Is Myocardial Iron Overload Still Relevant as the Main Pathophysiology of Heart Failure in Thalassemia Major? A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Thalassemia is a global health issue, with an estimated 300-400 thousand thalassemia infants born each year, necessitating lifelong blood transfusions. Prolonged transfusions and increased iron absorption cause myocardial iron overload which is believed to be the primary cause of heart failure in these individuals. The purpose of this study is to determine the correlation between myocardial iron overload and left ventricular dysfunction in thalassemia major patients through meta-analysis.

Methods: This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. Systematic search was conducted in several international databases including Google Scholar, PubMed, EBSCOhost, and Proquest from 2000 to 2023. After applying Fisher's r-to-z transformation, correlation coefficient (r) values were extracted from each study and meta-analysis of the pooled correlation coefficient were calculated using RevMan 5. Newcastle-Ottawa Scale to measure the risk of bias. Egger's test funnel plot was used to assess the potential publication bias for this study.

Results: Nine studies were eligible for the meta-analysis, comprising 515 patients. Based on the meta-analysis of the pooled correlation coefficient of the included studies, the authors found that the overall effect size of the study was 0.33 (95% CI: 0.20-0.46) and exhibited a notable heterogeneity (I2 = 60%; P = 0.01).

Conclusions: The correlation between myocardial iron overload and left ventricular dysfunction in thalassemia major is weak. The pathophysiology of heart failure in thalassemia focusing on myocardial iron overload may need to be reconsidered.

INTISARI

Latar Belakang: Thalassemia merupakan masalah kesehatan global, dengan perkiraan 300-400 ribu bayi thalassemia lahir setiap tahunnya, sehingga memerlukan transfusi darah seumur hidup. Transfusi yang berkepanjangan dan peningkatan penyerapan zat besi menyebabkan deposisi zat besi pada miokardium yang diyakini sebagai penyebab utama gagal jantung pada orang-orang ini. Tujuan penelitian ini adalah untuk mengetahui korelasi deposisi zat besi pada miokard dengan disfungsi ventrikel kiri pada pasien thalassemia mayor melalui meta-analisis.

Metode: Penelitian ini dilakukan sesuai dengan Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020. Pencarian sistematis dilakukan di beberapa database internasional termasuk Google Scholar, PubMed, EBSCOhost, dan Proquest dari tahun 2000 hingga 2023. Setelah melakukan Transformasi r-to-z Fisher, nilai koefisien korelasi (r) diekstrak dari setiap penelitian dan meta-analisis dari koefisien korelasi gabungan dihitung menggunakan RevMan 5. Skala Newcastle-Ottawa untuk mengukur

risiko bias. Uji Egger digunakan untuk menilai potensi bias publikasi untuk penelitian ini.

Hasil: Sembilan penelitian memenuhi syarat untuk meta-analisis, yang terdiri dari 515 pasien. Berdasarkan meta-analisis dari koefisien korelasi gabungan dari penelitian yang dimasukkan, penulis menemukan bahwa ukuran dampak keseluruhan dari penelitian tersebut adalah 0,33 (95% CI: 0,20-0,46) dan menunjukkan heterogenitas yang mencolok (I2 = 60%; P = 0,01).

Kesimpulan: Korelasi antara deposisi zat besi pada miokard dengan disfungsi ventrikel kiri pada thalassemia mayor termasuk dalam kategori lemah. Patofisiologi gagal jantung pada talasemia yang berfokus pada kelebihan zat besi miokard mungkin perlu dipertimbangkan kembali

INTRODUCTION

Thalassemia is a congenital autosomal recessive haemoglobin (Hb) impairment with a high prevalence in the Indian subcontinent, Mediterranean and Middle Eastern countries, and Southeast Asia.[1] According to reports, roughly 300-400 thousand infants are born each year with hereditary significant Hb disorders, and approximately 80 million are carriers of thalassemia.[2] This condition is characterized by a reduction or absence in the synthesis of the β-globin chain, leading to ineffective erythropoiesis and malfunctioning hemoglobin A (HbA). Depending on the severity, patients may require frequent blood transfusions.[3,4]

All thalassemia patients are at risk of iron overload, especially those with transfusion-dependent thalassemia (TDT). Iron deposition in cardiac myocytes can lead to cardiac complications.[5] It is believed that iron deposition can affect the heart's structure and function, called cardiac siderosis, that become a significant contributor to morbidity and mortality in thalassemia patients, leading to ventricular diastolic and systolic dysfunction, cardiac rhythm disturbances, and even sudden death.[6]

Cardiac iron overload is a slowly progressive process that may take decades to be detectable by conventional laboratory and clinical measures.[7] Early diagnosis and iron chelation therapy can improve the quality of life and prevent severe complications.[4] Routine monitoring in thalassemia patients includes assessing Hb levels, serum ferritin, echocardiography, and magnetic resonance imaging (MRI) are required to maintain a balance between anemia management and cardiac hemosiderosis.[8] Namun, beberapa penelitian yang menggunakan MRI telah mempertanyakan korelasi antara keparahan cardiac hemosidosis dengan disfungsi ventrikel kiri. The purpose of this study is to determine the correlation between myocardial iron overload and left ventricular dysfunction in thalassemia major patients through meta-analysis.

METHODS

Search Strategy and Selection Criteria

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] A computerized search was conducted in Google Scholar, PubMed/MEDLINE (U.S. National Library of Medicine), EBSCOhost, and Proquest to

identify potentially eligible articles published from January 1st, 2000 to February 1st, 2023. The search was expanded by screening the references listed in the articles. The keywords used to search for articles were "thalassemia", "magnetic resonance imaging", and "cardiomyopathies" with various variations of word derivatives and combinations of Boolean operators according to the protocol in each database.
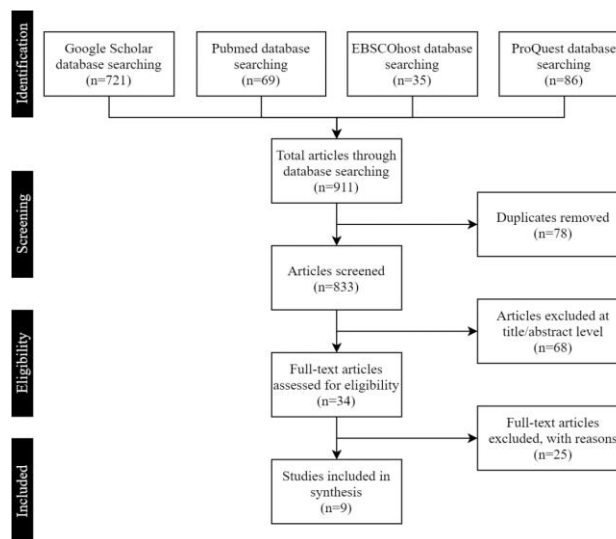

Figure 1. PRISMA Diagram

Table 1. Quality Assessment

Study	Selection	Comparability	Exposure/ Outcome	Total (Max 10)
Anderson, 2001	3	2	3	8
Tanner, 2006	2	2	3	7
Leonardi, 2008	2	2	3	7
Beshlawy, 2013	3	2	3	8
Quatre, 2014	2	2	3	7
Alvi, 2016	2	1	3	6
Pizzino, 2017	3	2	3	8
Abtahi, 2019	4	2	3	9
Ojha, 2021	4	2	3	9

Inclusion and Exclusion Criteria

Studies were included if they met all the following criteria: (1) Studies used MRI to examine myocardial iron overload; and (2) the study provides a detailed explanation of the MRI examination protocol, including the characteristics of the MRI equipment used. The exclusion criteria are as

follows: (1) The articles resulting from the search are reviews, guidelines, or editorials; and (2) the study did not report left ventricular ejection fraction values.

Data Extraction and Quality Assessment

Correlation coefficient data between myocardial T2* values (in ms) representing myocardial iron overload and left ventricular ejection fraction (in %) were extracted from the included studies. Assessment of the quality of research methodology was carried out using the Newcastle-Ottawa Quality Assessment Forms instrument. Heterogeneity between studies was assessed with the inconsistency index (I2): 0–40%, low heterogeneity; 30–60%, moderate heterogeneity; 50–90%, substantial heterogeneity; and 75–100%, considerable heterogeneity.[10] Two reviewers (A.N.A. and M.R.P.) independently performed data extraction and quality assessment. Differences of opinion are resolved through discussion.

Data Synthesis and Statistical Analysis

After the correlation coefficient value was transformed using Fisher's r-to-z transformation method, meta-analysis of the correlation coefficient between the myocardial T2* value (in ms) and left ventricular ejection fraction (in %) was carried out using random-effect modeling and shown in forest plot.[11] Publication bias for studies was assessed with Egger's test funnel plot.[12] Statistical analysis was performed in the Review Manager 5.

Study or Subgroup	Koefisien Korelasi	SE	Weight	Koefisien Korelasi IV, Random, 95% CI	Year
Anderson, 2001	0.61	0.1381	11.1%	0.61 [0.34, 0.88]	2001
Tanner, 2006	0.57	0.1465	10.5%	0.57 [0.28, 0.86]	2006
Leonardi, 2008	0.58	0.1491	10.3%	0.58 [0.29, 0.87]	2008
Beshlawy, 2013	0.376	0.2183	6.3%	0.38 [-0.05, 0.80]	2013
Quatre, 2014	0.22	0.0255	21.7%	0.22 [0.17, 0.27]	2014
Alvi, 2016	0.14	0.1428	10.8%	0.14 [-0.14, 0.42]	2016
Pizzino, 2017	0.23	0.1957	7.4%	0.23 [-0.15, 0.61]	2017
Abtahi, 2019	0.26	0.185	7.9%	0.26 [-0.10, 0.62]	2019
Ojha, 2021	0.13	0.106	14.0%	0.13 [-0.08, 0.34]	2021
Total (95% CI)			100.0%	0.33 [0.20, 0.46]	

Heterogeneity: Tau² = 0.02; Chi² = 20.01, df = 8 (P = 0.01); I² = 60%
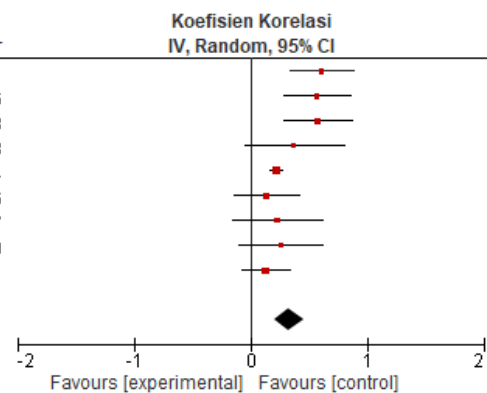Test for overall effect: Z = 5.08 (P < 0.00001)

Figure 1. Forest Plot

DISCUSSION

In the meta-analysis that we conducted on 9 studies (comprising 515 patients), it was found that the pooled correlation coefficient of the included studies, the authors found that the overall effect size of the study was 0.33 (95% CI: 0.20-0.46). It is known that the correlation coefficient of 0.20 – 0.399 indicates the strength of the correlation is included in the weak category.[13] The accumulation of iron in cardiac myocytes as a result of frequent blood transfusions has been identified as the primary cause of myocardial dysfunction in individuals with thalassemia major[14], but this study shows that the occurrence of heart failure in thalassemia patients may not be caused by myocardial iron overloaded, but by other things. This means that iron chelation may be postponed because it has been reported that adverse effects in the form of abdominal pain, nausea, vomiting, and elevation of liver enzymes are relatively common[15], even liver cirrhosis secondary to haemochromatosis which is fatal.[16] Simultaneously, it is necessary to re-examine the pathophysiology of heart failure in thalassemia patients.

