

Meta-Analysis Effects of Diabetes Mellitus on Mortality in Patients with Chronic Heart Failure

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ABSTRACT

Background: Patients with diabetes mellitus have a higher risk of developing heart failure. Heart failure patients with diabetes mellitus will experience further health problems that are worse than heart failure patients without diabetes mellitus. This study was aimed to analyze the effect of diabetes on mortality in heart failure patients using a meta-analysis.

Subjects and Method: This was a meta-analysis study using PRISMA flowchart guidelines. The PICO model used was Population= patients with chronic heart failure. Intervention= with diabetes mellitus. Comparison= not with diabetes mellitus. Outcome= mortality. The article search process was carried out between 2012 and 2021 using online databases from PubMed, Science Direct and Google Scholar. The keywords used in the article search were “Chronic Heart Failure” AND “Diabetes” AND “Mortality”. The inclusion criteria used in this study were full-text articles using a cohort study design, the research subjects were chronic heart failure patients, the study outcome was mortality, multivariate analysis with adjusted Hazard Ratio (aHR). The analysis was carried out using RevMan 5.3 software.

Results: A total of 9 articles reviewed in the meta-analysis showed that diabetes mellitus increased the risk of mortality in patients with chronic heart failure 1.24 times compared with patients without diabetes mellitus (aHR= 1.24; 95%CI= 1.15 to 1.34; p< 0.001).

Conclusion: Diabetes mellitus increases mortality in patients with chronic heart failure.

Keywords: chronic heart failure, diabetes mellitus, mortality

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BACKGROUND

Based on the International Diabetes Federation (IDF), people with diabetes mellitus are predicted to continue to increase to reach 28.57 million people in 2045. Indonesia occupies the 5th highest position globally for the number of people with diabetes mellitus as many as 19.47 million in 2021. Diabetes mellitus can cause several other health problems and death. In 2021,

according to data from the International Diabetes Federation (IDF), the number of deaths due to diabetes mellitus in Indonesia is quite large with a total of around 200 thousand people (Katadata, 2021).

WHO states that health problems that can arise due to diabetes mellitus include heart attacks, strokes, blindness, and kidney failure. The risk of having a heart attack increases 2-3 times for people with diabetes

mellitus compared to non-diabetics. A heart attack can lead to heart failure which can lead to death. Meanwhile, the condition of diabetes management in Indonesia has not been implemented optimally and comprehensively. Based on the results of Riskesdas 2018, 75% of the number of people with diabetes mellitus in Indonesia are not treated. This can increase the risk of further health problems caused by diabetes mellitus. Sembodo (2021) states that the lack of control of diabetes mellitus is caused by a lack of human resources or health workers and insufficient funding to meet drug needs.

Diabetes mellitus is a chronic disease in the form of metabolic disorders characterized by excessive blood sugar levels in the body. This disease is divided into two types based on the cause, among others, the first is type 1 diabetes mellitus which is caused by damage to pancreatic beta cells, so that there is no production of the hormone insulin which functions to break down sugar in the blood; the second is type 2 diabetes mellitus caused by decreased insulin secretion; and the third is gestational diabetes mellitus, which is an increase in blood sugar levels during pregnancy around the 24th week (RI, 2021).

Based on an observational study conducted by Dunlay et al. (2019), showed that cases of heart failure in people with diabetes mellitus were 2 times more than those without diabetes mellitus. Glycemic control has an important role in the management of patients with diabetes mellitus and heart failure, every 1% increase in hemoglobin A1c (HbA1c) increases the risk of heart failure by 8% (Dunlay et al., 2019). The cohort study conducted by Dauriz et al. (2017) showed that after monitoring for 1 (one) year, the cumulative effect of patients with diabetes mellitus was greater than those without diabetes mellitus. As many as

4.8% of patients with diabetes mellitus died from cardiovascular disease and as many as 13.8% of patients underwent first hospitalization due to worsening heart conditions. This number is more than 3.8% of patients died and 9.3% of patients whose heart condition worsened but did not suffer from diabetes mellitus (Dauriz et al., 2017).

Heart failure patients with diabetes mellitus will experience further health problems that are worse than heart failure patients without diabetes mellitus. According to MAGGIC (Global Group Meta-analysis in Chronic Heart Failure), diabetes mellitus is an independent risk factor for death in heart failure patients. (Dunlay et al., 2019).

