Bijlage Evidence tabellen

Evidence tabel module Markering

Vraag 1: Welke factoren bepalen de levensverwachting van patiënten met hartfalen NYHA klasse III-IV?

Systematische reviews

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
Ali 2024	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: Jan 2021 • Databases: CENTRAL, Medline • Study designs: RCTs, observational studies • N included studies: N=22	• Eligibility criteria: patients with any type of heart failure; reported all-cause mortality and/or hospitalization; reported disease-specific functional assessment tools rather than generic tools when predicting mortality and/or hospitalization; reported the following cutoff values: ≥ 5 for KCCQ, > 45 for MLHFQ and ≤ 200 m or 10 m increments for 6MWD, and classes [II, III, and IV] for NYHA; studies that were post hoc analyses of trials or observational studies that assessed independent association between baseline health/functional status and mortality and/or hospitalization	Quality of life Functional status	All-cause mortality • 6MWD: ○ 10 m increment studies: 4 studies, HR 0.98, 95%CI 0.98-0.99, p<0.01, I^2 28% ○ Dichotomization (≤200 m): 3 studies, HR 1.42, 95%CI 0.86-2.32, p=0.17, I^2 84% • KCCQ: ○ 5-point or higher increase: 3 studies, HR 0.94, 95%CI 0.91-0.96, p<0.01, I^2 0% • MLHFQ: ○ Score >45: 7 studies, HR 1.30, 95%CI 1.14-1.47, p<0.01, I^2 0%	• Review process by two independent researchers • No language restriction • Quality appraisal using Newcastle-Ottawa Scale for observational studies and Risk of Bias tool for post-hoc analyses of RCTs
Chen 2022	• Design: systematic review + meta-analysis • Funding: Guangdong Basic and Applied Basic Research Fund (Key project of Guangdong-Foshan Joint Fund)	• Eligibility criteria: (1) observational studies involving adult participants with a diagnosis of heart failure; (2) the prognostic nutritional index was recorded at enrolment; and (3) the association between prognostic nutritional	Prognostic Nutritional Index	All-cause mortality • Lower vs. higher score: ○ Unadjusted: 9 studies, HR 2.08, 95%CI 1.63-2.64, p<0.001, I^2 89% ○ Adjusted: 6 studies, HR 1.53, 95%CI 1.27-1.85, p<0.001, I^2 71% • Per 1 increment as continuous metric:	• Review process by two independent researchers • Restricted to English and Chinese language • Quality appraisal using Newcastle-Ottawa Scale

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	(2019B1515120044); CoI: none • Search date: Jan 2022 • Databases: PubMed, Embase, Cochrane Library, Google Scholar • Study designs: observational studies • N included studies: N=14	index score and the prognosis [including all-cause mortality or composite major adverse cardiac outcomes] of heart failure were reported during follow-up • Exclusion: (1) cross-sectional studies without follow-up evaluation; (2) reported other nutritional indexes but not prognostic nutritional index; and (3) duplicated publications from the same observational studies in such situations, only the most recently published data were included for analysis		○ Unadjusted: 5 studies, HR 0.90, 95%CI 0.87-0.94, p<0.001, I^2 93% ○ Adjusted: 6 studies, HR 0.94, 95%CI 0.88-0.96, p<0.001, I^2 78%	
Chen 2024	• Design: systematic review + meta-analysis • Funding: not reported; CoI: none • Search date: Aug 2022 • Databases: PubMed, Embase, Cochrane Library, Web of Science, CNKI (China National Knowledge Infrastructure), Wanfang Data Knowledge Service Platform, VIP Chinese Scientific Journals Full-text Database, and China National Biomedical Literature Database	• Eligibility criteria: patients with clinically confirmed heart failure, regardless of disease severity; investigation of the prognostic significance of frailty on heart failure patients; multivariable-adjusted hazard ratio (HR) or odds ratio (OR) • Exclusion: studies including patients who had undergone or were scheduled to undergo cardiovascular surgery, such as percutaneous coronary intervention, radiofrequency ablation, left ventricular assist device implantation, valve replacement, and heart transplantation	Frailty	All-cause mortality • Frailty vs. non-frailty: ○ HR: 19 studies, HR 1.73, 95%CI 1.50-2.00, p<0.001, I^2 56% ○ OR: 3 studies, OR 2.43, 95%CI 1.13-5.24, p=0.02, I^2 54%	• Review process by two independent researchers • Language restriction unclear • Quality appraisal using Newcastle-Ottawa Scale