Previous research has hypothesised that cardiac dysfunction unrelated to iron overload can emerge from a wide range of factors, the involvement of viral infections owing to recurrent blood transfusion exposure seems to be of key importance. Patients with beta-thalassaemia may be more susceptible to viral infections due to a weakened immune system and iron overload.[17] Kremastinos *et al* reported a 4.5% incidence of acute myocarditis at a mean age of 15 years in a large cohort of 1048 individuals with thalassemia major, with histopathologic confirmation in 50% of the cases. Chronic heart failure occurred in 27.6% of these individuals, on average, three years after the index event.[18] Other pathophysiologic mechanisms involved in the development of dilated cardiomyopathy in thalassemia patients include nutritional deficiencies (such as carnitine, thiamine, vitamin D, and selenium), endocrine disorders (such as hypothyroidism, hypoparathyroidism, and hypogonadism), and auto-antibodies.[14]

It needs to be noted that the meta-analysis we conducted exhibited a notable heterogeneity (I2 = 60%; P = 0.01). The meta-analysis that we have carried out uses a random effects model and the level of heterogeneity is identified based on the I2 value. To overcome this, the next appropriate step is to carry out meta-analysis in subgroups, for example based on diagnostic criteria, patient characteristics, sample size, year of publication, keywords used, and so on, as well as carrying out meta-regression. However, both analyzes were not possible for us to carry out due to the limited research reports available to divide into several subgroups. In addition, we have reported a low risk of bias based on the Newcastle-Ottawa Quality Assessment Forms instrument and analysis of publication

bias (using Egger's test funnel plot), so it can be confirmed that the heterogeneity obtained in this study does not affect the validity of the final results of the meta-analysis and Research conclusions can still be generalized to the general population.

Until this research report was written, there had been no systematic analysis with meta-analysis that raised a similar theme. This is the main advantage of this research because it provides novelty that can be used as a theoretical basis, especially in understanding the pathophysiology of heart failure in thalassemia patients. The meta-analysis that we have conducted has several limitations. First, there were studies that used a relatively small number of research subjects. Second, this study has notable research heterogeneity and variations in analytical techniques cannot be used to reduce it. Third, meta-analysis was not carried out in subgroups and meta-regression was not carried out because the results of data extraction showed that both analyzes were not possible to carry out.

CONCLUSION

The correlation between myocardial iron overload and left ventricular dysfunction in thalassemia major is weak. The pathophysiology of heart failure in thalassemia focusing on myocardial iron overload may need to be reconsidered.

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Description of Neutrophil Lymphocyte Ratio (NLR) in Coronary Heart Disease Patients at Haji Adam Malik General Hospital

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ABSTRACT

Introduction: Cardiovascular disease is the largest cause of death in the world, WHO explains that there are 17.9 million deaths from cardiovascular disease. Of all cases of death by cardiovascular disease, 7.4 million (42.3%) were caused by Coronary Heart Disease (CHD). Neutrophil Lymphocyte Ratio (NLR) is one of the examination biomarkers that aims to assess the level of inflammation that is currently occurring in a disease. NLR has a significant relationship in increasing the Framingham risk score (FRS) in predicting CHD mortality, NHANES-III states that NLR should be used as a biomarker in assessing CHD inflammation.

Methods: This study is a descriptive study with a cross-sectional approach that uses secondary data from patient medical records with collected using total sampling.

Results: The average NLR level of CHD patients was 4.438, the NLR cut-off point in this study was categorized into (<2.5) and (>2.5). Based on the age group, NLR level increased more in the young adult age group (45-60 years) there are 41 patients (27%), based on gender, the NLR level increased in males there are 62 patients (41%). The average NLR was 4.4 and based on gender the majority of NLR levels increased in male. NLR levels by age group is dominated by adult age group, as we get older the function of organs and immune system will not work optimally.

Conclusion: The NLR levels at Haji Adam Malik General Hospital Medan in CHD patients is increasing, especially in the young adult age group and patients with male gender.

INTRODUCTION

According to WHO, cardiovascular disease is the leading contributors to death [1]. Furthermore, American Heart Association reports cases of death in the United States due to cardiovascular disease is 49.2% and 9.3% is coronary heart disease (CHD) [2]. Among 35% Asia's death cases in 2019, cardiovascular disease was the main cause of death in people under 70 age [3]. Based on the Surveillance Information System for Non-Communicable Diseases, 2,228 out of 4,920 diagnoses of CHD categorized by gender at the Indonesian Health Center were in the elderly category (age >60 years), and included 2,320 males and 2,600 women. North Sumatra ranks 10th highest in terms of the prevalence of CHD cases among hospital inpatients [4]. The Institute for Health Metrics and Evaluation (IHME) shows that 14.4% of deaths in Indonesia are most commonly caused by CHD, also predicted raise to 23.3 million deaths in 2030 and it was reported that CHD is the main and first cause of all deaths in Indonesia, four times higher than the mortality rate caused by cancer [5].

Neutrophil Lymphocyte Ratio (NLR) is one of biomarkers that can determine the level of inflammation in a disease and also be a predictor of survival. An article points that there is a significant linkage between NLR in rising the Framingham risk score (FRS) in predicting CHD death. Research by the National Health and Nutrition Examination-III (NHANES-III) likewise proved that NLR can predict CHD death so that NLR should be used as a biomarker in CHD inflammation [6]. Research conducted by Siregar (2019) also states that a high NLR value can predict poor coronary artery collateral conditions in patients with stable CHD with multivessel disease [7].

Due to the enormous number of cases of cardiovascular disease that had occurred in Indonesia and even around the world, particularly CHD. Furthermore, NLR is a biomarker that plays an important role in assessing the prognosis, severity, and development of a disease. Therefore, this study aims to assess the average NLR biomarker of CHD patients based on age and sex in Haji Adam Malik General Hospital, Medan.

METHODS

This study used descriptive method with a cross-sectional approach. This study had received ethical clearance from health research ethics commission Medical Faculty, Universitas Sumatera Utara (No.699/KEPK/USU/2022). The number of samples from this study was determined based on Slovin formula. The data used is secondary data through a medical records of CHD patients at Adam Malik General Hospital from 1 January to 31 December 2021. The data that has been collected furthermore entered and analyzed into a computer using data processing software, namely the Statistical Program and Service Solution (SPSS).

RESULT

Table 1. Frequency Distribution of Characteristics Research Respondents

Characteristics of Respondents	Frequency n(%)	Total(%)
Gender		
• Male	127 (83,6)	152 (100)
• Female	25 (16,4)	
Age		
• 18-45 years old	10 (6,6)	152 (100)
• 45-60 years old	81 (53,3)	
• >60 years old	61 (40,1)	

Most of the respondents are male (83.6%) and the age group 45-60 years (53.3%).

Table 2. Gender Frequency Distribution by Age Group

	Early Adulthood (n)	Middle Adulthood (n)	Late Adulthood (n)
Male	10	71	46
Female	0	10	15

Male CHD patients showed that middle adulthood age group is the highest (71 patients). Meanwhile, female CHD patients mostly in the late adulthood group (15 patients).

Table 3. Mean sample difference of NLR levels

	Frequency (n)	Minimum	Maximum	Mean
Neutrophil Lymphocyte Ratio (NLR) levels	152	0,63	47,25	4,4383

Mean of NLR levels is 4.4 with minimum 0.63 and maximum 47.25.

Table 4. Sample Frequency Distribution Based on NLR Levels

Neutrophil Lymphocyte Ratio (NLR) Levels	Frequency n (%)
Decreased (<2.5)	73 (48)
Increased (>2,5)	79 (52)

NLR levels showed that 48% had a decreased NLR level and 52% had an increased NLR level.

Table 5. NLR in patients with different Gender

Neutrophil Lymphocyte Ratio (NLR) Levels	Frequency n(%)	Total (%)
Male		
• Decreased	65 (43)	152 (100)
• Increased	62 (41)	
Female		
• Decreased	8 (5)	
• Increased	17 (11)	

The distribution of NLR levels in CHD patients was more increased in male sex (41%) and NLR levels decreased by 43%, while in female sex is 11% and decreased by 8 patients (5%).

Table 6. NLR in patients with different age group

Neutrophil Lymphocyte Ratio (NLR) Levels	Frequency n(%)	Total (%)
Early Adulthood		
• Decreased	8 (5)	152 (100)
• Increased	2 (1)	
Middle Adulthood		
• Decreased	40 (26)	
• Increased	41 (27)	
Late Adulthood		
• Decreased	25 (16)	
• Increased	36 (24)	

The frequency distribution of NLR levels by age group was found to be more increased in the middle adulthood age group (27%), whereas in the young adult age group the NLR levels increased by only 1%, and in the elderly group the NLR levels increased 24%.

DISCUSSION

Incidence of CHD in Adam Malik General Hospital is very high. The total number of patients suffering from heart disease from medical record data in 2021 is 355 patients and those with atherosclerosis exceed 152 patients, this will continue to increase over time. Male represent the majority of the study group, according to table 1; Siregar (2019) and Alhikmah (2020) also did similar research [7,8]. Based on the theory, there are several risk factors that cause more men to suffer from heart disease including stress, diet, lifestyle, and hormones. Low testosterone levels can trigger the development of heart disease [9]. Men have a higher risk of heart disease but this will change after women go through menopause [10]. A study says that female hormone levels before menopause can protect women from disorders of heart disease [11].

Based on age, data shows that the number of patients with CHD is more affected in the adult age group. In men, CHD sufferers are more dominated by the adult age group and women are dominated by the elderly group. This is in line

with the research by Sari, Widiastuti and Fitriyasti (2020) which was conducted at the Siti Rahmah Padang RSI Heart Polyclinic in 2017-2018 which showed that there were more CHD sufferers in the age range 50-59 years [12], which related to the menopause phase [13].

