Meta-Analysis

MORTALITY AMONG HEART FAILURE PATIENTS IN THE PRESENCE OF CACHEXIA

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ABSTRACT

Despite the fact that obesity has long been recognized as a risk factor for cardiovascular disease, the mortality rate of heart failure (HF) patients with cachexia is still high. Several studies have been conducted to investigate the association between cachexia and mortality in HF patients. However, the research results vary, as do the diagnostic criteria employed to assess cachexia. This meta-analysis aimed to conclusively summarize the association between cachexia and mortality in HF patients. The data were obtained from prospective or retrospective cohort studies with full texts in English or Indonesian and keywords related to "cachexia," "heart failure," and/ or "mortality". Studies that did not assess mortality in HF patients with cachexia and had no full text accessible were omitted. A literature search was conducted through four databases (PubMed, Web of Science, Scopus, and SAGE Journals) using keywords, reference searches, and/ or other methods on April 2022 in accordance with the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Data from the selected studies were presented and analyzed using qualitative and quantitative synthesis methods. The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias in the selected cohort studies. The qualitative synthesis contained nine studies, whereas the quantitative synthesis (meta-analysis) included six studies. Cachexia was found in 16.0% of the 4,697 patients studied. During the 180-1,876-day follow-up period, 33.0% of the patients died, with a mortality rate of 38.8% among the patients with cachexia. The pooled analysis revealed cachexia to be a significant predictor of mortality in HF patients (hazard ratio (HR)=3.84; 95% CI=2.28-6.45; p<0.00001), but with significant heterogeneity (p<0.00001; I^2=88%). In conclusion, cachexia worsens HF prognosis.

Keywords: Cachexia; heart failure; cardiovascular disease; mortality; well-being

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Highlights:

1. Around 38.8% of heart failure patients with cachexia died during the 180-1,876-day follow-up period.
2. Cachexia increases the risk of mortality in heart failure patients.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome caused by structural or functional problems with ventricular filling or blood ejection (Ponikowski et al. 2016). HF patients may experience a variety of symptoms, including breathlessness, decreased exercise tolerance, and ankle swelling. This may be accompanied by signs such as elevated jugular venous pressure, gallop rhythm, pulmonary crackles, and peripheral edema (Yancy et al. 2013, Ponikowski et al. 2016, Bangsa et al. 2021). HF frequency varies greatly across the world, but its mortality rate remains around 50% following five years of diagnosis (Yancy et al. 2013, Virani et al. 2021).

Obesity and overweight are defined as abnormal fat

accumulations that can be risk factors for the development of a variety of diseases. Obesity has long been recognized as a risk factor for any cardiovascular-related diseases (Yancy et al. 2013, Ponikowski et al. 2016). However, many studies have found substantial evidence of an obesity paradox, in which being overweight or obese leads to a better prognosis for HF patients than being normal or underweight (Valentova et al. 2016, Carbone et al. 2017). Several factors were assumed to be responsible for how this obesity paradox occurred, with cachexia in HF patients being the most plausible (Carbone et al. 2017). Cardiac cachexia is a condition that is exacerbated by cardiac obesity.

Cachexia is a metabolic syndrome characterized by involuntary and severe loss of edema-free muscle mass, which may or may not be accompanied by a reduction in fat mass. It appears following chronic diseases such as cancer and other inflammatory conditions (such as heart failure). Clinical manifestations of cachexia include skeletal muscle wasting, anemia, anorexia, and altered immune function, all of which contribute to fatigue, decreased quality of life, and decreased survival (Pureza & Florea 2013).

Cachexia includes rare conditions in which fat accumulation becomes protective rather than a risk factor (Selthofer- Relatić et al. 2019). Cardiovascular visceral obesity refers to fat accumulation in the heart, which includes intramyocardial fat, epicardial adipose tissue, and cardiac steatosis. It has been associated to the development of ischemic cardiomyopathy, cardiac microcirculatory dys-function, hypertension, atrial fibrillation, athero-sclerosis, and diabetic cardiomyopathy, but it reduces the risk of cardiac cachexia in heart failure (Soto et al. 2022).