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	• Study designs: cohort and case-control sudies • N included studies: N=31				
Chokshi 2023	• Design: systematic review • Funding: not reported; CoI: not reported • Search date: unclear • Databases: Cochrane Library, Embase, MEDLINE, PubMed, Scopus and Web of Science • Study designs: all • N included studies: N=31	• Eligibility criteria: 1) frailty assessed using valid measurement tools; 2) confirmed diagnosis of heart failure	Frailty	Narrative presentation: • Boxer 2010: frailty is significantly associated with increased mortality and cardiovascular death; abnormal 6-minute walk test (6MWT) and frailty scores were independently predictive of mortality, with HR of 0.82 (95%CI 0.72-0.94) and 1.64 (95%CI 1.19-2.26) • Eight studies determined that lower Barthel Index scores were a strong predictor of increased mortality • Conversely, higher prehospital admission Barthel Index scores (i.e., less frail) were correlated with reduced all-cause, 3-month post-discharge mortality (HR 0.981; 95%CI 0.975-0.986, p,0.001) • The Fried Frailty Phenotype/modified Fried Frailty Phenotype has also been widely utilised to assess frailty and demonstrate the increased risk of mortality: two studies demonstrated frailty was associated with increased risk of 12-month all-cause mortality (HR 2.15, 95%CI 1.23-3.76) and (HR 2.13, 95%CI 1.07-4.23), respectively • Frailty is also a significant risk factor for cardiovascular death using the Comprehensive Geriatric Assessment (CGA) (HR 1.94, 95%CI 1.58-2.38, p,0.001)	• Review process by two independent researchers • Restricted to English language • Quality appraisal using Critical Appraisal Skills Programme (CASP) checklist
Dhaliwal 2023	• Design: systematic review • Funding: none; CoI: none	• Eligibility criteria: (a) cohort of adult patients diagnosed with heart failure, (b) quantitative data on serum iron metabolism	Markers of iron metabolism	All-cause mortality: 16 studies, narrative overview: • Combination of ferritin and transferrin saturation:	• Selection process by two independent researchers, unclear for data extraction

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	• Search date: Sep 2022 • Databases: PubMed • Study designs: observational studies • N included studies: N=26	biomarkers or ranges of these biomarkers used for definition of iron deficiency or other relevant exposure, and (c) report of the outcomes of interest (mortality, hospitalization rates, functional capacity, QoL, and cardiovascular events) • Exclusion: (a) studies not pertaining to iron deficiency or iron metabolism biomarkers, (b) biomarkers studied after pharmaceutical intervention (e.g., iron supplementation), (c) inadequate data on baseline characteristics or outcomes		○ Jankowska 2010: HR 1.58, 95%CI 1.14-2.17, p<0.01 ○ Klip 2013: HR 1.42, 95%CI 1.14-1.77, p=0.002 • Ferritin as standalone marker: ○ Nakano 2018: levels < 100 µg/L associated with 50% higher mortality (HR 1.50, 95%CI 1.02-2.21, p=0.040) • Low transferrin saturation: ○ HFrEF: ▪ Okonko 2011: HR 3.38; 95%CI 1.48-7.72; p=0.004 ▪ Grote Beverborg 2018: HR 2.78; 95%CI 1.22-6.34, p=0.015 ▪ Gentil 2020: HR 2.3; 95%CI 1.11-4.85, p=0.026 ▪ Kurz 2020: HR 0.608, 95%CI 0.498-0.741, p<0.001 ▪ Fitzsimons 2021: HR 1.95, 95%CI 1.52-2.51, p<0.01 ○ Midrange to preserved LVEF: ▪ Ambrosy 2020: aHR 1.42, 95%CI 1.20-1.68 ▪ Palau 2021: HR 1.75, 95%CI 1.08-2.83; p=0.024 ▪ Fitzsimons 2022: HR 1.69, 95%CI 1.10-2.59 ▪ Masini 2022: HR 1.27; 95%CI 1.14-1.43; p<0.001	• Restricted to English language • Quality appraisal using Newcastle-Ottawa Scale
El Iskandarani 2021	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: Jan 2019	• Eligibility criteria: patients diagnosed with heart failure; studies clearly reporting association of serum albumin and one or more outcomes of interest	Serum albumin	• Acute heart failure, in-hospital mortality: 10 studies, OR 3.77, 95%CI 1.96-7.23 ○ Studies with multivariate analysis: 5 studies, OR 3.05, 95%CI 1.36-6.82, p=0.007	• Review process by two independent researchers • Restricted to English language • Quality appraisal using Hayden method