Cut-off value used in this study is 2.5, where the levels of the NLR were categorized as increasing if >2.5 and decreasing if <2.5. This cut-off value has a sensitivity of 62% and a specificity of 69% and can predict the severity of the development of atherosclerosis in CHD patients [14]. From this study, it was found that the average NLR was 4.4 and based on gender, the majority of NLR levels increased in patients with male sex. This is in line with the study of Sharma et al., (2017) where NLR levels were more elevated in patients with male sex with an average of 5.2 [15]. There are many factors that can affect NLR levels including age, medical history, obesity, anemia, and stress. Distribution of NLR levels by age group is dominated by the adult age group. As we get older the function of all organs and the immune system will not work optimally, NLR levels will increase if accompanied by various factors such as high blood pressure and weight excess weight [16]. Research in Italy, also said that NLR increased in patients who were severe is the older age, so NLR in Covid-19 could be used as an initial screening test [17]. Research conducted by Fuad et al., (2021) also said that Covid-19 patients also had comorbidities. So that the increasing number of comorbidities suffered by patients can be a risk factor for an increase in biomarkers from the NLR examination which is a marker of systemic inflammation. The survival of patients who have a decreased NLR can be greater, the inflammatory process decreases and is in line with clinical improvement, but when compared to patients who have a more increased NLR, it can mean that the inflammatory process is also higher accompanied by clinical worsening so that NLR levels those with a high risk of death are greater [18]. The limitations in the research is to make more specific for which type of CHD you want to study and uses the latest and most relevant international references and journals so that you can make NLR an important and accurate biomarker in assessing inflammation and prognosis of CHD.

CONCLUSION

Number of CHD patients in RSUP. H. Adam Malik Medan, 1st January, 2021– 31st December, 2021 was found 48.0% had decreased NLR levels and 52.0% had increased NLR levels. It was found that the average patient's NLR value was 4.438. Based on age group, NLR levels were found to be more elevated in the adult age group (45-60 years) in 41 patients (27%). Based on gender, NLR levels were found to be more elevated in male patients with a total of 62 patients (41%).

ACKNOWLEDGEMENTS

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Serum Creatinine and Coronary Plaque on Atherosclerosis, More or Less?

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ABSTRACT

Background: The risk of coronary atherosclerosis increased in all stages of the impairment of renal function. Serum creatinine (sCr) is proposed as the marker of renal function and coronary artery disease (CAD). However, the relation between sCr and coronary plaque characteristics still remains unclear. This study was designed to evaluate the relationship between sCr and the presence and severity of coronary atherosclerosis in subjects undergoing MSCT coronary angiography for suspected CAD.

Methods: This cross-sectional study includes 444 subjects from the MSCT coronary angiography registry in Hasan Sadikin General Hospital Bandung from January 2020 until September 2022. Severe stenosis was defined as lesions causing >70% luminal stenosis or Left Main >50% or 3-vessel obstructive (≥70%) disease. All images were interpreted immediately after scanning by an experienced cardiologist.

Results: Three hundred and forty-five (77.7%) subjects had atherosclerotic plaque and 99 (22.3%) had none. Furthermore, after multivariate adjustment with gender, hypertension, and DM, sCr level independently increased the risk of developing atherosclerotic plaque [OR 6.671, (1.67-26.49, p-value 0.007)] and after multivariate adjustment with age, and gender, sCR independently also increased the risk of developing severe stenosis [OR 2.99, (1.15-7.71, p-value 0.024)].

Conclusions: This study demonstrated that sCr has significant association with the presence and severity of coronary atherosclerosis detected by MSCT. Further studies are needed to promote its use in predicting whether patients with high sCr need more aggressive risk modification and/or treatment regarding CAD.

INTISARI

Latar Belakang: Risiko kejadian aterosklerosis meningkat pada kondisi gangguan fungsi ginjal. Serum kreatinin merupakan suatu indikator fungsi ginjal dan penyakit jantung koroner (PJK). Namun, hubungan antara serum kreatinin dengan karakteristik plak koroner belum jelas diketahui. Studi ini bertujuan untuk menilai hubungan antara serum kreatinin dengan kejadian aterosklerosis koroner dan tingkat keparahannya pada subjek yang dicurigai PJK dan menjalani Multi-Slice Computed Tomography (MSCT) angiografi koroner.

Metode: Studi potong lintang ini mencakup 444 subjek dari registri MSCT angiografi koroner di RSUP Hasan Sadikin Bandung sejak Januari 2020 hingga September 2022. Stenosis berat didefinisikan sebagai lesi yang menyebabkan stenosis lumen >70% atau Left Main >50% atau penyakit obstruksi 3 pembuluh (≥70%). Semua gambar diinterpretasikan oleh kardiolog yang berpengalaman.

Hasil: Tiga ratus empat puluh lima (77,7%) subjek memiliki plak aterosklerosis dan 99 (22,3%) tidak. Selanjutnya, setelah analisis multivariat

dengan jenis kelamin, hipertensi, dan DM, tingkat serum kreatinin secara independen meningkatkan risiko timbulnya plak aterosklerosis [OR 6.671,

(1.67-26.49, nilai p 0.007)] dan setelah analisis multivariat dengan usia dan jenis kelamin, tingkat serum kreatinin juga secara independen meningkatkan risiko terjadinya stenosis berat [OR 2,99, (1,15-7,71, nilai p 0,024)].

Kesimpulan: Studi ini menunjukkan bahwa serum kreatinin memiliki hubungan yang signifikan dengan kejadian dan tingkat keparahan aterosklerosis koroner yang dideteksi oleh MSCT. Penelitian lebih lanjut diperlukan untuk meningkatkan penggunaannya dalam memprediksi apakah pasien dengan tingkat serum kreatinine tinggi memerlukan modifikasi risiko dan/atau pengobatan yang lebih agresif terkait PJK.

INTRODUCTION

Cardiovascular disease (CVD) remains a major clinical problem as it is still one of the leading causes of mortality worldwide, especially in Indonesia. Approximately one-third of all the deaths in Indonesia are attributable to cardiovascular disease, with stroke and coronary heart disease (CHD) serving as the primary causes of death in the country.[1] CVD risk increases as kidney function deteriorates, while its surging risk can be partially attributed to a higher prevalence of factors such as older age, hypertension, diabetes, dyslipidemia, and oxidative stress.[1–3] The most accessible clinical parameter for renal function used for daily practice is serum creatinine (sCr). Serum creatinine, which derives primarily from muscle metabolism and is the anhydride form of creatine. In addition, Serum creatinine (sCr) has been considered as an indicator not only of renal function but also coronary artery disease (CAD).[4,5]

Serum creatinine influences CVD mortality both in patients who already have conventional risk factors and those who do not have risk factors. Some studies showed that slightly elevated levels of serum creatinine served as an independent predictor of mortality from all causes and cardiovascular disease in various populations, such as those with hypertension, the elderly, and middle-aged population. Moreover, serum creatinine levels independently predicted mortality due to coronary artery disease (CAD) in individuals who were normotensive, non-obese, and had normal blood sugar levels following infarction.[6–11] In addition, serum creatinine levels influence other atherosclerosis diseases, it proved to be a strong and independent predictor of post-stroke mortality.[12] However, some data suggests serum creatinine exhibits a U-shaped correlation with CAD, particularly in women. This suggests that both abnormally low and high glomerular filtration rates are associated with an increased risk of CAD.[13]

In Indonesia, Multi-Slice Computed Tomography (MSCT) Coronary Angiography data is not yet widely available. Moreover, data regarding the relationship between serum creatinine and CTCA has not been explored to date. The relationship between CAD and serum creatinine levels has been investigated by several studies in other countries, but only limited data exists for the association of serum creatinine level with severity level of CAD. To investigate this possible correlation, we assessed the levels of serum creatinine in patients suspected for CAD with the presence and severity of coronary atherosclerosis in subjects undergoing MSCT coronary angiography.

METHODS

This cross sectional study included 444 subjects with suspected CAD aged >18 years, collected from MSCT coronary angiography registry in Hasan Sadikin General Hospital Bandung, Indonesia from January 2020 until September 2022. Subjects with a history of myocardial infarction, patients with previous coronary stent or graft, severe artifacts on imaging, and incomplete laboratory data were excluded from the study.

MSCT coronary angiography images were interpreted by an experienced cardiologist. Stenosis severity is categorized as severe and non-severe stenosis. Severe stenosis was defined as lesions causing >70% luminal stenosis or Left Main >50% or 3-vessel obstructive (≥70%) disease based on CAD-RADS classification. All subjects provided characteristics of their medical history, any medical medication at the time of MSCT coronary angiography examination. Blood biochemistry and lipid profile were taken from each patient. Serum creatinine levels are classified as elevated and within the normal range, with elevated levels defined as exceeding 1.25 mg/dL in men and 1.11 mg/dL in women. Diabetes mellitus (DM) was defined as history of being diagnosed with DM based on history taking or routinely taking anti-diabetic medication. Hypertension was defined as subjects who were previously diagnosed with hypertension or taking blood pressure medication regularly or systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg at the time of measurement. Dyslipidemi was defined as total cholesterol ≥ 200 mg/dL or being under treatment with at least one of lipid-lowering therapy. The smoking variable was described as any history of smoking at any point in a subject's life, regardless of whether they had ceased smoking by the time of measurement or not. Family history was characterized by a documented presence of cardiovascular disease in first-degree relatives among men younger than 55 years old or women younger than 65 years old. This study was approved by the local ethical committee and informed consent was received from each participant.

Statistical analysis was done using SPSS 26. Numerical data were presented as mean and standard deviation. Categorical data were presented as proportion in percentage. Association between categorical data were analyzed using chi-square, meanwhile association of categorical and continuous variables between two groups were performed using independent sample t-test. To determine independent predictors of presence and severity of coronary atherosclerosis, multiple logistic regression analysis was performed. The variables with p < 0.25 in bivariate analysis were then analyzed using multivariate analysis. p value <0.05 was considered statistically significant.

RESULT

Between January 2020 and September 2022, a total of 444 patients who were admitted to the Cardiology department that underwent MSCT coronary angiography were enrolled in the study. Among these, 223 were male (50.2%), mean age ± SD 55.98 ± 10.98 years. Baseline characteristics of the subjects are shown in Table 1.

Table 1. Baseline characteristics of patients enrolled in the study

Variable	Subjects (n = 444)
Age (years)	55.98 ± 10.98
Gender (male)	223 (50.2)
Hypertension	217 (48.9)
Diabetes Mellitus	50 (11.3)
Smoking	102 (23.0)
Family History of CVD	24 (5.4)
Dyslipidemia	320 (72.1)
BMI	26.28 ± 8.65
Serum Creatinine (men)	1.10 ± 0.23
Serum Creatinine (women)	0.84 ± 0.27

Values are mean SD (range) or percentage of patients.

Abbreviations: BMI – body mass Index; CVD – cardiovascular disease

Among the study population 48.9% had hypertension, 11.3% had diabetes mellitus, 72.1% had dyslipidemia, 23% were smokers, and 5.4% had family history of CVD. An association between several cardiovascular risk factors including age, hypertension, gender (male), diabetes mellitus, family history, serum creatinine and coronary atherosclerosis was found when patients were group into two categories to the presence or absence of coronary atherosclerosis, as shown in Table 2 (p = < 0.05).

