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Meta-Analysis

Effect of Dapagliflozin in Lowering Risk of Heart Failure Severity: Meta-Analysis

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ABSTRACT

Background: Heart failure is a progressive health problem with high mortality and morbidity rates in developed as well as developing countries including Indonesia. Dapagliflozin is one of the oral antidiabetic medicines of the class of sodium-glucose cotransporter-2 (SGLT2) inhibitors, used in people with type 2 diabetes mellitus (DMT2). Unlike other oral anti-diabetes that work to stimulate insulin secretion or increase insulin sensitivity, dapagliflozin works in the kidneys by competitively inhibiting the SGLT2 protein reversibly which serves in glucose reabsorption in the glomerulus thereby lowering blood sugar levels in T2DM patients. This study aimed to determine the estimated effect of dapagliflozin on the severity of heart failure patients.
Subjects and Method: This study was a systematic review and meta-analysis with PICO. Population= Heart failure patients over 18 years old. Intervention= administration of dapagliflozin. Comparison= Placebo. Outcome= severity of Heart Failure. The articles used PRISMA flowchart guidelines. The article search process was conducted from 2019 to 2022 using databases from PubMed, Google Scholar, and Scopus with the search keywords Dapagliflozin, Heart Failure, and Placebo. The analysis was performed using RevMan 5.4 software.
Results: A total of 8 articles from across 2 continents, America and Asia, reviewed in the meta-analysis, showed that administering Dapagliflozin could reduce the risk of heart failure severity by 0.99 units compared to without dapagliflozin, however, it was statistically insignificant (OR= 0.99; 95% CI= 0.92 to 1.06; p= 0.710).
Conclusion: The administration of Dapagliflozin lowers the risk of heart failure severity and is statistically significant.

Keywords: dapagliflozin, heart failure, placebo

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BACKGROUND

Heart failure is a progressive health problem with high mortality and morbidity rates in developed and developing countries including Indonesia. In Indonesia, the age of heart failure patients is relatively younger than in Europe and America accompanied by more severe clinical appearance (Hersunarti et al., 2020). The prevalence of heart failure itself is increasing because patients who experience acute heart damage can continue to be chronic heart failure. The World Health Organization (WHO) illustrates that the increasing number of heart failure diseases in the world, including Asia, is due to the increasing number of smokers, obesity rates, dyslipidemia, and diabetes. The incidence rate of heart failure increases also with age. Data

from the PP PERKI (Heart Failure Working Group) registry recorded that at least more than 50% of heart failure cases were men aged 50-60 years with major risk factors such as smoking and hypertension.

Heart failure is a clinical syndrome that includes cardinal symptoms and signs (shortness of breath, swelling in the lower limbs, rapid fatigue, increased jugular vein pressure, pulmonary disease) due to abnormalities in the structure and function of the heart associated with increased intracardiac pressure and or reduced cardiac output at rest or exercise. Heart failure is mainly caused by myocardial dysfunction that can interfere with systolic, diastolic, or both functions. Identification of the etiology of cardiac dysfunction is part of the management of heart failure in determining specific therapies. Heart failure management continues to develop today as an effort to reduce mortality and recurrent hospitalization in this population (Boulton et al., 2013).

The EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 studies are the preliminary study of SGLT2-i as a diabetes medicine to discover cardiovascular outcomes in patients who already have cardiovascular disease or patients with cardiovascular risk factors. The results of the studies show the results of reduced mortality and retreatment due to heart failure in type 2 diabetic patients with the use of Empagliflozin and Canagliflozin. Studies using Dapagliflozin show a decreased hospitalization rate in heart failure without affecting mortality in diabetic patients (Zinman et al., 2015). Meta-analysis shows that the class of SGLT2-i medicines has a good effect in reducing cardiovascular mortality caused by the decreased number of hospitalizations for heart failure. The results of these three studies show the effectiveness of SGLT2-i in reducing the incidence of heart failure in patients with type 2 diabetes, subsequently becoming the major hypothesis that this medicine can be used in heart failure patients without type 2 diabetes (Zelniker, 2019).

