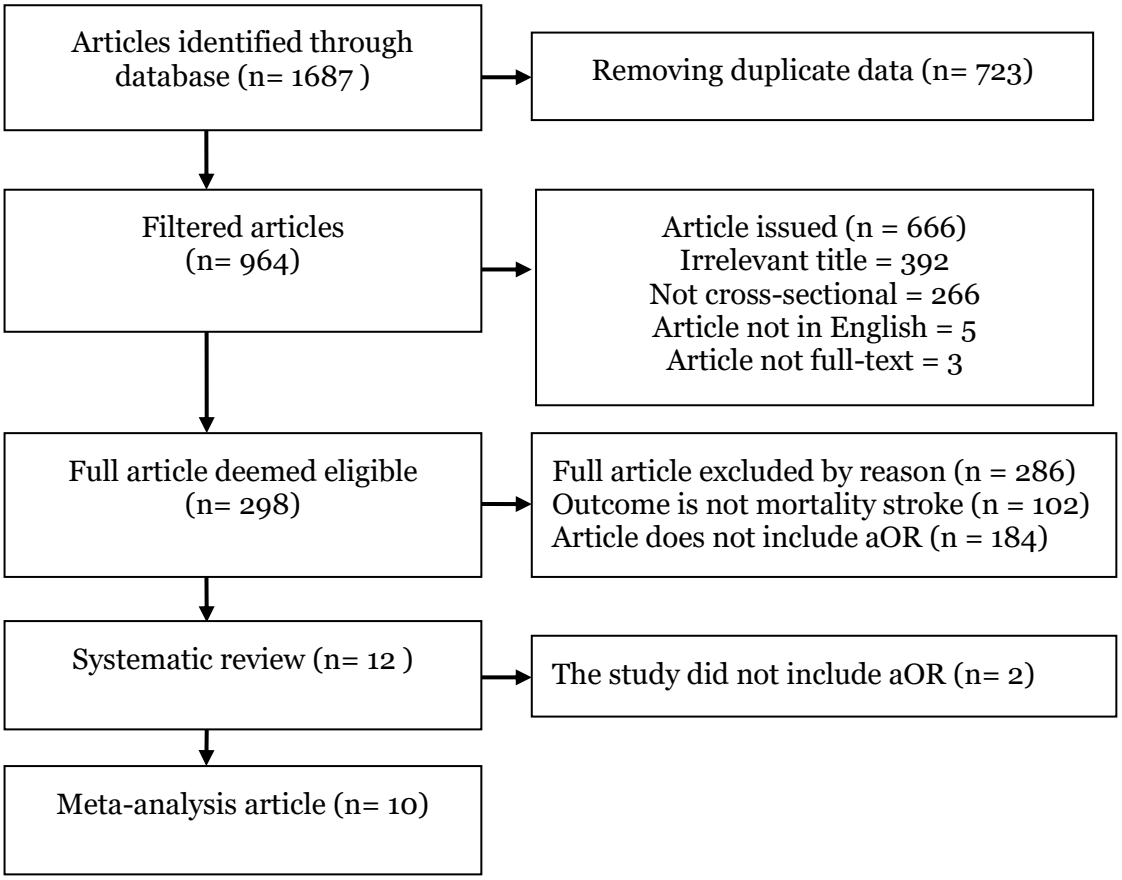

Figure 1. Flowchart of the review process

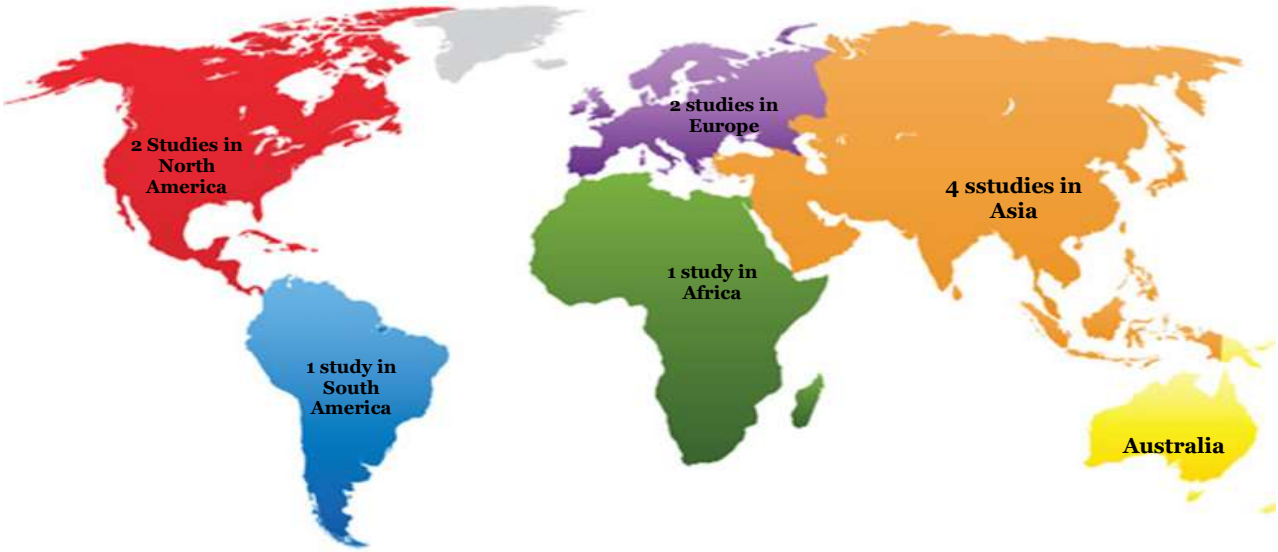

Figure 2. Map of the study area

1. Obesity

Table 1 shows that there were 5 obese observational study articles which reported the predictors of mortality in stroke patients.

Table 1. Effects of obesity predictors on mortality in stroke patients

Author (year)	Country	aOR	95% CI	p
Reklaitine et al. (2012)	Italy	1.65	0.81-3.40	0.167
Zhao et al. (2014)	China	1.06	0.81-1.38	0.664
Kongbunkiat (2014)	Thailand	0.72	0.26-2.02	< 0.001
Sun et al. (2017)	China	1.11	0.83-1.47	< 0.001