Patients having coronary atherosclerosis in MSCT coronary angiography had higher levels of serum creatinine when compared to subjects without atherosclerosis (0.833± 0.200 vs 0.994± 0.278; p < 0.001, respectively) (Table 2). Additionally, patients having severe luminal stenosis detected by MSCT had higher level of serum creatinine when compared to patients having coronary atherosclerosis but non severe luminal stenosis (1.06 ± 0.29 vs 0.93 ± 0.25; p <0.001) (Table 4). Thus, severity of

coronary atherosclerosis was also related to serum creatinine level.

In the multivariate analysis evaluating the relationship between serum creatinine and the presence of coronary atherosclerosis, after multivariate adjustment with gender, hypertension, and DM, sCr level independently increased the risk of developing atherosclerotic plaque [OR 6.671, (95% confidence interval 1.67-26.49, p-value 0.007)]. Apart from serum creatinine, age, gender (male), and hypertension were found to be significantly associated with the presence of coronary atherosclerosis (Table 3).

In the severity of coronary atherosclerosis, higher levels of serum creatinine are associated with severe luminal stenosis (p<0.001). In addition, age, gender (male) were found to be associated with severity of coronary atherosclerosis (Table 4). Furthermore, after multivariate adjustment with age, and gender, serum creatinine independently increased the risk of developing severe stenosis [OR 2.99, (1.15-7.71, p-value 0.024)] (Table 5).

Table 2. Comparison of patients with coronary plaque versus patients without coronary plaque detected by MSCT coronary angiography

Cardiovascular Risk factors	Coronary plaque (-) (n=99)	Coronary plaque (+) (n=345)	p-value
Age ≥60 years old (%)	5.6	94.4	<0.001
Hypertension (%)	14.6	85.4	0.002
Gender (male) %	12.6	87.4	<0.001
Diabetes Mellitus (%)	8.3	91.7	0.023
Smoking (%)	15.7	84.3	0.141
Family History (%)	39.1	60.9	0.027
Dyslipidemia (%)	22.0	78.0	0.336
BMI (Mean± SD)	25.94+-5.51	26.35+-9.36	0.692
Serum Creatinine (Mean± SD)	0.833±0.200	0.994±0.278	<0.001

Table 3. Multivariate logistic regression analysis demonstrating the association between cardiovascular risk factors including serum creatinine and the presence of coronary plaque.

CV Risk factors	OR	95% CI	p Value
Age	7.26	8.08-3.95	<0.001
Gender (male)	0.433	0.229-0.822	0.010
HT	2.029	1.18-3.48	0.010
DM	2.85	0.93-8.71	0.065
Serum Creatinine	6.671	1.67-26.49	0.007

Table 4. Comparison of patients with severe coronary atherosclerotic plaque versus patients with non severe coronary atherosclerotic plaque detected by MSCT coronary angiography

CV Risk factors	Non Severe Stenosis (n=164)	Severe Stenosis (n=181)	p Value
Age >= 60 years	37.7	62.3	<0.001
Hypertension (%)	45.3	54.7	0.24
Gender (male) %	37.6	62.4	<0.001
Diabetes Mellitus (%)	45.2	54.8	0.678
Smoking (%)	35.3	64.7	0.006
Family History (%)	50.0	50.0	0.89
Dyslipidemia (%)	49.8	50.2	0.377
BMI	26.15+-4.34	26.47+-12.39	0.759
Serum Creatinine	0.93±0.25	1.06±0.29	<0.001

Table 5. Multivariate logistic regression analysis demonstrating the association between cardiovascular risk factors including serum creatinine and the severity of coronary plaque.

CV Risk factors	OR	95% CI	p Value
Age	2.67	1.68-4.25	<0.001
Gender (male)	0.412	0.246-0.689	0.001
Serum Creatinine	2.99	1.15-7.71	0.024

DISCUSSION

Previous studies have shown that a higher serum creatinine level was proposed to be an independent predictor of all cause cardiovascular mortality in elderly, hypertensive individuals, and middle-aged population.[14] Culleton et al. stated that mortality for cardiovascular disease for both men and women were higher in the renal impairment group compared to those with normal sCr values.[2] A study by Hsieh et al. found that patients with CAD were older, had higher sCr levels and body mass index, and had lower high-density lipoprotein (HDL-c) levels. In addition, serum creatinine level more than 1.5mg/dl was found to be an independent risk for CAD in diabetic men, while sCr levels >1.4mg/dl were independently associated with CAD in women.[4,15] A study by Nakano et al, conducted on autopsy results of Japanese elders, also demonstrated a gradual increase in the incidence of advanced atherosclerosis as eGFR decreased.[16]

However, there was an interesting study from Onat et al stating that CHD risk curve in women was U-shaped, the lowest and highest creatinine level exhibiting OR 1.4 times risks developing CHD. However, they postulated that this was as a result of women in the lower creatinine group having an impaired atheroprotective properties such as low HDL, average apoA-I, and Lp(a) concentrations. Dysfunction of apolipoprotein A-I, even when Metabolic Syndrome is not present, may provide an explanation for its connection to an elevated risk of cardiovascular disease, despite having low creatinine levels. [13,17]

Study by Bagheri et al stated that serum creatinine level has significant association with CAD, but after multivariate adjustment it was not associated independently.[18] Meanwhile, our study found that higher level serum creatinine were independently associated with the presence and severity of coronary atherosclerosis apart from other traditional cardiovascular risk factors, and this

relationship still persisted after multivariate adjustment with other cardiovascular risk factors.

Increased sCr level could be an indicator of an early nephrovasculopathy, which correlates with early development of atherosclerosis. Cerne et al stated that CAD patients with increased serum creatinine could be associated with renal artery stenosis despite the fact that they had no clinical indication of suspected ischemic kidney disease. An increased serum creatinine level may serve as a sensitive marker for the early onset of nephrovasculopathy, which are linked to the early stages of atherosclerosis and its underlying conditions.[14] The HOPE randomized trial revealed that the cumulative prevalence of cardiovascular death, acute myocardial infarction, and stroke was more frequent in individuals with sCr levels >1.4 mg/dl compared to those with lower SCr level.[19]

The British Regional Heart Study mentioned that among elderly men, cardiovascular mortality in patients with mild to moderate renal insufficiency was related not only to conventional risk factors but also to increased inflammation and impaired endothelial function.[20] Moreover, it was reported that sCr level behaves as a marker of pro-inflammatory state, and inflammation-mediated endothelial dysfunction that has been shown to be associated with the occurrence of cardiovascular events. In frequent cases of chronic kidney disease, there is an increase in inflammatory mediators and activation of the renin-angiotensin system. This contributes to the acceleration of atherosclerosis in renal and other vascular areas through the generation of reactive oxygen species.[13,18,21]

The primary advantage of our research lies in its pioneering exploration of the relationship between serum creatinine as marker of renal function and coronary atherosclerosis as detected using a less invasive method, MSCT coronary angiography, which can detect early morphological changes before manifestation of clinical symptoms. Nevertheless, there are some limitations in this study. Primarily, this is a cross-sectional study that aims to investigate the relationship between serum creatinine and coronary atherosclerosis. Therefore, we did not investigate the predictive role of serum creatinine level. Lastly, our evaluation of plaque structure was limited to a single aspect, namely calcification as assessed by MSCT.

CONCLUSION

This study provided evidence that serum creatinine is a variable significantly associated with both the occurrence and severity of coronary atherosclerosis, as identified by MSCT. An increase in sCr elevates the risk of the presence of severe coronary atherosclerosis. Further studies are needed to enhance the utilization of sCr as a tool for predicting whether patients with elevated sCr levels require more intensive risk management and/or CAD treatment.

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Correlation Between HbA1C, TG, and LDL Levels with Angiography Results in CHD Patients at Telogorejo Hospital Semarang

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ABSTRACT

Background: Coronary heart disease (CHD) or coronary artery disease is a heart condition with a formation of atherosclerotic plaques in the lumen of the coronary arteries, causing disruption of blood flow and oxygen supply to the myocardium. This study has novelty value because the correlation between the three independent variables (HbA1C, TG, LDL) and coronary angiography results in CHD patients has never been studied simultaneously before.

Objectives: To analyze the correlation between HbA1C, TG, and LDL levels with angiography results of CHD patients at Telogorejo Hospital Semarang.

Methods: The research method used is cross-sectional approach. The study population included patients who underwent coronary angiography in 2020 to 2022 and met the study criteria. A total of 34 patients parcitipated in the study. Data analysis was performed using the Spearman Rank test.

Results: Findings showed there was a significant relationship (r = 0.402) between HbA1C levels with the results of angiography in CHD patients, while TG levels and LDL levels were not statistically related to the results of angiography in CHD patients.

Conclusion: This study shows that HbA1C levels have a significant relationship with angiography results in CHD patients with a moderate positive correlation rate. LDL and TG levels did not show a statistically significant relationship.

INTISARI

Latar Belakang: Penyakit jantung koroner (PJK) atau disebut penyakit arteri koroner adalah kondisi jantung dengan pembentukan plak aterosklerotik dalam lumen pembuluh darah koroner sehingga menyebabkan gangguan aliran darah dan suplai oksigen ke miokardium. Penelitian ini meneliti korelasi ketiga variabel independen (HbA1C, TG, LDL) dengan hasil angiografi koroner pada pasien PJK yang belum pernah diteliti secara bersamaan sebelumnya.

Tujuan: Mengetahui hubungan antara kadar HbA1C, trigliserida, dan low-density lipoprotein (LDL) dengan hasil angiografi pasien PJK di RS Telogorejo Semarang.

Metode: Metode penelitian yang digunakan yaitu metode observasional analitik dengan pendekatan cross-sectional. Analisis data dilakukan menggunakan uji Spearman Rank.

Hasil: Terdapat hubungan yang signifikan sebesar r= 0,402 antara kadar HbA1C dengan hasil angiografi pasien PJK, sedangkan kadar trigliserida dan kadar LDL tidak berhubungan secara statistik dengan hasil angiografi pasien PJK.

Kesimpulan: Penelitian ini menunjukkan hasil bahwa kadar HbA1C mempunyai signifikansi hubungan dengan hasil angiografi pada pasien PJK dengan tingkat korelasi positif moderat. Kadar LDL dan trigliserida tidak menunjukkan hubungan bermakna secara statistik.