DAPA-HF is the first study to discover the effectiveness of Dapagliflozin in the treatment of heart failure with a left ventricular ejection fraction (LVEF) of ≤40% in the group of patients with or without type 2 diabetes. The use of Dapagliflozin 10 mg compared to placebo will decrease mortality and prevent the worsening of heart failure as well as improve quality of life. Most of the study population has obtained standard treatments for heart failure such as renin-angiotensin inhibitors (RAAS-blockers), beta-blockers, and mineralocorticoid receptor antagonists (MRAs). The DAPA-HF study that involves 4744 patients with LVEF ≤40% with NYHA II-IV discover primary outcomes of cardiovascular mortality or worsening heart failure (hospitalization with a diagnosis of heart failure or urgent visits to the polyclinic with association (HR= 0.74; 95%CI= 0.65 to 0.85; p<0.001) with a median length of observation of 18.2 months (McMurray et al., 2019). The results of the sub-analysis show improvements in quality of life after 8 months assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). No serious side effects are found in these two groups. Dapagliflozin has the same effectiveness in the groups with and without type 2 diabetes, at high levels of NT-proBNP and lower ejection fractions, and does not depend on HbA1C values. In this study, Dapagliflozin is given to patients with an estimated glomerular filtration rate (LFG) of ≥30 mL/min/1.73 m2 (Petrie et al., 2020).

Another study using Canagliflozin (CREDENCE) shows similar results in terms of decreased cardiovascular mortality and advanced kidney failure disease. About 15% of the CREDENCE population already has a history of previous heart failure. Canagliflozin lowers the primary outcomes of advan-

ced kidney disease and prevents elevated creatinine levels or death from kidney disease or cardiovascular mortality (HR= 0.70; 95%CI= 0.59 to 0.82; p<0.001). For secondary outcomes, Canagliflozin lowers the hospitalization rate of heart failure (HR= 0.61; 95%CI= 0.47 to 0.80; p<0.001). This study shows that prevention of heart failure can be administered in patients with type 2 diabetes with chronic concomitant kidney disease (Perkovic et al., 2019).

A subsequent study discovers how the effect of SGLT2-i administration in heart failure patients with LVEF ≤40% on functional capacity improvement output. From the DEFINE-HF study, the administration of Dapagliflozin does not bring a positive outcome in terms of a significant decrease in NT-proBNP levels but it is discovered that the proportion of patients who experienced improved functional status (through KCCQ assessment) or decreased NT-proBNP levels is elevated by more than 20%. The determine-reduced study discovers the effect of administering Dapagliflozin 10 mg on quality of life and functional capacity in 3 months of treatment compared to placebo. The results of this study show that Dapagliflozin improves functional status (through KCCQ improvement) at 16 weeks of observation mainly in the group with more severe ailments, however, this study does not show an improvement in the 6-minute walk test with Dapagliflozin (Nassif et al., 2019).

The EMPEROR-Reduced study involving 3,730 chronic heart failure patients with FEVKi ≤ 40% shows Empagliflozin 10 mg to have significance for mortality and cardiovascular care outcomes in patients with or without type 2 diabetes (19.4% in the Empagliflozin group and 24.7% in the placebo group (HR= 0.75; 95% CI= 0.65 to 0.86). The use of Empagliflozin also indicates a slowdown in decline of LFG. Meta-analysis of DAPA-HF and EMPEROR-Reduced shows the effectiveness of Empagliflozin and Dapagliflozin on reduced hospitalization rates for heart failure, cardiovascular mortality, and death due to any cause as well as improving renal protection outcomes in heart failure patients without a background of type 2 diabetes (Packer et al., 2021).

The combination agent of SGLT1-i and SGLT2-i that is Sotagliflozin in the SCORED study, shows a protective effect in DM patients in terms of cardiovascular mortality and hospitalization for heart failure. Likewise, the SOLOIST study discovers the effects of this medicine on hospitalized diabetic patients with heart failure. Administration of Sotagliflozin after stabilization of acute heart failure or 3 days before discharge can reduce cardiovascular mortality and hospitalization rates for heart failure regardless of LVEF restrictions (Bhatt et al., 2021). This study aimed to determine the estimated effect of dapagliflozin on the risk of severity of heart failure patients.

SUBJECTS AND METHOD

1. Study Design

This study was conducted using a meta-analysis study design with PRISMA flow diagram guidelines. The article search was performed using the following databases: PubMed, Google Scholar, and Scopus with publication years between 2019 to 2022. Some of the keywords used were "Dapagliflozin AND Heart Failure AND Placebo.