Cachexia is diagnosed when there is a 5% weight loss in <12 months or a a body mass index (BMI) of <20 kg/m2, an underlying chronic disease, and at least three of five other criteria are met (Farkas et al. 2013, Vanhoutte et al. 2016). Cachexia incidence was observed in the majority of significant diseases, including infection, cancer, heart disease, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and stroke (Farkas et al. 2013). The prevalence of cachexia ranged between 0.5-1% in the general population of the United States, Europe, and Japan. Cachexia happens in 5-15% heart failure patients, with 20-40% death rates each year (Haehling et al. 2016). Global epidemiological data are still scarce and uneven in many parts of the world. Given the extremely high mortality rate among HF patients with cachexia, more research and development are urgently required.

Several observational studies on the association between cachexia and mortality in HF patients have been conducted (Castillo-Martínez et al. 2012, Saboe et al. 2015, Sato et al. 2020, Song et al. 2014). However, the studies employed different diagnostic criteria to assess cachexia, and the results were varied. Therefore, this meta-analysis was carried out to conclusively summarize the association between cachexia and mortality among HF patients.

MATERIALS AND METHODS

A literature search was performed using key concepts of “cachexia”, “heart failure”, and “mortality”. The comprehensive literature search was conducted in April 2022 through four databases (PubMed, Web of Science, Scopus, and SAGE Journals) using reference searches, citation matching, and/ or other search methods in accordance with the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al. 2021). During the literature search, no limitations on language or publication year were applied. A filter for "observational study" was utilized in the Pubmed database search.

The studies were selected independently by three people, i.e., the second author with the assistance of two other capable individuals, using inclusion and exclusion criteria. Disagreements in opinion among the researchers were discussed until an agreement was reached. The PRISMA flowchart documented the study selection process and the reasons for the study selection (Page et al. 2021).

The following criteria were employed for the literature search in this study: studies with a prospective or retrospective cohort study design and full text in English or Indonesian. The selected literature investigated adult patients (over 18 years old) with a heart failure diagnosis, as well as the intervention or exposure to cachexia based on any diagnostic criteria and/ or assessment setting. The literature also included studies comparing patients with and without cachexia and studies that had mortality outcomes from any diagnostic criteria and/ or measurement setting in any follow-up period. Studies that did not discuss mortality in patients with cachexia were omitted.

The following data were extracted from the selected studies: first author, publication year, region or country, title of study, population, study design, diagnostic criteria of cachexia, mean age, sex ratio, mean BMI, follow-up period, number of samples, number and proportion of patient with cachexia, and mortality assessment results. For the seelcted cohort studies, the Newcastle-Ottawa Scale (NOS) was employed to assess the risk of bias. Each study was

required to meet three criteria (selection, comparability, and outcomes). The study's quality would be rated "good" if the NOS assessment scores were 3 or 4 stars in selection, 1 or 2 in comparability, and 2 or 3 in outcomes; "fair" if the scores were 2 stars in selection, 1 or 2 in comparability, and 2 or 3 in outcomes; or "poor" if the scores were 0 or 1 star in selection, 0 in comparability, and 0 or 1 in outcomes (Sharmin et al. 2017).

The extracted data from the selected research were summarized and narratively presented using text and tables. A meta-analysis was performed to analyze the hazard ratio (HR) for mortality outcomes in HF patients with and without cachexia, which was reported with 95% confidence intervals (CI). The pooled analytic data included HR value and lower 95% CI, or β-coefficient as log (HR) value and standard error (SE) (Centre for Evidence-Based Medicine 2023). A random-effects model was applied due to the high heterogeneity, which was calculated using the I^2 statistical test. It would be considered statistically significant if $p<0.05$ (Higgins et al. 2022). This meta-analysis employed the Review Manager software version 5 (Cochrane), also known as RevMan 5. The protocol of this meta-analysis has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the title "Association between Cachexia and Mortality in Heart Failure Patients: A Systematic Review" (ID: CRD42022315507).

RESULTS

A total of 844 titles and abstracts were found, 832 through database searches and 12 through reference searches, citation matching, and/ or other search method. Following the removal of duplicates (n=172), 672 titles and abstracts were screened using the inclusion and exclusion criteria. A total of 640 titles and abstracts were eliminated as irrelevant, leaving 32 titles and abstracts for which full text was retrieved. After removing 23 studies for various reasons (listed in Figure 1), the remaining studies that met the inclusion criteria were 9 studies for the qualitative synthesis and 6 studies for the quantitative synthesis (meta-analysis). The PRISMA flowchart outlined the overall selection process and reasons for exclusion.