INTRODUCTION

Coronary heart disease (CHD), also known as coronary artery disease (CAD), is a heart disease in which atherosclerotic plaques form in the lumen of the coronary arteries, causing impaired blood flow and oxygen supply to the heart muscle.[1] Cardiovascular disease is one of the leading causes of death worldwide. According to the World Health Organization (WHO), an estimated 17.9 million people will die from cardiovascular disease in 2021, accounting for 32% of all deaths worldwide.[2] Research from the Global Burden of Disease states that worldwide, people with CHD are 126 million individuals (1,655 per 100,000), about 1.72% of the world's population. There were 9 million deaths due to CHD worldwide. Men are more at risk than women. Incidence usually begins in the fourth decade of life and increases with age. The global prevalence of CHD is increasing. It is estimated that the prevalence rate will increase to 1,845 by 2030.[3]

Coronary heart disease can be diagnosed by performing non-invasive examination or invasive examination. Coronary angiography, an invasive examination, uses a percutaneous catheter to determine the severity of the disease.[4] Angiography results in CHD patients are assessed using the vessel disease score. Vessel disease is measured based on the number of coronary arteries that have stenosis (narrowing of the lumen) of more than 50-70%. Single vessel disease (SVD) refers to patients with stenosis of one coronary artery, while multiple vessel disease (MVD) refers to patients with stenosis of two or more coronary arteries.[5,6] Patients with MVD have a higher risk of death than those with SVD. The mortality rate increases significantly in patients with MVD.[7]

Coronary heart disease (CHD) risk factors consist of non-modifiable and modifiable risk factors. Non-modifiable risk factors comprise age, gender, family history, and previous history of cardiovascular disease. Modifiable risk factors include smoking, hyperglycemia, dyslipidemia, hypertension, excessive alcohol consumption, sedentary lifestyles, obesity, and stress.[8]

The risk of coronary heart disease increases 2-4 times in patients with hyperglycemia, which is caused by insulin resistance. Insulin resistance or deficiency may lead to disorders in lipid metabolism, hypertension, inflammation, oxidative stress, and coagulation.[9] Hyperglycemia could trigger microthrombus due to various processes, such as heightened aggregation, increased vascular permeability, increased neovascularization, elevated total cholesterol as an atherogenic factor, and decreased fibrinolytics.[10] To determine blood glucose levels, the glycosylated hemoglobin A1C (HbA1C) examination is used. The HbA1C test is utilized for diagnosing and determining the risk factors for DM in patients with a risk of cardiovascular disease, including CHD.[11,12]

Dyslipidemia is characterized by elevated total cholesterol, low-density lipoprotein (LDL), and/or triglyceride (TG) levels along with decreased high-density lipoprotein (HDL) levels and is a significant contributor to the development of atherosclerosis in blood vessel walls. Atherosclerosis is the underlying cause of both CHD and stroke.[13] To assess dyslipidemia, lipid profile laboratory tests are commonly used. The present study investigated levels of LDL and TG. Low-density lipoprotein (LDL) is a crucial factor in the development of atherosclerosis, as it contributes to plaque buildup and inflammation. Meanwhile, triglycerides (TG) are associated with elevated levels of small, dense LDL and increased oxidative stress, leading to endothelial dysfunction and ultimately contributing to atherosclerosis.[14]

A study showed that there was a significant association of metabolic syndrome (obesity, hypertension, hyperglycemia, hypertriglyceridemia, and LDL cholesterol) with the risk of CHD.[15] In contrast, another study stated that there was no correlation between LDL, TG and the degree of stenosis in CHD patients.[16] Research conducted by Yang, et al. states that HbA1C, LDL levels are associated with the prevalence of 3-vessel disease.[17] Similarly, Ahmed, et al. found a statistical association between HbA1C and the severity of CHD.[18]

Due to the high prevalence of CHD patients and the mortality rate associated with the disease, along with the expected continuation of the CHD incidence, this study aims to analyze the correlation of three independent variables (HbA1C, TG, LDL) with the results of coronary angiography in CHD patients. Previous studies have shown inconsistent results, and this study aims to analyze these variables in CHD patients who have never been studied simultaneously before.

METHODS

Study design and participants:
This cross sectional study was conducted at The Medical Record Department of Telogorejo Hospital in Semarang, Indonesia. Data obtained from the patients' medical record, which is shown on supplementary data.
 A total of 34 patients were retrospectively enrolled from January 2020 to November 2022. Inclusion criteria included (1) patients diagnosed with CHD based on medical records, (2) CHD patients who had undergone angiography and had laboratory results of HbA1C, triglyceride, and LDL levels collected before angiographic examination, and (3) patients with significant coronary lumen stenosis (lesions estimated to be ≥ 50%). Exclusion criteria included (1) patients with incomplete medical record data, (2) patients with blood

disorders such as anemia (Hb < 12 g/dL in non-pregnant women, Hb < 11 g/dL in pregnant women, Hb < 13 g/dL in men), sickle-cell disease, thalassemia or those who did not fast during the HbA1C lab examination.

Invasive coronary angiography was performed at the Telogorejo Hospital Semarang. SVD was diagnosed in patients with stenosis in one coronary artery, while MVD was diagnosed in patients with stenosis in two or more coronary arteries. The study was approved by the Health Research Ethics Committee of Telogorejo Hospital Semarang.

Statistical Analysis:

Demographic and clinical variables were analyzed by overall group and by gender. Continuous variables were summarized as mean and standard deviation and categorical variables as frequency and percentage. The Spearmank-rank test was used to determine the correlation between variabels. A 2-sided p value smaller than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 24.

RESULT

The research data were obtained from Telogorejo Hospital in Semarang, based on patients who underwent coronary angiography between 2020 and 2022 and met research criteria. A total of 34 patients' data was collected.

Patient characteristics are presented in the following data (Table 1):

Table 1. Characteristics of the study population

Coronary Heart Disease (CHD) (n=34)		
Sex	Male	5 (14.7%)
	Female	29 (85.3%)
Age (years)	Mean (SD)	61.15 (9.29)
	Median	63
	Range	35-79
Coronary Angiography Result	SVD	12 (35.3%)
	MVD	22 (64.7%)
HbA1C	Mean (SD)	7.2 (1.76)
	Median	6.62
	Range	5 – 12.1
TG	Mean (SD)	152.16 (77.1)
	Median	135.15
	Range	33 – 373.3
LDL	Mean (SD)	119.98 (49.6)
	Median	118.25
	Range	36 – 228.3

HbA1C: haemoglobin glycated A1C, TG: triglyceride, LDL: low-density-lipoprotein

There were five female patients (14.7%) and 29 male patients (85.3%) and the average age of the patients was 61.15. A total of 12 patients (35.3%) had single vessel disease and 22 patients (64.7%) had multiple vessel disease. The mean HbA1C is 6.62%, with a minimum value 5% and a maximum value 12.1%. The mean triglyceride level is 135.15 mg/dl, with a minimum of 33 mg/dl and a maximum of 373 mg/dl. The mean level of LDL is 119.9 mg/dL (SD 49.6), with minimum value 36 mg/dL and maximum value 228 mg/dL.

Table 2. Angiographic Characteristics Based on Patient Gender

Sex	Angiography result				Total	
	SVD		MVD			
	n	%	n	%	n	%
Female	3	8,8	2	5,8%	5	14,7
Male	9	26,4	20	58,9%	29	85,3
Total	12	35,3	22	64,7	34	100

SVD: single vessel disease, MVD: multiple vessel disease

Table 2 shows the angiographic characteristics of patient gender. There were 3 female patients with SVD (8.8%) and 9 male patients with SVD (26.4%). Two out of 34 (5.8%) MVD patients were female, while 20 out of 34 (58.9%) were male.

The following is a bivariate analysis of the correlation between HbA1C, TG, and LDL levels and angiographic results in CHD patients:

Table 3. Correlation analysis between HbA1C, TG, and LDL levels and angiography results.

Spearman Correlation		Correlation Coefficient (r)	p-value
HbA1C	Coronary Angiography Result	0.402*	0.018
Triglyceride	Coronary Angiography Result	0.307	0.077
LDL	Coronary Angiography Result	-0.025	0.888

*Correlation is significant at the 0.05 level (2-tailed)

HbA1C   : haemoglobin glycated A1C

LDL   : low-density lipoprotein

There is a statistically significant relationship between HbA1C levels and patient angiography results, with an obtained p value of 0.018 (p < 0.05) and r = 0.402, as shown in Table 3. In contrast, the relationship between triglyceride levels and patient angiography results is not statistically significant, with an obtained p value of 0.077 (p>0.05) and r = 0.307. There is no statistically significant relationship between LDL levels and the results of angiography, as indicated by a p-value of 0.888 and a correlation coefficient of -0.025

DISCUSSION

Vessel disease is caused by atherosclerosis, which occurs due to the formation of plaques. Narrowing of coronary arteries due to atherosclerotic plaques can be classified as either single vessel disease (SVD) or multiple vessel disease (MVD). MVD tends to have a worse clinical outcome than SVD, with a more severe atherosclerotic process, poor endothelial dysfunction, increased platelet reactivation and thrombin activation.[19] In this study, MVD was more common, accounting for 64.7% of patients. The aforementioned discovery was also reported in a study conducted by Jiang Wang, et al. This study had a prevalent case of MVD, accounting for 65.1% of the patients.[20]

Another study by Anggi Yulianti, et al similarly reported a majority of patients with MVD.[21]

Most of the CHD patients in this study were male (85.3%) and also the majority of patients were male who suffered from MVD at 58.9%. These results are in line with research by Jiang Wang, et al which shows that male have MVD more often than female.[20] Research by Xiang Wang, et al also states that the majority of patients are male (69.02%).[6] Thus, based on these findings, it can be concluded that there is a higher incidence of CHD in male than in female, potentially due to lower levels of estrogen hormones found in male. Estrogen has cardioprotective abilities and reduces the risk of CHD in female. Estrogen plays a crucial role in maintaining and repairing the endothelium. In addition, estrogen regulates nitric oxide synthase (NOS) through the Phosphoinositide 3-kinase (PI3K) pathway, increasing nitric oxide levels that function as vasodilators, inhibitors of platelet aggregation and adhesion, and inhibitors of vascular smooth muscle cell proliferation.[22]

This study suggest that elevated HbA1C levels may lead to an increase in coronary artery stenosis. This finding aligns with previous research conducted by Mosin Ahmed, et al[18] and also supported by a study conducted by Jiayu Wang, et al that found a significant association between HbA1C levels and the severity of coronary heart disease (CHD).[20] Hyperglycemic conditions can contribute to the development of atherosclerosis, as residual advanced glycation end-products (AGEs) are formed from glucose, protein, nucleic acid, and lipid metabolism. AGEs accumulate in the vasculature and trigger a pro-inflammatory response since they are difficult to remove. Under hyperglycemia, the formation of AGEs impedes the reverse cholesterol transport, resulting in cholesterol retention in peripheral tissues. Additionally, hyperglycemia can decrease dilation and increase blood vessel constriction by reducing nitric oxide levels.[23]

In this study, there was no significant relationship between triglyceride levels and angiographic results of CHD patients. The results of this study are in line with research conducted by Katarina Noviyanti, et al[16] and research by Raheem Sharhah, et al.[24] Nevertheless, Jiayu Wang et al.'s (54) study reported different results regarding the association of triglycerides and the severity of coronary heart disease based on vessel disease.[20] Triglycerides can contribute to the development of atherosclerosis through the lipolysis process, which generates free fatty acids and monoglycerides. This leads to an increase in the concentration of cytotoxic free fatty acids. Subsequently, free fatty acids and their remnants trigger inflammatory mediators and proatherogenic adhesion molecules. Macrophages that secrete lipoprotein lipase to break down fats cause localized hydrolysis conditions and the remaining breakdown can produce cytotoxic and inflammatory effects. Furthermore, triglycerides can cause endothelial dysfunction and activate the coagulation cascade, leading to increased platelet aggregation and ultimately plaque formation.[25]

There was no statistically significant relationship between LDL levels and angiographic results of CHD patients. This study provides different results from the previous study conducted by Raheem Sharhah, et al which could be due to the insufficient number of patients studied.[24] This study did not collect treatment history and treatment duration, thus providing different results from previous study.[20] In that study, data on the use of drugs that can reduce lipid levels (hypolipidemic drugs) were also included. The use of hypolipidemic drugs, especially statins, may intervene the effect of LDL on the severity of CHD based on vessel disease.