2. Steps of Meta-Analysis

Meta-analysis is carried out through 5 steps as follows:

1) Formulate research questions in PICO (Population, Intervention, Comparison and Outcome).
2) Searching for primary study articles from various databases including Google Scholar and Science Direct
3) Perform screening and conduct critical quality primary studies.

4) Perform data extraction and enter the estimated effect of each primary study into the RevMan 5.3 application.
5) Interpretation the results and draw conclusions

3. Inclusion Criteria

The inclusion criteria of this study was the Randomized Controlled Trial (RCT) article. The study subjects were heart failure patients over 18 years old. The study outcome was a reduced risk of heart failure and interpreted in Odd Ratio (OR).

4. Exclusion Criteria

Exclusion criteria were articles published in non-English languages and before 2015.

5. Operational Definition of Variables

The article search was conducted by considering the eligibility criteria determined following PICO. Population Heart failure patients over 18 years old. Intervention= administration of dapagliflozin. Comparison= Placebo administration. Outcome= severity of Heart Failure.

6. Study Instruments

The study adopted PRISMA flow diagrams and used the Critical Appraisal Skills Program tool for the assessment of the quality of study articles (CASP, 2018).

7. Data Analysis

The study data were analyzed using the RevMan 5.4 application, to calculate the effect size and heterogeneity of the study. The results of data processing were presented in the form of forest plots and funnel plots.

RESULTS

The article review process using the PRISMA flowchart can be seen in Figure 1. The total articles obtained were 8 articles that originated from 2 continents, America and Asia. Figure 1 shows an assessment of the quality of research on 8 articles.

Figure 2 shows 8 articles originated from 2 continents, America and Asia. The forest plot in Figure 3 showed that childrens who applied dapagliflozin lowered the risk of heart failure severity by 0.99 and that result was statistically significant. The plot funnel in Figure 4 showed publication bias with an overestimated effect characterized by a symmetrical distribution between the right and left plots.