Ideta et al. (2018)	Hawaii	2.02	1.81-2.26	<0.001

b. Forest plot

Figure 1 shows the results of the forest plot on the effect of obesity as a predictor of mortality in stroke patients. Forest plot results show that stroke patients with obesity can increase stroke mortality by 1.51 times compared to stroke patients who do not have obesity. The result is statistically significant (p= 0.001). Heterogeneity (I^2)= 78% indicates heterogeneous data distribution (random effect model).

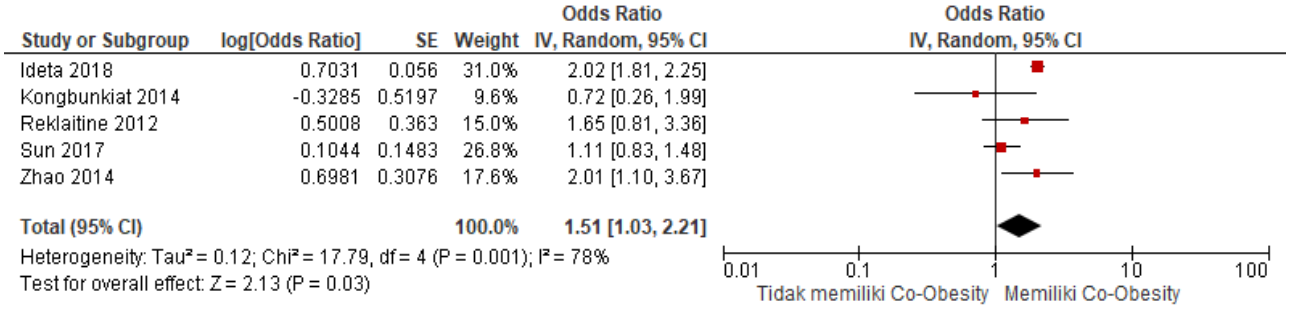

Figure 1. Forest plot of the effect of obesity as a predictor of mortality in stroke patients