Among the nine investigations included, two were conducted in the United Kingdom (UK) (Sze et al. 2018), two in Japan (Sato et al. 2020, Kamisaka et al. 2021), and the others in Portugal (Araújo et al. 2011), Mexico (Castillo-Martínez et al. 2012), Indonesia (Saboe et al. 2016), South Korea (Song et al. 2014), and Poland (Sobieszek et al. 2021). Most of the studies (n=8) were prospective cohort studies, with one being a retrospective cohort study. Seven studies selected subjects with chronic HF criteria, two of which specifically indicated stable chronic HF, and two studies recruited subjects with decompensated HF and acute or aggravated HF. The total number of participants gathered from those studies was 4,697, with each study having 39-1,480 subjects. Tables 1 and 2 provide summaries of all studies covered.

Most studies recruited elderly patients (≥60 years old), with only a few pre-elderly participants (45-59 years old). Six studies found that cachexia patients were typically older, while three additional studies found the opposite. The proportion of male participants was higher in the cachexia (n=3), without cachexia (n=2), and both (n=3) groups, while one research solely recruited male patients. In eight studies, the median and mean BMI of patients with cachexia ranged from 18.2 to 28.6, making them slimmer than patients without cachexia, who had a BMI of 21.1 to 30.4. Six of the eight studies found that patients with cachexia had a lower BMI than those without cachexia.

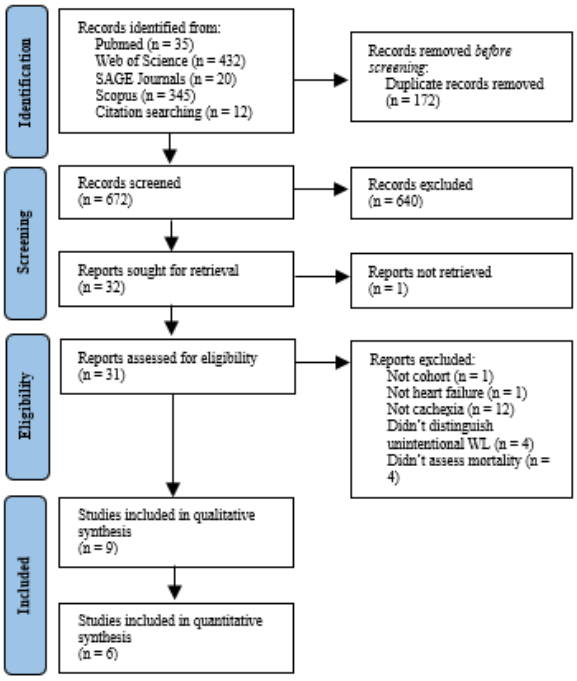

Figure 1. Flowchart of literature selection process and reasonsfor the excluded studies.

Table 1. Characteristics of the selected studies for this meta-analysis.