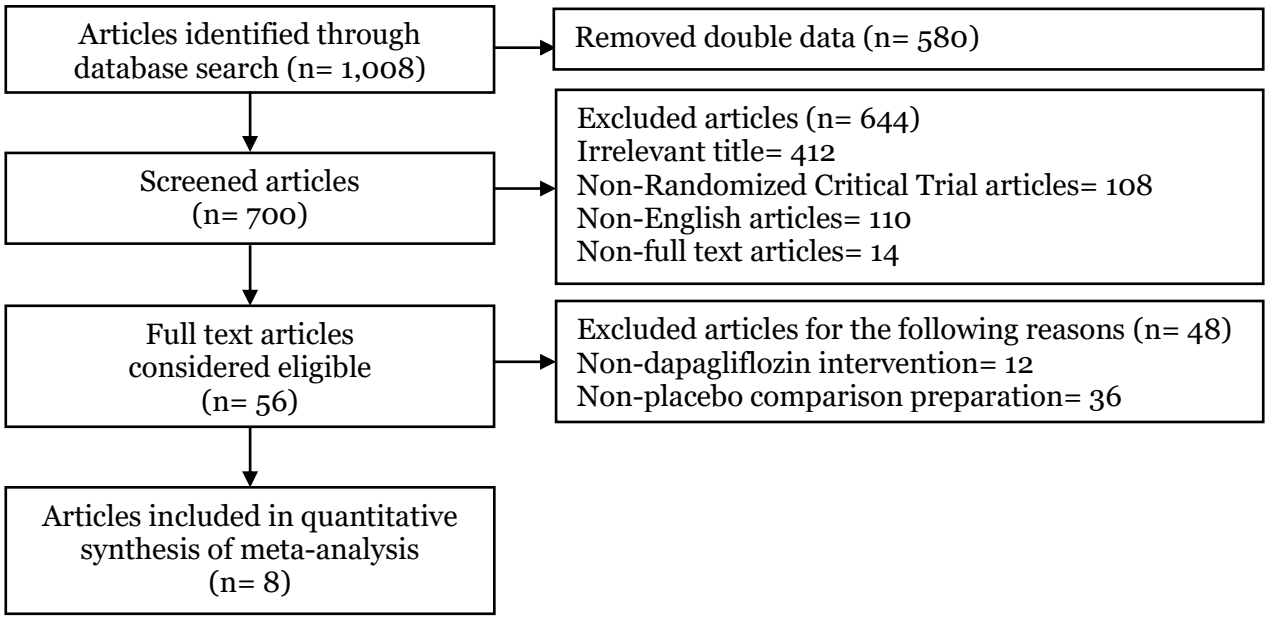

Figure 1. PRISMA Flowchart

Figure 2. Map of study area on reduced risk of heart failure severity

Quality research in research in this study was carried out based on the CASP Randomized Controlled Trial (RCT) Study Checklist worksheet from the Critical Appraisal Skills Program in the cohort study design with 12 steps.

Table 1. Results of the quality assessment from studies of dapagliflozin administration against a decrease in the risk of heart failure

Studies	Question Criteria												
	1	2	3	4	5	6	7	8	9	10	11	12	Total
McMurray et al. (2019)	2	0	2	2	2	2	2	1	2	2	2	2	21
Kosiborod et al. (2020)	2	0	2	2	2	2	2	1	2	2	2	2	21
Petrie et al. (2020)	2	0	2	2	2	2	2	1	2	2	2	2	21
Butt et al. (2022)	2	0	2	2	2	2	2	1	2	2	2	2	21
Docherty et al. (2020)	2	0	2	2	2	2	2	1	2	2	2	2	21
Adamson et al. (2021)	2	0	2	2	2	2	2	1	2	2	2	2	21
Butt et al. (2021)	2	0	2	2	2	2	2	1	2	2	2	2	21
Docherty et al. (2022)	2	0	2	2	2	2	2	1	2	2	2	2	21

Description of the question criteria:

1= Was the assignment of the participant to the intervention group randomized?
2= Is the allocation for the treatment group hidden?
3= Was the treatment group similar at the beginning?
4= Were the participants blind to treatment tasks?
5= Were those who give treatment blind to the task of treatment?
6= Were researchers blind to the task of treatment?
7= Was the treatment group treated identically in apart from the desired intervention?
8= Was the follow-up complete, and if not are the differences between the groups in terms of follow-up adequately explained and analyzed?
9= Were participants analyzed in random groups?
10= Did the results measure in the same way for the treatment group?

11= Were results measured reliably?
12= Was statistical analysis appropriate to use?

Answer score description:

0= No
1= Can't tell
2= Yes

Table 2. Summary of primary randomized control trial study articles with each PICO (N=37,649)

Author	Country	Sample	P	I	C	O
McMurray et al. (2019)	UK	4,744	Heart Failure Patients aged ≥18 years	10 mg Dapagliflozin	Placebo	Heart Failure Severity
Kosiborod et al. (2020)	USA	4,443	Heart Failure Patients aged ≥18 years	10 mg Dapagliflozin	Placebo	Heart Failure Severity
Petrie et al. (2020)	USA	4,744	Heart Failure Patients aged ≥18 years	10 mg Dapagliflozin	Placebo	Heart Failure Severity
Butt et al. (2022)	New York	4,744	Heart Failure Patients aged ≥18 years	10 mg Dapagliflozin	Placebo	Heart Failure Severity
Docherty et al. (2020)	USA	4,744	Heart Failure Patients aged ≥18 years	10 mg Dapagliflozin	Placebo	Heart Failure Severity
Adamson et al. (2021)	New York	4,742	Heart Failure Patients aged ≥18 years	10 mg Dapagliflozin	Placebo	Heart Failure Severity
Butt et al. (2021)	New York	4,744	Heart Failure Patients aged ≥18 years	10 mg Dapagliflozin	Placebo	Heart Failure Severity
Docherty et al. (2022)	USA	4,744	Heart Failure Patients aged ≥18 years	10 mg Dapagliflozin	Placebo	Heart Failure Severity

Tabel 3. Odds Ratio (OR) study of dapagliflozin administration against a decrease in the risk of heart failure (N=37,649)