c. Funnel plot

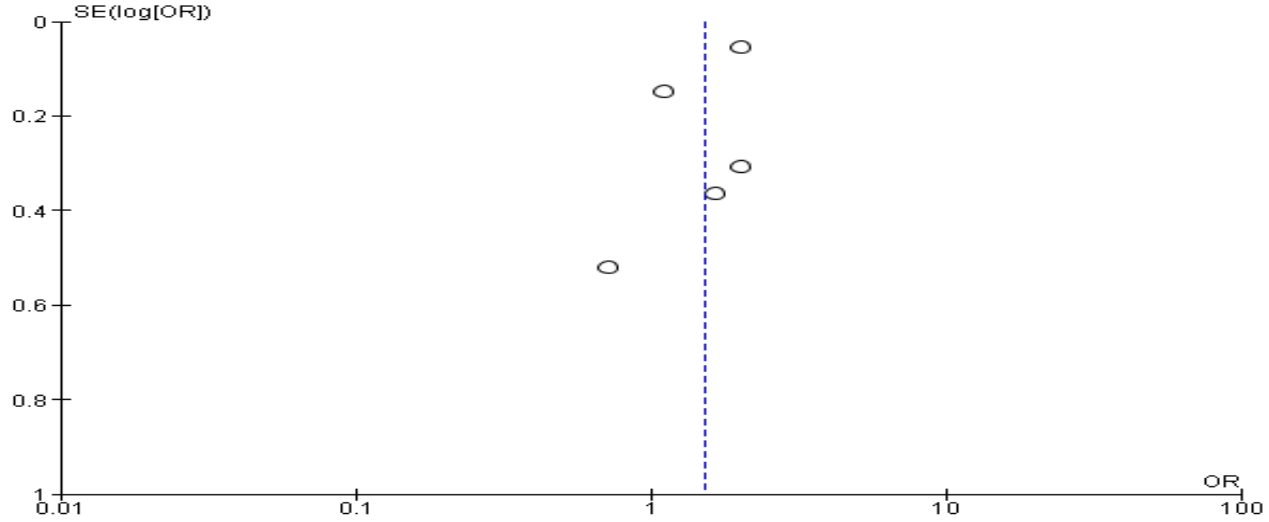

Figure 2. Funnel plots the effect of obesity as predictor of mortality in stroke patients

Figure 2 shows that there is a publication bias marked with asymmetric form on the graph, there are 3 plots on the right and 2 plots on the left. The left plot has a standard error of 0.4 to 0 while the plot on the right has a standard error between 0.6 and 0.2. Bias also occurs from unbalanced distances between studies in both the right plot and the left plot where the study on the left has more distance than the study in comparing the right plot.

2. Diabetes Melitus

Table 2 shows that there were 8 observational studies of diabetes mellitus which were predictors of mortality in stroke patients.

Table 2. Effect of diabetes mellitus as a predictor of mortality in stroke patients

Author (year)	Country	aOR	CI 95%	p
Andrade et al. (2012)	Brazil	7.34	3.73-14.46	<0.001
Rikleitine et al. (2012)	Italy	2.23	0.80-6.24	0.125
Doehner et al. (2013)	Germany	1.72	1.27-2.31	0.010
Kongbunkiat et al. (2014)	Thailand	1.28	1.15-1.42	<0.001
Zhao et al. (2014)	China	1.10	0.91-1.33	0.339
Akpalu et al. (2018)	Ghana	2.03	1.05-3.92	0.030
Bravata et al. (2019)	US	1.44	0.64-3.23	0.070
Yeo et al. (2019)	Singapore	1.81	1.38-2.36	<0.001

b. Forest plot

Figure 3 is a forest plot of the effect of diabetes mellitus as a predictor of mortality in stroke patients. Forest plot results show that stroke patients who have DM can increase stroke death by 1.75 times compared to stroke patients who do not have DM. Results were statistically significant (p<0.001). Heterogeneity of I^2= 82% indicates heterogeneous data distribution.