This study has several limitations. Firstly, it is a single-center study. Secondly, patient medical record data at the research site was only available from 2020 onwards, which resulted in a small sample size since data from previous years could not be accessed. Third, the design of this study is cross-sectional, rather than cohort, which precludes the ability to track treatments involving drug administration and disease progression due to risk factors. And lastly, statistical results may be biased because this study did not collect treatment duration and doses of antiplatelet, antilipidemic, and antidiabetic drugs.

CONCLUSION

This case report demonstrates that although P. vivax infection is less likely to impact organ damage than p. falciparum. Also, it is rare to have vivax malaria related to cardiovascular manifestation. But as a tropical country and endemic area for malaria. We have to consider of cardiac complication when patients have chest pain in vivax malaria. By reducing level of parasitaemia, the cardiac symptom can be treated.

CONCLUSION

In conclusion, in this cross-sectional study, we found that HbA1C levels have a significant relationship with angiography results in CHD patients with a moderate positive correlation rate. LDL and TG levels did not show a statistically significant relationship.

Although triglyceride and LDL levels are not significantly associated with CHD severity as determined by coronary angiography, this does not negate the potential impact of triglycerides and LDL on the occurrence of CHD. Medical literature and studies indicate that triglycerides and LDL are risk factors that cause narrowing of the heart's blood vessels.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Tolvaptan Add-on Therapy for Diuretic Resistance Heart Failure (DR-HF): Systematic Review and Meta-analysis

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ARTICLE INFO

ABSTRACT

Introduction: Congestion on heart failure is a primary reason for emergency department admissions. Diuretic resistance is an indicator or predictor of mortality. The objective of this meta-analysis was to evaluate the effects of the addition of tolvaptan on diuretic resistance heart Failure (DR-HF).

Methods: Four electronic databases (PubMed, Science Direct, Cochrane Library and Google Scholars) were searched from their starting dates to June 30, 2023. We included randomized controlled trials (RCTs) to assess the efficacy and safety indicators for DR-HF patients. Efficacy indicators encompassed, changes in body weight, urine volume and relief of dyspnea by likert scale. Patient safety indicators encompassed worsening renal function (WRF) and mortality.

Results: Seven RCTs with a total of 1031 patients, were included for analysis.. Compared with the control, tolvaptan improve in reducing body weight (SMD −0.48, 95% CI −0.71 to −0.25, p < 0.00001, I2=64%), and increased urine volume (SMD 1.02, 95% CI 0.34 – 1.71, P = 0.003, I2 = 87%) from baseline, ameliorated symptoms of dyspnea in 48 h (RR 1.20; 95% CI 1.06 – 1.36, , P = 0.004, I2 = 0%). However, tolvaptan did not improve incidence of WRF (RR 0.71, 95% CI 0.38 to 1.33, p=0.29) and mortality (RR 0.96; 95% CI 0.49–1.87), with diuretic resistance heart failure.

Conclusion: This meta-analysis suggest that the addition of tolvaptan can improve the decrease of body weight, increase of urine volume, and relief of dyspnea, without exacerbate worsening renal failure and increase mortality in patients with diuretic resistance heart failure.

INTISARI

Pendahuluan: Kongesti pada gagal jantung merupakan penyebab utama masuk ke unit gawat darurat. Resistensi diuretik merupakan indikator atau prediktor mortalitas. Tujuan dari meta-analisis ini adalah untuk mengevaluasi efek penambahan tolvaptan pada gagal jantung resistensi diuretik (DR-HF) dan membandingkannya dengan efek terapi konvensional atau plasebo.

Metode: Empat database elektronik (PubMed, Science Direct, Cochrane Library, dan Google Scholars) ditelusuri dari tanggal mulainya hingga 30 Juni 2023. Kami menyertakan uji coba terkontrol secara acak (RCT) untuk menilai indikator kemanjuran dan keamanan untuk pasien DR-HF. Indikator kemanjuran meliputi perubahan berat badan, volume urin dan pengurangan dispnea berdasarkan skala likert. Indikator keselamatan pasien mencakup perburukan fungsi ginjal (WRF) dan kematian.

Hasil: Tujuh uji coba terkontrol secara acak dengan total 1031 pasien, dimasukkan untuk analisis. Dibandingkan dengan kontrol, tolvaptan

mengurangi berat badan dari baseline (SMD −0.48, 95% CI −0.71 hingga −0.25, p <0.00001, I2=64%), peningkatan volume urin (SMD 1.02, 95% CI 0.34 – 1.71, P = 0,003, I2 = 87%), dan perbaikan gejala dispnea dalam 48 jam (RR 1,20; 95% CI 1,06 – 1,36, , P = 0,004, I2 = 0%). Namun, tolvaptan tidak meningkatkan perburukan fungsi ginjal (RR 0,71, 95% CI 0,38 hingga 1,33, p=0,29) dan kematian (RR 0,96; 95% CI 0,49–1,87), pada gagal jantung resisten diuretik.

Kesimpulan: Meta-analisis ini menunjukkan bahwa penambahan tolvaptan dapat meningkatkan penurunan berat badan, peningkatan volume urin, dan menghilangkan dispnea, tanpa memperburuk gagal ginjal yang memburuk dan meningkatkan mortalitas pada pasien dengan gagal jantung yang resistan terhadap diuretik.

INTRODUCTION

Heart Failure (HF) is a disorder due to a problem in the structure of the heart or heart function so that it cannot distribute oxygen throughout the body.[1] HF is a terminal cardiac condition that significantly contributes to morbidity and mortality and continues to be a major global health concern, impacting 26 million individuals worldwide.[2] Congestion is the primary reason for emergency department admissions among patients experiencing acute heart failure (AHF), although the degree of decongestion varies significantly among individuals. In a European study, 83% of hospitalized patients with AHF had manifestations of congestion.[3] The present guidelines for heart failure recommend loop and/or thiazide diuretics to alleviate clinical manifestations of congestion in patients.[4,5]

A large cohort study found a prevalence of diuretic resistance (DR) of 21% in elderly patients admitted to hospital with acute decompensated heart failure (ADHF). The exact prevalence of DR remains uncertain, primarily due to the absence of a universally agreed-upon definition. Nonetheless, DR can serve as an indicator or predictor of mortality.[6] Failure to achieve effective reduction of congestion despite receiving or increasing the dose of diuretics is referred to the general definition of DR.[7,8,9] Other definition of DR as diuretic response by bodyweight change ≤ 2.7 kg or production of urine <1400 ml after 40 mg furosemide (or equivalent).[10] Tolvaptan act as a competitive vasopressin V2 receptor antagonist, operating distally to the nephron. By inhibiting the interaction between antidiuretic arginine vasopressin hormone and V2 receptors, it effectively preventing the activation of the aquaporin channel system, resulting in a net excretion of free water.[11]

This analysis was aimed to evaluate and compare the effects of the addition of tolvaptan on DR-HF patients to conventional therapy or placebo.

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This analysis was aimed to evaluate and compare the effects of the addition of tolvaptan on DR-HF patients to conventional therapy or placebo.

METHODS
Search strategy / Data sources and search

A systematic electronic search method was utilized to filter and explore randomized controlled trials (RCTs) investigating the efficacy of adding tolvaptan in treating heart failure with diuretic resistance. The searches were performed on PubMed, Cochrane Library, Science Direct, and Google Scholar to identify relevant studies. The search for published sources up to June 30, 2023, focusing on full-text publications that are relevant to the study and written in English. Some of the keywords used in the study search are "Tolvaptan", "Heart Failure", "Congestive Heart Failure", Acute Heart Failure", and "Diuretic Resistance". Publications obtained from these keywords were subjected to duplicate removal using the Zotaro application. Following this, the suitability of inclusion or exclusion in this study was assessed based on predetermined criteria by

carefully screening the titles to abstracts of the remaining publications.

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, ensuring a structured and comprehensive approach to the research process.[12]

Study selection

All RCTs concerning the treatment of patients with DR-HF were identified and evaluated. The focus was on using tolvaptan as a diuretic adjunct, typically combined with a loop diuretic, to address CHF. Publications excluded from the review were: observational studies, conference abstracts, reviews, editorials, medical reports, retrospective clinical trials, protocols, non-human studies, policy statements, and guidelines. Additionally, studies lacking relevant data were also excluded.

Data estraction and quality assessment

The first assessment is carried out by three investigators (DSA, SP and APK), then will be supervised by the fourth investigator (FP). The results of the assessment of the selected publications will be extracted from the outcome results and independent variables carried out by the same investigator. Any disagreements were resolved through discussion. On this basis, local ethics approval was not required. The methodological quality of each study was assessed using Cochrane's revised risk of bias tool for randomized controlled trials (RoB 2), ensuring a comprehensive evaluation of the research methods used.

Qualitative analysis

Demographic data, details regarding the study's design and information about the diuretic drugs and control groups under investigation were collected. RCTs gathered essential information, including the initial author, publication year, sample size, patient details, criteria for diuretic resistance, follow-up duration, study outcomes, and region. Efficacy measures included changes in body weight and urine volume observed from the beginning of trials to the point of discharge. Also we analyzed relief of dyspnea by likert scale of 48 hour treatments. Patient safety indicators encompassed worsening renal function (WRF) and mortality.

Statistical analysis

We used RevMan 5.4.1 to conduct the procedures of meta-analytic. We chose the standardized mean difference (SMD), risk ratio (RR) and 95% confidence interval (95% CI) were calculated according to the intention-to-treat principle. Statistical significance was determined with $P < 0.05$.

To measure between-study heterogeneity, we utilized the I^2 tests to calculate the fraction of total variance due to between-study variation. The inverse variance (IV) fixed-effect or random-effect model was employed base on the heterogeneity. Sensitivity analysis was performed to confirm data stability and assess publication bias using funnel plots.