First author, publication year Country	Study title Population (P) Study design	Diagnostic criteria of cachexia	Age (y/o) Gender (M/F) BMI (kg/m^2)*		Follow-up period***
			Non-cachexia	Cachexia	
Anker, 1997 London, UK	Wasting as independent risk factor for mortality in chronic heart failure P: chronic heart failure patients Prospective cohort	Non-edematous and non-intentional weight loss of more than 7.5% of the previous normal non-edematous weight over a period of at least 6 months.	60±10 88.8% -	65±12 96.4% -	688±317 days
Araújo, 2011 Porto, Portugal	Nutritional markers and prognosis in cardiac cachexia P: stable chronic heart failure patients Prospective cohort	Non-edematous and non-intentional weight loss of more than 7.5% of the previous normal non-edematous weight over a period of at least 6 months.	72±11 66% 24.8±2.8	71±14 66% 23.2±3.0	486±174 days (16.2±5.8 months)
Castillo-Martínez, 2012 Mexico City, Mexico	Cachexia assessed by bioimpedance vector analysis as a prognostic indicator in chronic stable heart failure patients P: stable chronic heart failure patients Prospective cohort	Patients with vectors out of the 95% tolerance ellipse of the reference population at the lower right quadrant on BIVA evaluation as an assessment of lean body mass.	59.6±15.8 48.6% 30.4±7.2	67.2±16.4 65.8% 26.2±5.6	870±330 days (29±11 months)
Kamisaka, 2021 Nagoya, Japan	Impact of weight loss in patients with heart failure with preserved ejection fraction: Results from the FLAGSHIP study P: acute or exacerbated heart failure patients Prospective cohort	Non-obese patients with ≥5% weight loss within 6 months from discharge	81.0 (75.0-86.0)** 49.1% 21.1 (18.9-22.7)**	81.0 (72.5-86.0)** 63.3% 21.6 (19.6-22.9)**	540 days (18 months)
Saboe, 2015 Bandung, Indonesia	Cardiac cachexia and its impact on survival in heart failure patients P: chronic heart failure patients Retrospective cohort	Basic of chronic disease and weight loss >5% in 12 months or BMI <20 kg/m2 plus at least 3 of 5 criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, abnormal biochemistry[a]	59±9 30.3% 23.10±3.18	49±17 83.3% 18.39±0.89	180 days (6 months)
Sato, 2020 Fukushima, Japan	Prognostic factors in heart failure patients with cardiac cachexia P: decompensated heart failure patients Prospective cohort	Combination of BMI < 20 kg/m2 and at least one of the biochemical abnormalities[a]	68.0 (58.0-76.0)** 62.3% 23.4 (21.5-26.0)**	76.0 (67.0-81.0)** 48.9% 18.2 (17.2-19.1)**	1295 days
Sobieszek, 2021 Lublin, Poland	Soluble ST2 proteins in male cachectic patients with chronic heart failure P: chronic heart failure patients Prospective cohort	≥5% weight loss or more in 12 months or less due to underlying illness, plus three of the following criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, abnormal biochemistry[a]	72±14 100% 29.61±5.0	75±12.5 100% 28.27±6.6	1800 days (60 months)
Song, 2014 Seoul, South Korea	The link of unintentional weight loss to cardiac event-free survival in patients with heart failure P: chronic heart failure patients Prospective cohort	Weight loss greater than 6% of discharge body weight within 6 months in the absence of dieting or other primary causes	59±15 64.4% 24.1±3.4	68±7 40% 23.5±4.6	360 days (12 months)
Sze, 2018 Kingston upon Hull, UK	Effect of beta-adrenergic blockade on weight changes in patients with chronic heart failure P: chronic heart failure patients Prospective cohort	Weight loss of >6% between baseline and 1 year.	Increased weight: 70 (62-77)** 71% 25.9 (22.9-29.2)** Fixed weight: 72 (64-78)** 78% 27.9 (24.9-31.1)**	Decreased weight: 73 (66-78)** 68% 28.6 (24.8-32.7)**	1876 days

[a]: elevated inflammatory markers (CRP >5.0 mg/L), anemia (Hb < 12 g/dL), and/or low serum albumin levels (< 3.2 g/dL)
*: data is presented in average and/ or percentage except for 3 studies (**) which are presented in median (interquartile range)
***: follow-up periods are presented in days with an assumption of conversion for 1 month=30 days
BMI: body mass index, JVP: jugular venous pressure, ICU: intensive care unit, ESRD: end-stage renal disease, AIDS: acquired immunodeficiency syndrome, BIVA: bio-impedance vector analysis, DM: diabetes mellitus, EF: ejection fraction

Table 2. Data from the mortality assessment of patients with and without cachexia.

Study	N	Cachexia	Non-cachexia	Mortality*		Other Mortality Assessment Results
				Cachexia	Non-cachexia	
Anker, 1997	171	28 (16.4%)	143 (83.6%)	14 (50%)	35 (24.5%)	Cachexia is a predictor for all-cause mortality (HR=3.73, 95% CI: 1.93–7.23, P=0.0003)
Araújo, 2011	94	38 (40.4%)	56 (59.6%)	15 (39.4%)	6 (10.7%)	–
Castillo-Martínez, 2012	519	196 (37.8%)	323 (62.2%)	39 (19.9%)	38 (11.7%)	BIVA-cachexia is an independent predictor for mortality (β=0.504, SE=0.234, β coefficient=1.66, 95% CI: 1.05-2.62, P=0.03)
Kamisaka, 2021	452	49 (10.8%)	403 (89.2%)	17 (34.7%)	9 (2.2%)	Cachexia was a risk factor for all-cause death (HR=4.85, 95% CI: 2.15-10.81, P<0.01)
Saboe, 2015	39	6 (15.4%)	33 (84.6%)	5 (83.3%)	9 (27.3%)	Cardiac cachexia is an independent predictor for mortality (HR=50.95, 95% CI: 6.98 – 372.08, P<0.001)
Sato, 2020	1608	176 (10.9%)	1432 (89.1%)	98 (55.7%)	321 (22.4%)	Cardiac cachexia predicts all-cause mortality (HR=3.246, 95% CI: 2.587–4.071, P<0.001)
Sobieszek, 2021	91	40 (44%)	51 (56%)	19 (47.5%)	12 (23.5%)	Patients with cachexia and unfavorable factors have mortality risk for almost 7-fold higher (HR=6.89, P<0.001)
Total	2974	533	2441	207 (38.8%)	430 (17.6%)	
				637 (21.4%)		
Song, 2014	243	35 (14.4%)	208 (85.6%)	20 (8.2%)		Cachexia predicted cardiac-related death and re-hospitalization (HR=3.17, 95% CI: 1.84-5.45, P<0.001)
Sze, 2018	1480	185 (12.5%)	1295 (87.5%)	894 (60%)		Cachexia is an independent predictor for all-cause mortality (HR=1.62, 95% CI: 1.30-2.02, P<0,001)
Total	4697	753 (16.0%)	3944 (84.0%)	1551 (33.0%)		