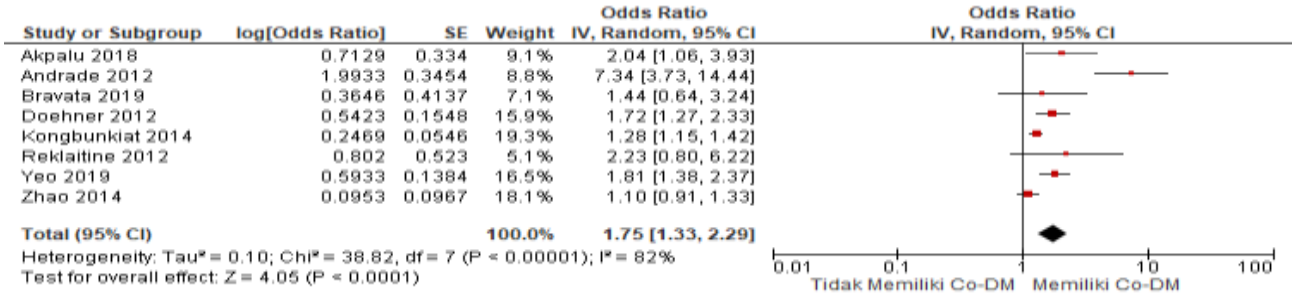

Figure 3. Forest plot of diabetes mellitus as predictor of mortality in stroke patients

c. Funnel plot

Figure 4 shows that there is no publication bias which is indicated by the symmetry axis which shows the balance of the right and left plots where there are 3 right plots and 3 plots on the left and 2 plots right on the line. The left plot has a standard error of 0.4 to 0 while the plot on the right has a standard error between 0.6 and 0.2.

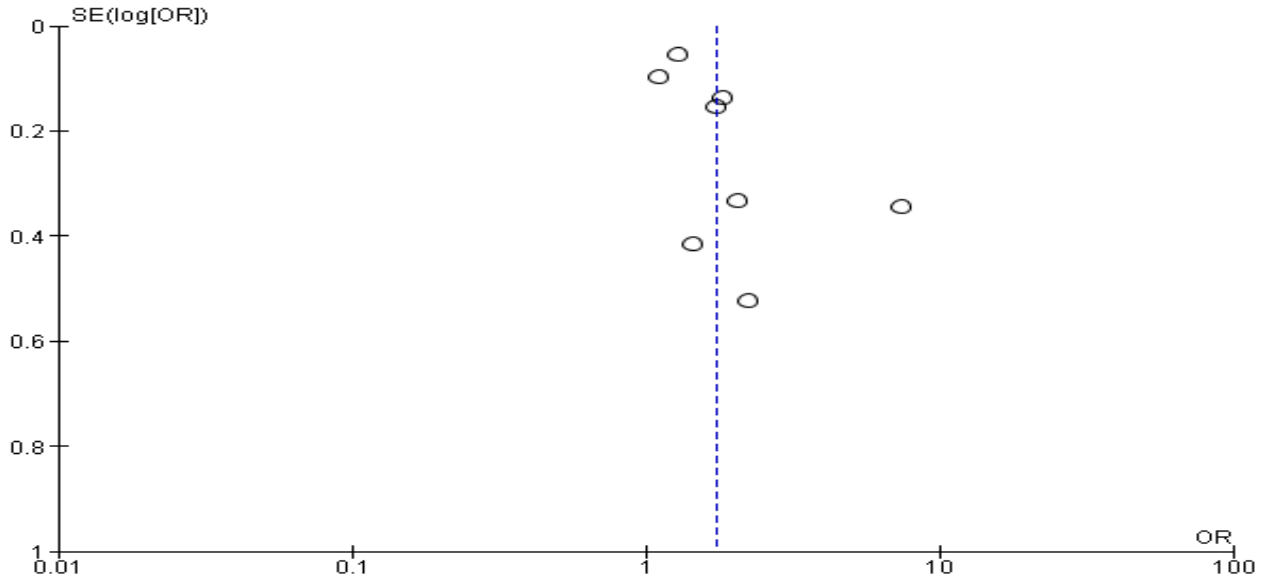

Figure 4. Funnel plot of the effect of diabetes mellitus as predictor of mortality in stroke patients

DISCUSSION

This systematic review and meta-analysis research theme of the influence of obesity and diabetes mellitus comorbidity on stroke mortality. The independent variables analyzed were obesity comorbidity and diabetes mellitus comorbidity. Study that discusses data on stroke mortality is considered important because of its rarity. The number of relevant studies published and accessible is still small and also has a problem of data excess (data duplication) (Murti, 2018). Most of the statistical results reported are in percent or crude odd ratio (cOR), where the study did not control for confounding factors.