Result

Three-hundred forty-one articles were found from the database: 36 of PubMed, 18 of Science Direct, 96 of the Cochrane Library and 191 of the Google Scholars, also thirteen articles got from citation searching. Total 354 article were retrieved based on the established search. Seven article were included to the analysis after assessing the inclusion and exclusion criteria. The flowchart of study selection is shown in Figure. 1.
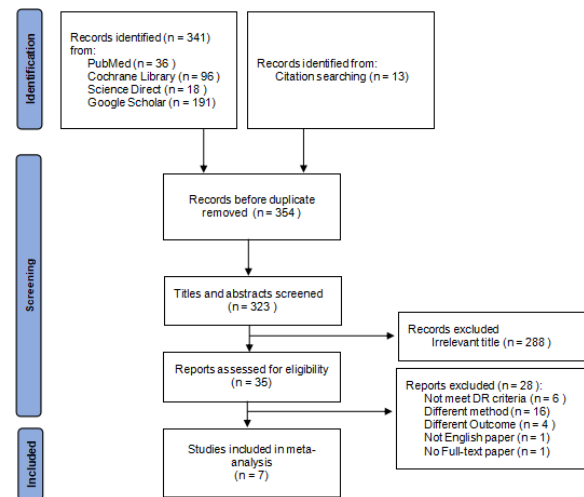

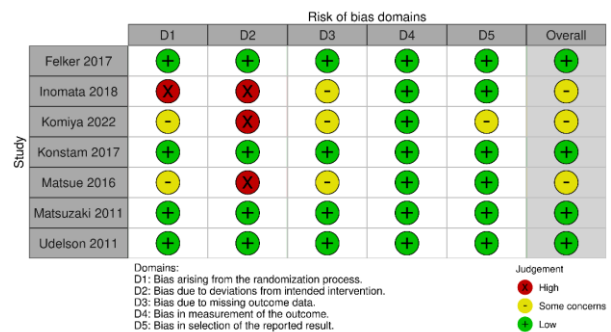Figure 1. A flowchart of patients selection in our study

Study characteristics quality

Table 1 displays information from seven randomized controlled trials conducted in the USA and Japan, involving a total of 1031 patients. The duration of follow-up study ranged from 3 to 8 days. All of the studies include participants with at least one sign/symptoms of fluid retention.[16-22] Three of studies focuses on the AHF patients.[16, 19, 20] Six out of seven studies define DR as congestion or volume overload despite the use of daily diuretic or conventional therapy with diuretic.[16-18, 20-22] Konstam et al[19] define DR as urine output ≤125 ml/h during the initial 8 h after administration IV diuretics.

Table 1. Baseline characteristics of patients included in our study

Study /year /reference	Population	Sample	Definition	Initial Treatment	Dose Considered	Follow up	Main Outcome	Location
Felker et al 2017[13]	Patients with AHF	257	Congestion signs despite taking daily diuretics	Furosemide	40 mg	72 h	Dypsnea relief (likert scale), renal function, body weight, fluid loss, worsening HF and 30 day mortality	USA
Inomata et al 2018[14]	HF patients with fluid retention	81	Congestion signs despite taking daily diuretics	Furosemide or equivalents	≥ 40 mg	7 d	Urine Output, Body weight, congestive sign and symptoms, WRF	Japan
Komiya et al 2022[15]	HF patients with fluid retention	33	Congestion signs despite taking daily diuretics	Furosemide	20-100 mg	3 d	Urine volume, WRF, body weight, serum sodium	Japan
Konstam et al 2017[16]	Patients with AHF	250	urine output ≤125 ml/h during any ≥2-h period during the initial 8 h after administration IV diuretics	Furosemide or equivalents	40 mg	7d	Dyspnea relief (likert scale), body weight, WRF, diuretic doses death or rehospitalization for HF through 30 days	USA
Matsue et al 2016[17]	AHF patients with renal dysfunction	217	Congestion signs despite taking daily diuretics	Furosemide	Not specified	48 h	Urine output, bodyweight, WRF	Japan
Matsuzaki et al 2011[18]	HF patients with fluid retention	110	Volume overload despite the use of conventional diuretics	Furosemide	≥ 40 mg	7 d	Body weight, congestive symptoms, urine volume, serum electrolyte	Japan
Udelson et al 2011[19]	Patients with diagnosis of HF (NYHA II or III)	83	Volume overload despite the use of conventional therapy include diuretic	Not specified	Not specified	8 d	Bodyweight, urine volume, urine sodium and potassium	USA

We use RoB 2 to assess the potential bias in the study with the majority of items in the tool were deemed to carry low risk, although a few studies lacked sufficient information about specific items, suggesting that the RCTs included in the meta-analysis were of relatively high quality (Figure 2).
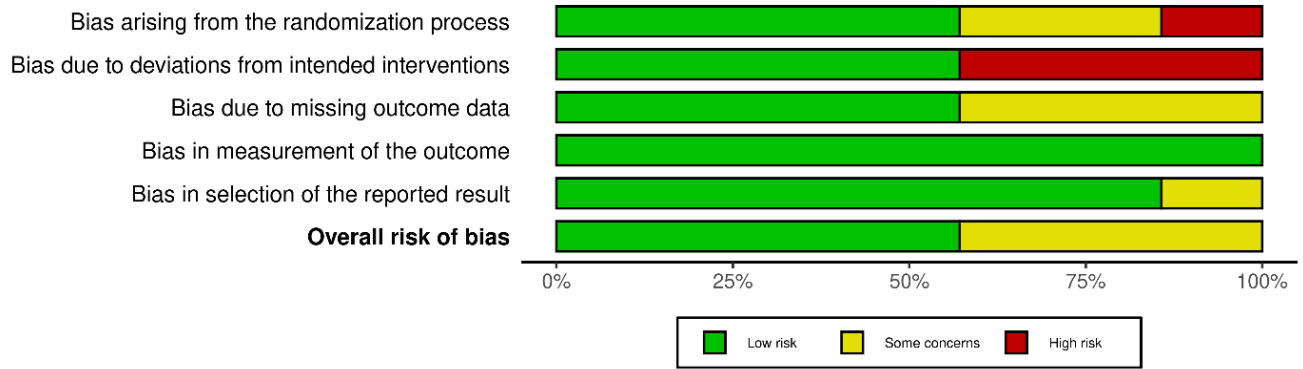

Risk of bias domains

Study	D1	D2	D3	D4	D5	Overall
Felker 2017	+	+	+	+	+	+
Inomata 2018	X	X	-	+	+	-
Komiya 2022	-	X	-	+	-	-
Konstam 2017	+	+	+	+	+	+
Matsue 2016	-	X	-	+	+	-
Matsuzaki 2011	+	+	+	+	+	+
Udelson 2011	+	+	+	+	+	+

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
● High
- Some concerns
+ Low

Figure 2. Risk of bias summary.

Effect of add-on tolvaptan on body weight

Six studies[13,14, 16-19] were evaluate the changes of body weight from the baseline in this meta-analysis. The tolvaptan add-on therapy group shows significant difference in body weight change against the control group (SMD −0.48, 95% CI −0.71 to −0.25, p < 0.00001, I^2 = 64%) (Figure 3).
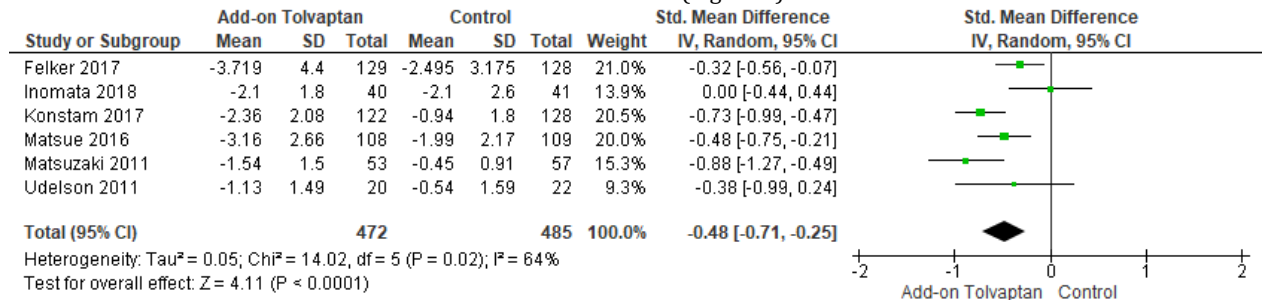

Figure 3. Forest Plot of change body weight from baseline

Effect of add-on tolvaptan on urine volume

In these studies, conventional therapy was found to be worse than add-on tolvaptan therapy at increasing urine volume for patients with DR-HF (SMD 1.02, 95% CI 0.34 – 1.71, $P = 0.003$, I^2 = 87%)[21-23] (Figure 4).
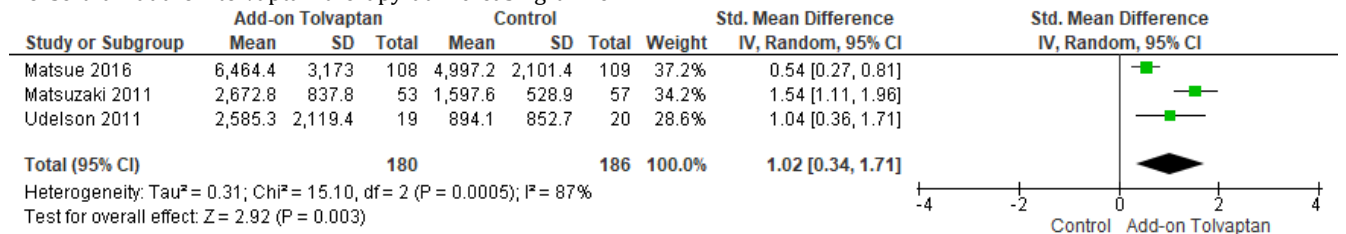
Figure 4. Forest plot of urine volume

Effect of add on tolvaptan on dyspnea relief

There three studies[13,16,17] demonstrated the effect of add-on tolvaptan on dyspnea improvement by Likert scale at 48 h. The result showed statistical significance (RR 1.20; 95% CI 1.06 – 1.36, $P = 0.004$, I^2 = 0%) of the dyspnea improvement (Figure 5).