Studies	OR	95%CI	
		Lower Limit	Upper Limit
McMurray et al. (2019)	1.15	1.08	1.23
Kosiborod et al. (2020)	0.84	0.78	0.90
Petrie et al. (2020)	1.12	1.30	1.22
Butt et al. (2022)	1.19	1.09	1.29
Docherty et al. (2020)	1.15	1.08	1.23
Adamson et al. (2021)	1.16	1.03	1.30
Butt et al. (2021)	1.14	1.06	1.24
Docherty et al. (2022)	1.19	0.89	1.61

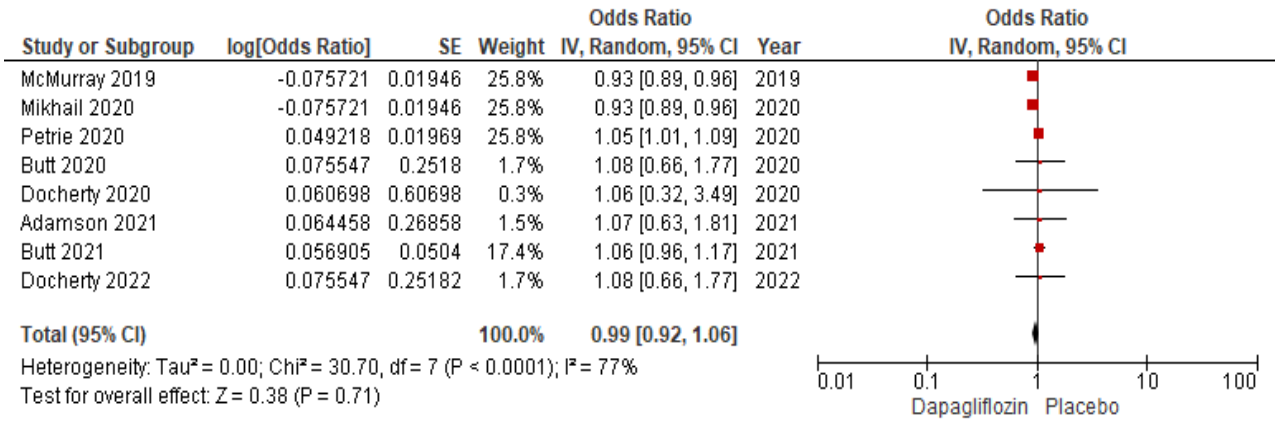

Figure 3. Forest plot effect of dapagliflozin on decreased heart failure

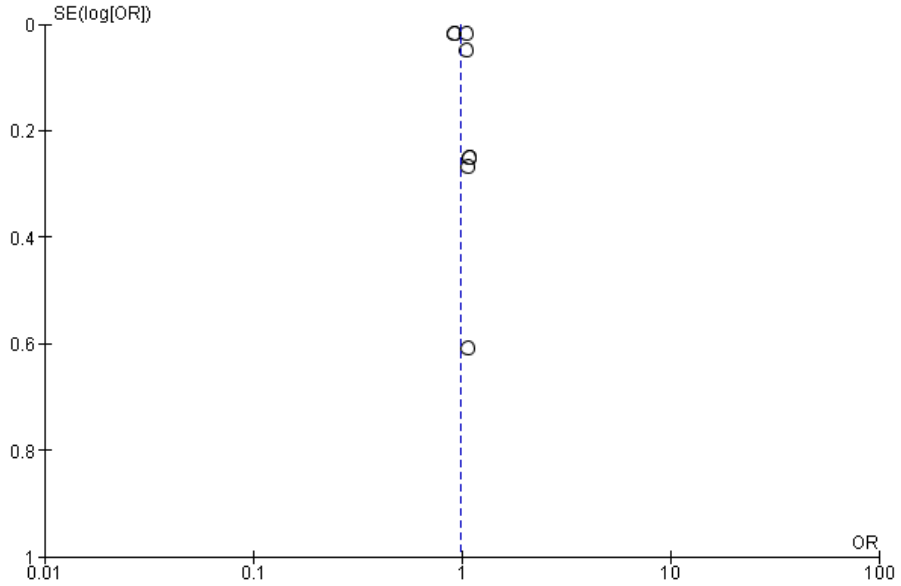

Figure 4. Funnel plot the influence of dapagliflozin on the reduced heart failure

DISCUSSION

This systematic study and meta-analysis examined the effect of Dapagliflozin on reduced risk of heart failure. The analyzed independent variable was the Dapagliflozin administration. The analyzed dependent variable was decreased heart failure. This study discussed the administration of Dapagliflozin on the decreased risk of heart failure. The administration of Dapagliflozin is considered important as an effective therapeutic option in lowering the risk of heart failure.