*Mortality percentage was calculated independently by each group (cachexia and non-cachexia)
N: number of samples, HR: hazard ratio, CI: confidence interval, P: Pearson value, SE: standard error

Table 3. Risk of bias assessment of the selected studies.

	Exposure					Comparability		Outcome				
	Representativeness of the exposed cohort (*)	Selection of the non-exposed cohort (*)	Ascertainment of exposure (*)	Outcome of interest was not present at start of study[a] (*)	Total (*****)	Comparability of cohorts on the basis of the design or analysis (**)	Total (**)	Assessment of outcome (*)	Was follow-up long enough for outcomes to occur (*)	Adequacy of follow up of cohorts (*)	Total (****)	Quality score
Anker, 1997	*	*	*	-	***	*	*	*	*	*	***	Good
Araújo, 2011	*	*	*	-	***	-	-	*	*	*	***	Poor
Castillo-Martínez, 2012	*	*	*	-	***	*	*	*	*	-	**	Good
Kamisaka, 2021	*	*	*	-	***	**	**	*	*	*	***	Good
Saboe, 2015	*	*	*	-	***	**	**	*	*	-	**	Good
Sato, 2020	*	*	*	-	***	**	**	*	*	-	**	Good
Sobieszek, 2021	*	*	*	-	***	*	*	*	*	-	**	Good
Song, 2014	*	*	*	-	***	**	**	*	*	*	***	Good
Sze, 2018	*	*	*	-	***	-	-	*	*	-	**	Poor

[a]In the case of mortality studies, outcome of interest is still the presence of a disease/incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

Table 1 summarizes the various diagnostic criteria employed to assess cachexia in the studies. The total number of patients with cachexia in this meta-analysis was 753 (16.0%) out of 4697 patients, with each study having 6-196 (10.8-44%) patients (Table 2). In each study, follow-up was carried out over a 180-1,876-day period. During those periods, 1,551 (33.0%) of the 4,697 patients died. Seven studies reported that the mortality rates were 38.8% (n=207/533) in patients with cachexia and 17.6% (n=430/2,441) in patients without cachexia. It indicated that mortality was higher among patients with cachexia than those without cachexia.

Six studies in the pooled analysis showed that cachexia could significantly predict mortality in HF patients (HR=3.84, 95% CI=2.28-6.45, P<0.00001). A significant level of heterogeneity was found (P<0.00001, I^2=88%) (Figure 2). Due to a lack of data, the three other studies were not included.

Table 3 shows the results of the risk of bias assessment. Seven studies were rated as good quality, while two others were rated as poor quality. In the "exposure" category, no study received full stars since the "outcome of interest was not present at the start of the study" criteria could not be met. In the case of a mortality study, a statement of no history of disease or incident earns a star since the outcome of interest is still the presence of a disease, rather than death.

The studies were divided into two subgroups: weight loss studies (n=3) and low/lean BMI studies (n=2). Both subgroups had lower significance and heterogeneity values than the pooled analysis results. Low/lean BMI predicts a higher mortality risk than weight loss in HF patients with cachexia, with HR values of 3.96 (2.49-6.30) and 2.87 (1.35-6.09), respectively. The difference between the two subgroups was not significant (P=0.48, I^2: 0%), as demonstrated in Figure 3.