Heart failure is a complex clinical syndrome characterized by a reduced ability of the heart to pump or fill blood. From a physiological point of view, heart failure can be defined as cardiac output that is inadequate to meet the metabolic demands of the body. Heart failure is classified into three subtypes, namely heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF) and heart failure with intermediate ejection fraction (HFmrEF). Heart failure is a global problem because of its very high incidence, up to 26 million people in the world are affected by this disease (Greenberg, 2002).

An assessment of the pathology of diabetes mellitus and chronic heart failure is necessary in order to determine how to control the incidence of these diseases so as to reduce mortality. In addition, a global assessment of the prevalence, incidence, severity, and death from chronic heart failure with diabetes mellitus would be more beneficial because it would produce global conclusions and would be beneficial for the Indonesian people. Therefore, the researchers conducted a meta-analysis of the effects

of diabetes mellitus on mortality in patients with chronic heart failure.

SUBJECTS AND METHOD

1. Study Design

This research design uses a meta-analysis study, namely the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method. Articles were obtained from online databases, namely PubMed, Science Direct and Google Scholar. The keywords used in the article search were “Chronic Heart Failure” AND “Diabetes” AND “Mortality” in the years between 2012 and 2021.

2. Inclusion Criteria

The inclusion criteria used in this study were full-text articles using a cohort study design, the research subjects were patients with chronic heart failure, the study outcome was mortality, multivariate analysis with adjusted Hazard Ratio (aHR) to measure the estimated effect.

3. Exclusion Criteria

The exclusion criteria in this research article were: articles published in languages other than English, statistical results reported in the form of bivariate analysis, articles before 2012.

4. Definition of Operational Variables

Articles included in this study were screened according to the PICO (Population, Intervention, Comparison, & Outcome) model. The PICO model used is Population= patients with chronic heart failure. Intervention= with diabetes mellitus. Comparison= not with diabetes mellitus. Outcome= mortality.

Chronic heart failure is a complex clinical syndrome characterized by a reduced ability of the heart to pump or fill blood. The measurement scale is categorical.

Diabetes Mellitus is a chronic disease in the form of a metabolic disorder characterized by excessive blood sugar levels in the

body. Based on the National Glycohaemoglobin Standardization Program (NGSP), the diagnosis of diabetes mellitus is stated if the Hb A1c examination is 6.5% or fasting blood sugar is 126 mg/dl or blood sugar is 200 mg/dl. The measurement scale is categorical.

Mortality is the permanent loss of all signs of life after live birth, i.e. loss of life functions after birth, without the possibility of resuscitation. The measurement scale is categorical.

5. Study Instruments

The research is guided by the PRISMA flow diagram and the assessment of the quality/feasibility of articles using the Critical Appraisal Checklist for Cohort Study (CASP, 2018). The 12 questions used, among others:

1. Does this research have a clear research focus?
2. Was the cohort research process clearly defined?
3. Is exposure accurately measured so as to minimize bias?
4. Are the results measured accurately to minimize bias?
5. Did the authors identify important confounding factors? Were confounding factors considered in the design or analysis?
6. Is the follow-up on the subject complete? Was the follow-up period sufficient?
7. Are the results of the study using aHR?
8. Are the research results accurate?
9. Do you believe the results of this study?
10. Can this research be applied to the local population?
11. Are the results of this study in accordance with the existing evidence?
12. What are the implications of the results of this study?

6. Data Analysis

The software used to perform the meta-analysis is Review Manager 5.3 (RevMan 5.3). Data processing is carried out by

calculating effect sizes and heterogeneity values to determine the combined research model and form the final meta-analysis in the form of forest plots and funnel plots.

RESULTS

The article review process using the PRISMA flow chart can be seen in Figure 1. The total articles obtained were 9 articles spread across 2 continents, namely Asia and Europe.

Table 1 shows the research quality assessment of 9 articles using critical appraisal questions for cohort studies. Table 2 shows 9 articles of a cohort study on the effect of diabetes mellitus on mortality in

patients with chronic heart failure that met both qualitative and quantitative requirements.

The forest plot in Figure 3 shows that diabetes mellitus in patients with chronic heart failure had a mortality risk of 1.24 times compared with heart failure patients without diabetes mellitus (aHR= 1.24; 95% CI= 1.15 to 1.34; $p < 0.001$).

The funnel plot in Figure 4 shows that there is no publication bias. It is characterized by a symmetrical distribution between the right and left plots. There are 4 plots on the right and 5 plots on the left. The plots on the right and left of the graph have a standard error (SE) between 0 and 0.5.