Confounding factors affect the relationship or effect of exposure to the occurrence of the disease estimated (estimated) by the study is not the same as the relationship or effect that actually occurs in the target population, aka the results of studies that are not valid (incorrect) (Murti, 2018). This systematic review and meta-analysis study uses studies that controls confounding factors which can be seen from the terms of study inclusion that is using multivariate analysis and the statistical results reported are adjusted odds ratio (aOR).

The combined estimates of the effect of comorbid obesity and diabetes mellitus on stroke mortality were processed using RevMan 5.3 application with generic inverse-variance methods (Widayati et al., 2016; Anulus et al., 2019). This method is used to analyze data in the form of rate, time-to-event, hazard ratio, ordinal scale, adjusted estimate, difference in average (difference of mean) or average ratio (ratio of mean).

The results of the systematic study and meta-analysis are presented in the form of forest plots and funnel plots. Forest plot shows visually the magnitude of variation (heterogeneity) (Akobeng, 2005 in Murti, 2018). Funnel plots show the relationship between the effect size of the study and the sample size of the various studies studied, which can be measured in a variety of different ways (Murti, 2018).

Funnel plots can be assessed from the asymmetry of the study by looking at the number of points on the right and left

compared to the standard error and the balance of the number of studies on the right and left (D'Osouza et al., 2002).

1. Obesity

Patients with severe obesity have more other predictors and complications leading to a poor prognosis. Obese patients have a higher risk of death (Ryu et al., 2011). Stroke mortality was higher in the extreme BMI group in overweight patients (7.1%) and patients with severe obesity (11.5%) (Zhao et al., 2014).

Obesity (BMI >35kg/m^2) is associated with higher mortality and overweight/ obesity is not a protective factor for survival in stroke patients (Zhao et al., 2014). Stroke can cause systemic catabolic imbalances and cause impaired metabolic efficiency and degradation of body tissues (Scherbakov et al., 2011; Zhao et al., 2014).

2. Diabetes Melitus

Non-communicable diseases including stroke and diabetes are increasingly becoming a major burden on public health in the country of Ghana (Bosu, 2012). Individuals with diabetes mellitus have a high sensitivity to the incidence of atherosclerosis (AHA, 2006 in Wayunah and Saefulloh, 2017).

Many pathophysiologists have proven that DM directly affects the central nervous system and limits brain capacity so that it can interfere with the success of stroke recovery (Biessels et al., 1999; Sweetnam et al., 2012).

Study by Akpalu et al. (2018) showed that the tendency for stroke patients with diabetes had poor results and had less survival compared to stroke patients without diabetes.

The condition of diabetes mellitus will cause damage to the arterial wall so that it forms a blood clot called a thrombus. In this process there will be a further decrease in blood flow. In some cases the thrombus will enlarge and close the arterial lumen, or the thrombus can be separated and form an embolism that will follow the blood flow and clog arteries in other areas.

The tissue that receives vascularization from the arteries that are blocked by the emboli will die due to the rapid loss of oxygen supply, which if it occurs in the heart will cause damage to the heart so that it becomes a heart disease, one of which is a stroke (Gofir, 2009 in Ramadany et al., 2013).

People who suffer from diabetes and diabetes complications have a greater risk for having a stroke (Bell, 1994; Benavente et al., 2011; Hill et al., 2009). Worsening health conditions and disabilities increase the risk of stroke in people in the United States/ Mexico at an older age (Otiniano et al., 2003).

Studies from other populations show that DM is associated with higher mortality due to stroke (Kaarisalo et al., 2005; Sun and Toh, 2009). Deaths at 3 to 6 months are found to be significantly higher among stroke patients with diabetes compared to those without diabetes in China (Jia et al., 2011).

A limitation of this study is that the article collected only articles published in the 2010-2019 range. In addition, the author only use 5 databases in finding articles used in research. Future researchers are expected to be able to broaden article search by adding indexing databases that have not been used and looking for articles that have a different time span than previous studies.

AUTHORS' CONTRIBUTION

Karlinda is the main author who selects topics, searches and collects research data; Didik Gunawan Tamtomo was instrumental in reviewing the article; Bhisma Murti plays a role in analyzing research data.

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CONFLICT OF INTEREST

There is no conflict of interest.

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