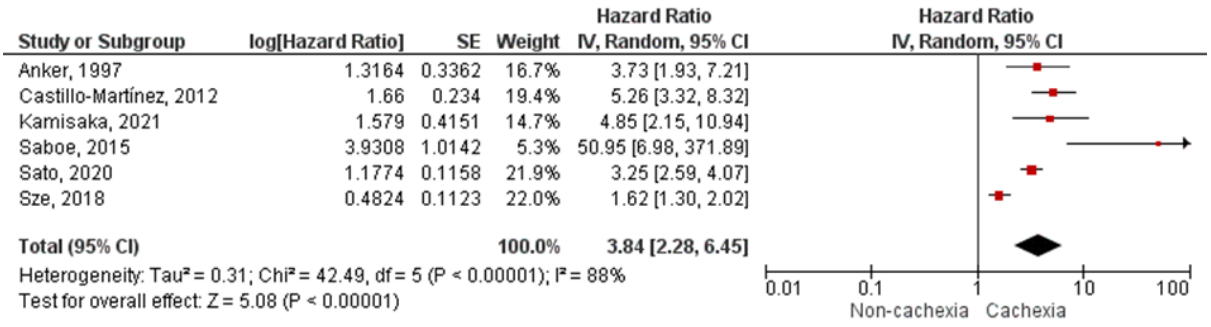

Figure 2. Hazard ratio of mortality in heart failure patients with cachexia.

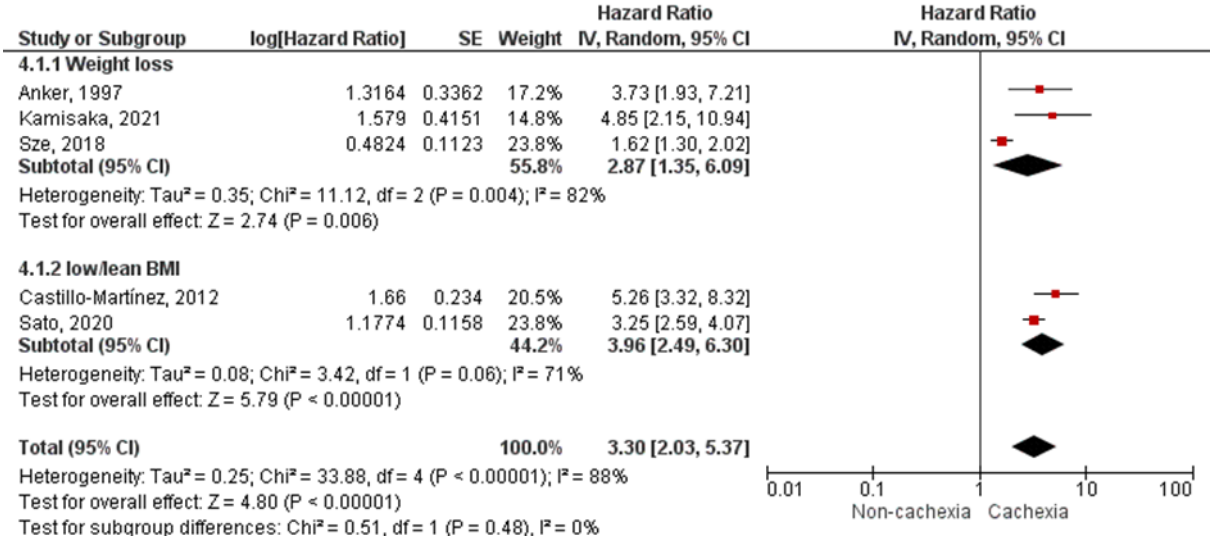

Figure 3. Analysis of mortality in the subgroups of heart failure patients with cachexia.

DISCUSSION

The prevalence of cachexia in HF patients was found to be slightly higher in this meta-analysis than in earlier studies (Haehling et al. 2016). In this meta-analysis, patients with cachexia had a lower BMI than patients without cachexia. This finding was consistent with prior research suggesting that a low BMI played a role in the diagnosis of cachexia. On the other hand, another study found higher BMI in cachexia patients (Sze et al. 2018), which is consistent with prior research that found weight loss occured more frequently in HF patients with higher BMI or obesity (Trullàs et al. 2013, Zamora et al. 2016). According to the "obesity paradox" theory, fat mass is a protective factor in HF patients, and obese patients may have higher metabolic reserve to better endure the catabolic state of HF (Zamora et al. 2016, Hamzeh et al. 2017, Krysztofiak et al. 2020). A study found that elevated BMI had no effect on the mortality and readmission of HF patients (Lestari et al. 2017). The presence of unintentional weight loss in cachexia, when the fat mass was primarily adipose tissue, might lead to a poor prognosis for HF patients with obesity (Melenovsky et al. 2013, Zamora et al. 2016, Valentova et al. 2020).