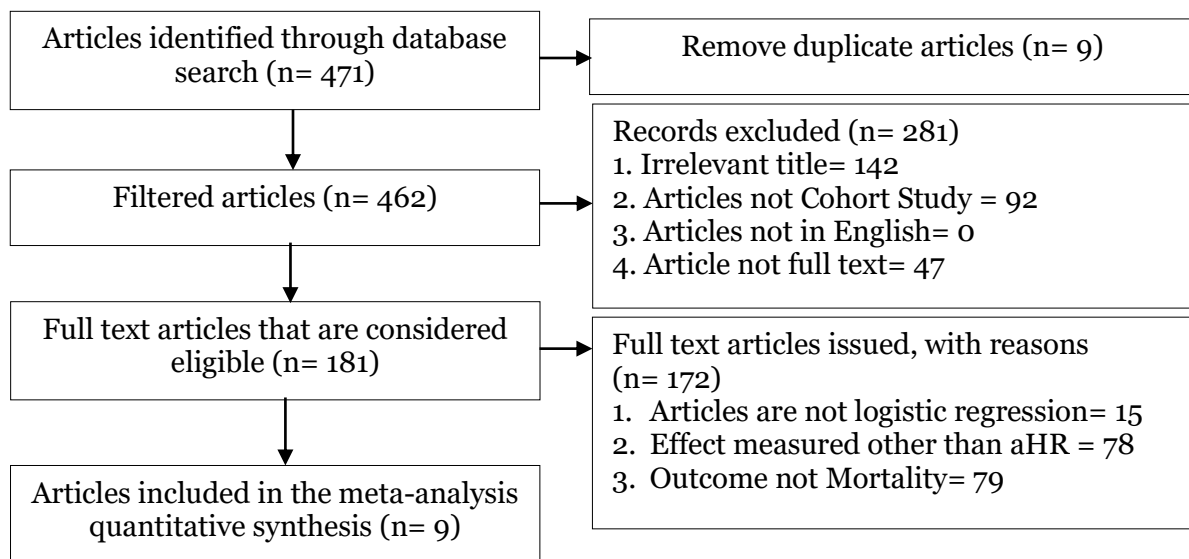


Figure 1. PRISMA flowchart



Figure 2. Map of the research area

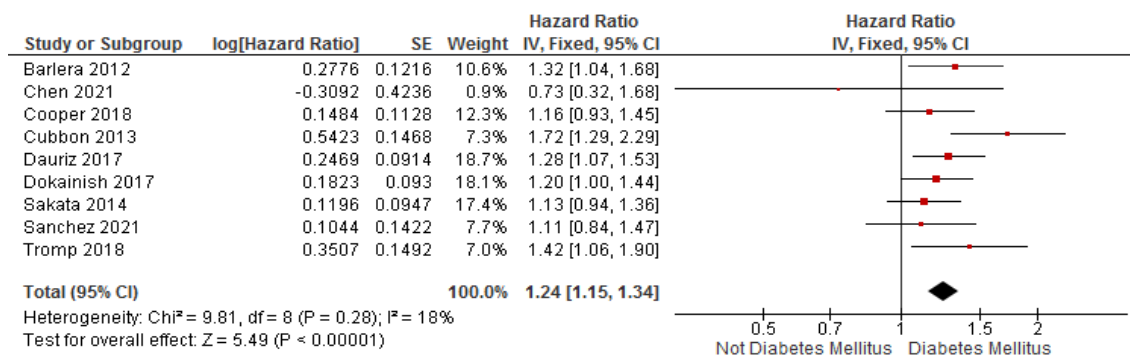


Figure 3. Forest Plot Effect of Diabetes Mellitus on Mortality in Chronic Heart Failure Patients