A total of 8 articles primary studies that met the criteria, 2 were from America and 6 others were from Asia continent. This study showed that the administration of Dapagliflozin was statistically significant in affecting decreased heart failure. The Forest plot showed that application of dapagliflozin could reduce the risk of heart failure by 1.02 times compared to placebo (OR= 1.02; 95% CI= 0.96 to 1.09; p=0.510). These results are in line with previous study of (McMurray et al, 2019) stating that administering Dapagliflozin is beneficial and able to expand the therapeutic role for diabetic patients as well as other non-diabetic patients.

Dapagliflozin is one of the oral antidiabetic medicines of the sodium-glucose cotransporter-2 (SGLT2) inhibitor class used in patients with type 2 diabetes mellitus. Unlike other oral antidiabetics that work to stimulate insulin secretion or increase insulin sensitivity, dapagliflozin works in the kidneys by competitively inhibiting the SGLT2 protein reversibly which serves in glucose reabsorption in the glomerulus, thus lowering blood sugar levels in people with T2DM. Several studies have been conducted to discover the inhibitory effects of SGLT2 in lowering cardiovascular events, such as Empagliflozin Cardiovascular Outcome Event Trial in Type-2 Diabetes Patients-Remove Excess Glucose, Canagliflozin Cardiovascular Assessment Study, and a multicenter study evaluating the effect of dapagliflozin on the incidence of cardiovascular events, namely Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) showed contradictory results. DECLARE-TIMI58 showed that dapagliflozin did not increase or decrease the risk of major adverse cardiovascular events (MACE) in contrast to other SGLT2 inhibitory medicines, but this study shows that dapagliflozin can reduce mortality and hospitalization rates due to heart failure (Docherty, 2022).

Based on two large studies, DAPA-HF and EMPEROR-Reduced, in chronic heart failure with LVET ≤40% the recommendation is SGLT2-i can be given in patients with or without type 2 diabetes with criteria of estimated glomerular filtration rate (GFR) of ≥ 30 mL/min/1.73 m2 in Dapagliflozin and ≥ 20 mL/min/1.73 m2 in Empagliflozin. The use of this drug should pay attention to changes in GFR because SGLT2-i can cause a decrease in GFR in the initial use. Doses of Dapagliflozin 10 mg and Empagliflozin 10 mg have been proven to reduce mortality in heart failure patients by considering contraindications, side effects, initiation methods, other clinical considerations, and management in conditions of acute onset as listed below (Inzucchi et al., 2021).

Dapagliflozin is an ADO that works in the kidneys by competitively inhibiting the sodium-glucose cotransporter-2 protein (SGLT2) reversibly thereby reducing the reabsorption of glucose filtrated by the glomerulus (90%). Inhibition of SGLT2 by dapagliflozin will lead to increased glucose excretion in the urine and decreased blood glucose levels. SGLT2 is a protein located in the S1 segment of the renal proximal tubule and functions to insert sodium and glucose back into the proximal tubule simultaneously (cotransporter) through an active transport mechanism. In oral administration, dapagliflozin is rapidly absorbed into the systemic circulation, where the level of the drug reaching systemic (bioavailability) ±78%. The time it takes to reach the maximum level in plasma (Tmax) ranges from 1 to 2 hours (depending on the presence or absence of food). Dapagliflozin binds to plasma proteins by ±91%, with a half-life of around 12.9 hours. A dapagliflozin dose of 10 mg exhibits an inhibitory effect of glucose reabsorption in the kidneys that is stable for 24 hours, so the dose is used in clinical practice with once a day frequency of administration (Adamson et al., 2021). The limitation of this study wer a language bias because the articles used are in English so they need to be read carefully. Based on the study conducted, it is concluded that dapagliflozin can reduce the severity of heart failure patients by 0.99 units and can be used as an alternative therapeutic option.

AUTHOR CONTRIBUTION

Andreza and Anis Nur Widayati were main researchers who selected the topic, searched, and collected study data. Isna Nur Rohmah analyzed data and reviewed study documents.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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