Although the mortality rate in patients with cachexia was lower than in those without cachexia, it should be noted that the number of HF patients with cachexia was also lower than in the overall population. Cachexia served as an independent mortality predictor, indicating a greater mortality rate as compared to when cachexia was absent. This meta-analysis found that cachexia had a nearly four-times worse prognosis in HF patients, which is consistent with prior studies. This signifies that HF patients with cachexia were nearly four times more likely to die than those without cachexia at any given time. HF patients diagnosed with cachexia based on low/lean BMI had a higher mortality risk than those diagnosed based on weight loss. However, no significant difference was observed in this meta-analysis between diagnosing cachexia by weight loss or low/lean BMI, indicating that both weight loss and low/lean BMI were relevant as the diagnostic criteria of cachexia.

According to the European Society of Cardiology (ESC) Guidelines, one of the comorbidities of HF is

cachexia, which can be caused by many factors, including catabolic-anabolic imbalances, neuro-hormonal disorders, pro-inflammatory cytokine activation, anorexia, malabsorption, and anabolic hormone resistance (Sandek et al. 2014, Okoshi et al. 2014, Valentova et al. 2016, Raposo André et al. 2017). Although it is unclear if cachexia directly causes death in HF patients, multiple observational studies have shown that cachexia indeed played a role in HF patients' poor prognosis.

Kalantar et al. (2013) found that elevated platelet count and activation, as well as arrhythmias, appeared to be the most likely contributors to the occurrence of sudden cardiovascular events, including death, in cachexia patients. Patients with cachexia might develop atherosclerotic plaques, which can increase the risk of developing acute coronary syndrome and/ or death due to sudden cardiac diseases, as a result of increased platelet count and activation accompanied by endothelial dysfunction and increased pro-inflammatory cytokines (Molnar et al. 2011, Fatkhullina et al. 2016, Anaszewicz & Budzyński 2017, Amalia et al. 2022). They could be more prone to developing arrhythmias, particularly atrial fibrillation (Arámbula-Garza et al. 2016, Anaszewicz & Budzyński 2017). Platelet-to-lymphocyte ratio (PLR) can be a supplementary biomarker for symptomatic HF, particularly in patients with acute coronary syndrome (ACS) (Intan et al. 2022). A study discovered that patients with tetralogy of Fallot (TOF), a congenital abnormality that interferes with proper cardiac blood flow, had a low BMI below the normal limit (Saputri et al. 2020). Furthermore, muscle loss in cachexia patients might lead to a decrease in cardiac contractility, which worsens the HF condition in these patients (Fulster et al. 2013, Drescher et al. 2015.

Strength and limitations

Recent studies to assess cachexia have employed various diagnostic criteria, resulting in varied outcomes. This meta-analysis has conclusively summarized the association between cachexia and mortality among HF patients. Several limitations should be noted in evaluating the results of this meta-analysis. First, the scarcity of research and the incompleteness of data from the selected studies. Second, it is important to understand and take into consideration that the mortality outcome employed in this meta-analysis was all-cause mortality. This suggests that mortality in the recruited patients was not necessarily caused by cachexia and/or HF, but could possibly be caused by other diseases or comorbidities, e.g., infection, diabetes, COPD, and kidney failure. Third, the pooled analysis revealed results with significant heterogeneity, most likely due to variations in the number of samples, diagnostic criteria, and length of follow-up period between studies.

CONCLUSION

Cachexia worsens the prognosis of heart failure patients. Mortality rates were higher among heart failure patients with cachexia compared to those without cachexia. Medical professionals should pay more attention to heart failure patients' nutritional state and cardiac cachexia in order to not worsen their prognosis.

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

AN conceptualized and supervised the study, as well as validated, reviewed, and finalized the manuscript. UN conceptualized the study, managed the administration, collected and analyzed the data, and wrote the manuscript. SW and MA validated and supervised the study, as well as reviewed and finalized the manuscript. HO validated, reviewed, and finalized the manuscript.

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