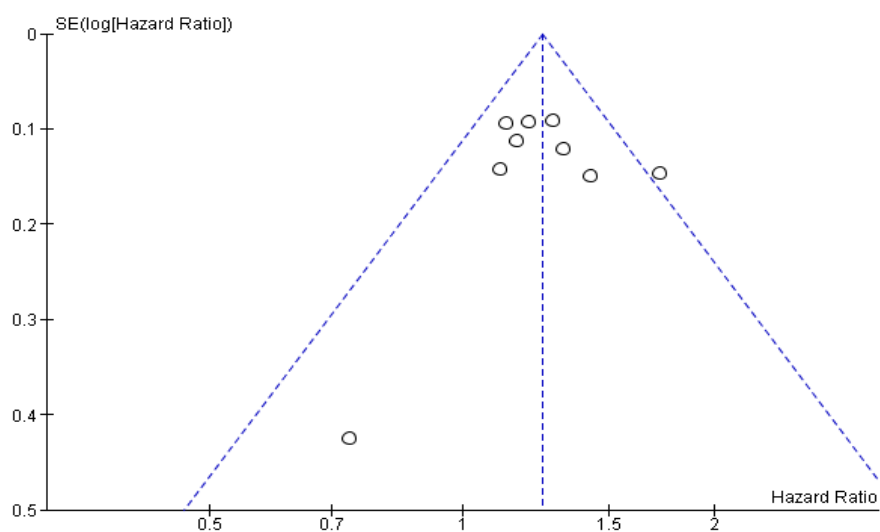


Figure 4. Funnel Plot Effect of Diabetes Mellitus on Mortality in Chronic Heart Failure Patients

Table 1. Research Quality Assessment of 13 Articles Using Critical Appraisal Questions for Cohort Study

No	Checklist Question	Publication (Author and Year)				
		Chen et al. (2022)	Sanchez et al. (2021)	Cooper et al. (2018)	Tromp et al. (2018)	Sakata et al. (2014)
1	Does this research have a clear research focus?	2	2	2	2	2
2	Is the cohort research process clearly defined?	2	2	2	2	2
3	Is exposure accurately measured so as to minimize bias?	2	2	2	2	2
4	Are results measured accurately to minimize bias?	2	2	2	2	2
5	Did the authors identify important confounding factors? Were confounding factors considered in the design or analysis?	2	2	2	2	2
6	Was the follow-up on the subject complete? Was the follow-up period sufficient?	2	2	2	2	2
7	Are the results of the study using aHR?	2	2	2	2	2
8	Are the research results accurate?	2	2	2	2	2
9	Do you believe the results of this study?	2	2	2	2	2
10	Can this research be applied to the local population?	2	2	2	2	2
11	Are the results of this study in accordance with the existing evidence?	2	2	2	2	2
12	Do the results of this study have any implications?	2	2	2	2	2
TOTAL		24	24	24	24	24

Description:

2: Yes; 1: Can't tell; 0: No

Table 2. Cont.

No	Checklist Question	Publication (Author and Year)			
		Dauriz et al. (2017)	Dokainish et al. (2017)	Cubbon et al. (2013)	Barlera et al. (2012)
1	Does this research have a clear research focus?	2	2	2	2
2	Is the cohort research process clearly defined?	2	2	2	2
3	Is exposure accurately measured so as to minimize bias?	2	2	2	2
4	Are results measured accurately to minimize bias?	2	2	2	2
5	Did the authors identify important confounding factors? Were confounding factors considered in the design or analysis?	2	2	2	2
6	Was the follow-up on the subject complete? Was the follow-up period sufficient?	2	2	2	2
7	Are the results of the study using aHR?	2	2	2	2
8	Are the research results accurate?	2	2	2	2
9	Do you believe the results of this study?	2	2	2	2
10	Can this research be applied to the local population?	2	2	2	2
11	Are the results of this study in accordance with the existing evidence?	2	2	2	2
12	Do the results of this study have any implications?	2	2	2	2
TOTAL		24	24	24	24

Description:

2: Yes; 1: Can't tell; 0: No

Table 3. Description of Primary Studies Included in Meta-Analysis

Author (Year)	Country	Study Design	Sample	P (Population)	I (Intervention)	C (Comparison)	O (Outcome)	aHR (95%CI)
Chen et al. (2022)	China	Retrospective Cohort	Total: 2,663 Diabetes: 886	Hospitalized patients with chronic heart failure (453 women and mean age 73 years)	Heart failure patients with diabetes mellitus	Heart failure patients without diabetes mellitus	Risk-30 day mortality	0.73 (0.32 to 1.68)
Sanchez et al. (2021)	Spain	Prospective Cohort	Total: 934 Diabetes: 446	Patients with chronic heart failure (52% male and mean age 80.2 years)	Heart failure patients with diabetes mellitus	Heart failure patients without diabetes mellitus	Total Mortality, Death or readmission to HF, Readmission due to Hf	1.11 (0.84 to 1.46)
Cooper et al. (2018)	Singapore	Prospective Cohort	Total: 6,214 Diabetes: 2,454	Chronic heart failure patients with multiple ethnicities (white, black, Chinese, Indian, Malay, Japanese/Korean)	Heart failure patients with diabetes mellitus	Heart failure patients without diabetes mellitus	1-year Mortality, 1-year HF hospitalization	1.16 (0.93 to 1.44)
Tromp et al. (2018)	Asia	Prospective Cohort	Total: 6,480 Diabetes: 2,656	Chronic heart failure patients (27% women and mean age 61.6 years)	Heart failure patients with diabetes mellitus	Heart failure patients without diabetes mellitus	All cause mortality, Hospitalization for Heart Failure	1.42 (1.06 to 1.92)
Sakata et al. (2014)	Japan	Retrospective Cohort	Total: 4,736 Diabetes: 1,652	Chronic heart failure patients with category C/D (68% Male and Mean age 69 years)	Heart failure patients with diabetes mellitus	Heart failure patients without diabetes mellitus	All Cause Death, CV Death, HF Admission	1.13 (0.97 to 1.36)