Figure 5. Forest plot of dyspnea relief by likert scale

Effect of add on tolvaptan on worsening renal failure

Meta-analysis (random effect model) have analyzed the effect of tolvaptan add-on therapy compared with conventional therapy on the incidence of WRF in patients with DR-HF. Four studies[13-15,19] showed tolvaptan add-on therapy had no significant incidence of WRF (RR 0.71, 95% CI 0.38 to 1.33, p=0.29) in DR-HF patients (Figure 6).
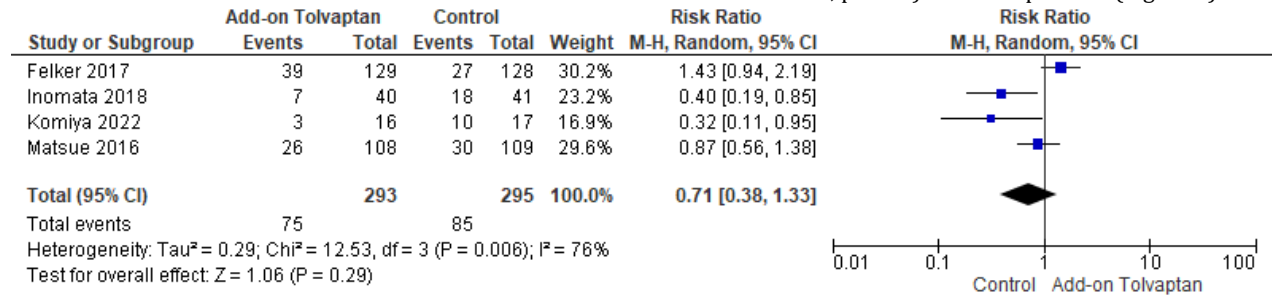

Figure 6. Forest plot of incidence worsening renal failure

Effect of add on tolvaptan on mortality

Three studies[13,16,19] reported the incidence of mortality of DR-HF patients after add-on tolvaptan therapy. Compared with the control, tolvaptan had no benefit on reducing incidence of mortality (RR 0.96; 95% CI 0.49–1.87) in patients with DR-HF (Figure 7).
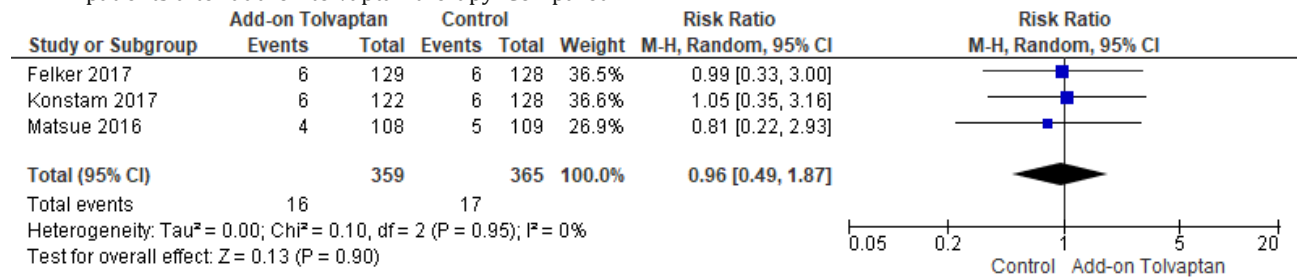

Figure 7. Forest plot of mortality

All outcomes displayed publication bias in the funnel plots (Figures 8-12). Sensitivity analyses were conducted to investigate the influence of individual studies on the overall risk estimate and assess study stability. These analyses revealed no substantial differences, indicating the consistency and reliability of the results.
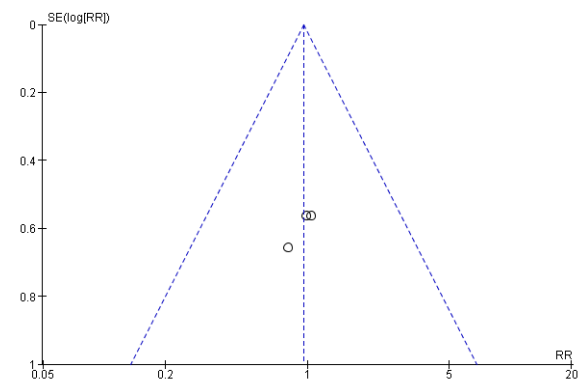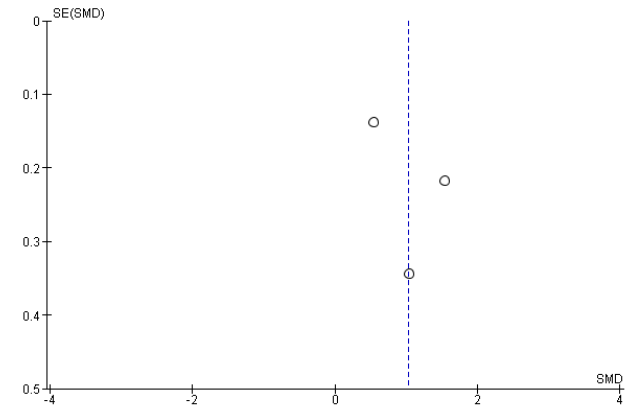

Figure 9. Funnel Plot of Urine Volume

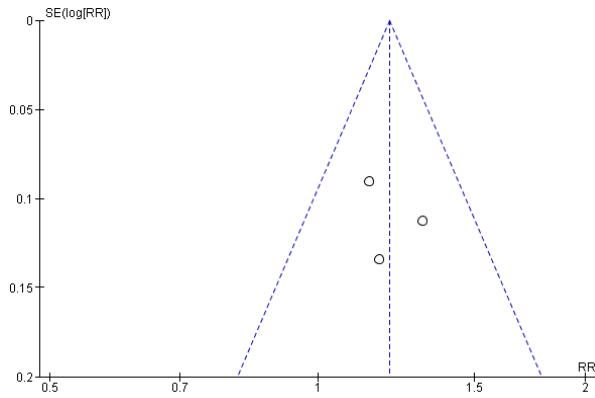Figure 8. Funnel Plot of Change of Bodyweight

Figure 10. Funnel Plot of Dyspnea Relief by Likert Scale
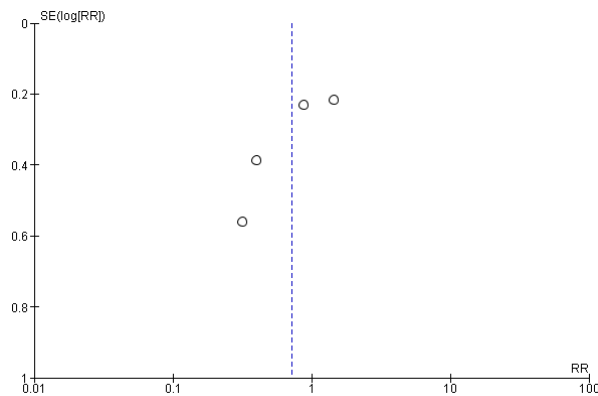

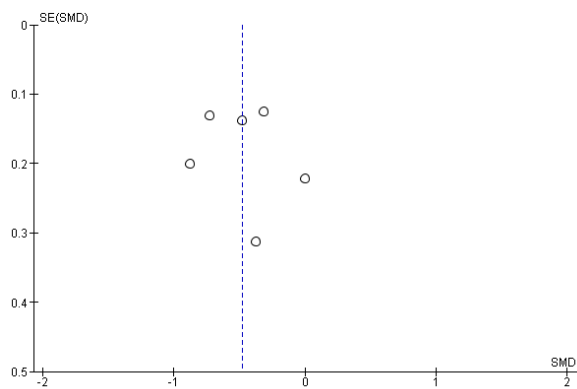Figure 11. Funnel Plot of Worsening Renal Failure

Figure 12. Funnel Plot of Mortality

DISCUSSION

The main findings of this study indicate that add-on tolvaptan therapy for DR-HF is more effective than the use of conventional therapy. This meta-analysis found that there is significant change of reduction of body weight, increase urine volume and ameliorate dyspnoea in patients with DR-HF. Also, adding tolvaptan with diuretic won't increase incidence of WRF. DR often leads to hospitalization due to congestion and worsening symptoms, but it can be prevented or reversed. A suboptimal response to diuretics serves as an indicator for potential adverse outcomes, such as subsequent mortality, hospital readmissions, or renal complications from congestive heart failure (CHF).[20] Weight reduction in the initial stages of AHF hospitalizations is notably linked to the absence of congestion within 72-96 hour. Furthermore, this early weight loss is modestly connected to a decreased likelihood of mortality, subsequent hospital readmission, or unplanned hospital visits during the 60-day period following discharge.[21]

Initiating decongestion promptly may enhance overall clinical results. In a study, patients who achieved a targeted urine volume (100 ml/h) within less than 24 hours exhibited reduced rates of all-cause mortality and readmissions in one-year, along with decreased incidence of WRF and shorter hospital stays. Furthermore, the administration of tolvaptan in the early setting was associated with achieving urine output target.[22] In a study by Komiya et al[15], also indicate adding tolvaptan with furosemide had significant increase the urine volume compared with increasing dose of furosemide. In this meta-analysis, adding tolvaptan had higher urine volume than the control group.

Dyspnea is the common initial symptom observed in individuals admitted to the hospital due to AHF.[23] A meta-analysis that analyzed the impact of tolvaptan on patients with AHF reached a conclusion that tolvaptan could significantly improve of dyspnea within the initial 12 hours and lasting through the 72-hour.[24] Furthermore, adding tolvaptan with standard therapy associated with modest amelioration of dyspnea when contrasted with standard therapy alone, particularly during the initial 12 hours after the first dose administration.[25] Result of this meta-analysis also demonstrated favorable outcomes in the improvement of dyspnea, as assessed using the Likert Scale.

Clinical trial findings indicate that the use of tolvaptan with loop diuretics is well received among congestive heart failure patients. This combined approach not only effectively reduces congestion-related symptoms but also ensures an adequate urine output, resulting in a reduction of loop diuretic dosage.[26] Administration of this medication must be used with supervision to prevent worsening renal failure at high doses.[27] In a previous meta-analysis, administration of low doses of tolvaptan with conventional therapy indicate have a role in protecting renal function correlating with a lower incidence of WRF compared to conventional diuretics alone.[28] In our analysis, adding Tolvaptan had no effect on increasing the incidence of WRF for patients with DR-HF. The findings indicate tolvaptan have a promising treatment option for individuals with DR-HF, possibly offering a protective effect on the kidneys.[29] In this meta-analysis also got the incidence of mortality stay had no statistical significance. As CHF progresses, patients usually require higher doses of diuretics. The associate between high diuretic doses and higher mortality rates indicates that diuretic resistance should be recognized as a prognostic factor for patients with chronic CHF.[30] Tolvaptan which known for its ability to induce aquaretic effects, also proves effective in decongestion. A retrospective study analysis for ADHF patients treated with

Tolvaptan revealed that its early administration resulted in reduced mortality rates.[31]

Our meta-analysis have many potential limitations should be considered. First, lack of definition diuretic resistance made different definition of diuretic resistance in each study. Second, limited number of RCTs analyze of diuretic resistance available for the meta-analysis. Only three included selected trials measured urine volume and incidence of worsening renal failure and limited study descript of incidence of mortality. Third, variations in the duration of Tolvaptan usage, dosage, and follow-up periods across the included studies could potentially impact the clinical outcomes.

CONCLUSION

This meta-analysis suggest that the addition of tolvaptan can improve the efficacy of conventional therapy by decrease body weight, increase urine volume, and ameliorate dyspnea, without exacerbate worsening renal failure and increase mortality in patients with diuretic resistance heart failure.

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DISCLOSURES AND ETHICS

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