Table 4. Cont.

Author (Year)	Country	Study Design	Sample	P (Population)	I (Intervention)	C (Comparison)	O (Outcome)	aHR (95%CI)
Dauriz et al. (2017)	Europe	Prospective Cohort	Total: 9,428 Diabetes: 3,440	Outpatients diagnosed with chronic heart failure (74.7% Male and age 67.1 ± 10.9 years)	Heart failure patients with diabetes mellitus	Heart failure patients without diabetes mellitus	1-year all cause death, CVD death, HF Hospilization	1.28 (1.07 to 1.54)
Dokainish et al. (2017)	Canada	Prospective Cohort	Total: 5,823 Diabetes: 1,728	Outpatients and inpatients with heart failure (61% Male and mean age 59 years, SD 15)	Heart failure patients with diabetes mellitus	Heart failure patients without diabetes mellitus	All Cause Mortality in 1 year	1.20 (1.00 to 1.50)
Cubbon et al. (2013)	UK	Retrospective Cohort	Total: 1,091 Diabetes: 280	Outpatients diagnosed with chronic heart failure (77.1% Male and mean age 69.1 years)	Heart failure patients with diabetes mellitus	Heart failure patients without diabetes mellitus	All Cause Mortality	1.72 (1.29 to 2.28)
Barlera et al. (2012)	Italy	Retrospective Cohort	Total: 1,969 Diabetes: 675	Chronic heart failure patients (19.2% women and mean age 71.4 years)	Heart failure patients with diabetes mellitus	Heart failure patients without diabetes mellitus	All Cause Death	1.32 (1.04 to 1.67)

DISCUSSION

This systematic review and meta-analysis research raised the theme of the effect of diabetes mellitus on mortality in patients with chronic heart failure. The independent variable analyzed was diabetes mellitus. The dependent variable analyzed was mortality in patients with chronic heart failure.

The primary studies that met the criteria were 9 articles from 5 European continents and 4 Asian continents. This study shows that diabetes mellitus has a statistically significant effect on mortality in chronic heart failure patients. The results of the forest plot showed that the magnitude of the effect of diabetes mellitus on the mortality of chronic heart failure patients, which was 1.24 increased the mortality of chronic heart failure patients (aHR= 1.24; 95%CI= 1.15 to 1.34; $p < 0.001$). The heterogeneity of the research data shows $I^2 = 18\%$ so that the distribution of the data is declared as Fixed Effect Model.

Diabetes Mellitus can increase the risk of mortality in patients with chronic heart failure, these results are in accordance with the hypothesis. According to research Cooper et al. (2018) diabetes mellitus increases morbidity and mortality in all ethnicities of patients with heart failure so that it requires special attention. This is supported by the research of Cubbon et al. (2013) concluded that diabetes mellitus is associated with an increased risk of death in patients with ischemic and non-ischemic chronic heart failure. The research of Dauriz et al. (2017) mentioned that the presence of diabetes mellitus markedly increased the risk of adverse clinical outcomes over 1 year in outpatients with chronic heart failure regardless of some common risk factors. More effective and personalized treatment for diabetes should

be considered in this at-risk patient population (Dauriz et al., 2017).

The increased mortality in chronic heart failure patients with diabetes mellitus indicates the need for more effective diabetes therapy and more personalized service management for the survival of this at risk population. The limitation of this research is the search for articles because in this study the researchers only used 3 databases (PubMed, Google Scholar, and Science Direct) thus ignoring other search sources.

AUTHORS CONTRIBUTION

Windya Kartika Paramita and Yeocelin Mega Pratiwi are the main researchers who select the topic, collect data, analyze and review research documents.

FUNDING AND SPONSORSHIP

This study was self-funded.

CONFLICT OF INTEREST

There was no conflict of interest in this study.

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