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	• Databases: Cochrane Library, Embase, MEDLINE, CINAHL • Study designs: prospective or retrospective studies • N included studies: N=48			○ Studies with univariate analysis: 5 studies, OR 5.62, 95%CI 1.86-16.95, p=0.002 • Mortality at 3 months: 3 studies, OR 2.12, 95%CI 1.19-3.37, p=0.01 • Mortality at 6 months: 6 studies, OR 1.16, 95%CI 1.03-1.36, p=0.013 • Mortality at 12 months: 7 studies, OR 2.44, 95%CI 2.05-2.91, p=0.000 • Long-term mortality: 5 studies, OR 1.49, 95%CI 1.13-1.96, p=0.004 • Diagnostic accuracy: 7 studies, AUC 0.73, 95%CI 0.67-0.78 ○ 1-year mortality: 2 studies, AUC 0.69, 95%CI 0.61-0.79 ○ In-hospital mortality: 3 studies, AUC 0.79, 95%CI 0.76-0.81	
Fan 2020	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: Jul 2019 • Databases: PubMed, Embase • Study designs: observational studies or post-hoc analyses of RCTs • N included studies: N=8	• Eligibility criteria: studies evaluating the prediction of all-cause and cardiovascular mortality with weight loss in patients with chronic heart failure • Exclusion: studies including patients with acute heart failure	Weight loss (loss of 5% of baseline body weight over 3 months or more)	• All-cause mortality: ○ Weight loss vs. stable weight: 8 studies, HR 1.74, 95%CI 1.35-2.24, I^2 84% • Cardiovascular mortality: ○ Weight loss vs. stable weight: 3 studies, HR 1.71, 95%CI 1.10-2.66, I^2 90%	• Selection process by two independent researchers, unclear for data extraction • Language restriction unclear • Quality appraisal using Newcastle-Ottawa Scale
Fan 2019	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: Nov 2017	• Eligibility criteria: (a) observational studies enrolling patients with heart failure; (b) baseline 6MWD as exposure; (c) reported multivariable-adjusted risk estimates of all-	6MWD	All-cause mortality • Shortest vs. longest 6MWD: 4 studies, RR 1.96, 95%CI 1.10-3.50, p=0.02, I^2 77% • 50 m decrease: 4 studies, RR 1.18, 95%CI 1.07-1.29, p=0.0004, I^2 51%	• Selection process by two independent researchers, unclear for data extraction • Language restriction unclear • Quality appraisal using Newcastle-Ottawa Scale

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	• Databases: Pubmed, Embase and Web of Science • Study designs: observational studies • N included studies: N=13	cause mortality, readmission or combined endpoint • Exclusion: studies not providing the quantitative risk estimate for the endpoint or enrolling acute decompensated patients with heart failure			
Fu 2024	• Design: systematic review + meta-analysis • Funding: National Natural Science Foundation of China (81904191, 82004348), Guang'anmen Hospital of China Academy of Chinese Medical Sciences (2018S420), Capital Health Development Research Special Project (2020–2–4153), Scientific and technological innovation project of China Academy of Chinese Medical Sciences (C12021A01603); CoI: none • Search date: June 2024 • Databases: PubMed, Embase, and Ovid Medline • Study designs: observational cohort studies • N included studies: N=8	• Eligibility criteria: (1) participants diagnosed with HFpEF and over 18 years old; (2) exposure: systemic inflammatory markers available from complete blood count, including neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), white blood cells (WBC), platelets, lymphocytes, and CRP, HDL(high-density lipoprotein)/CRP ratio; (3) outcome measures: hazard ratios (HR) or adjusted HRs for the occurrence of adverse outcomes in HFpEF (all-cause mortality/cardiovascular mortality/rehospitalization rate)	CRP	All-cause mortality, 1 individual study on hs-CRP: • Ferreira 2024: HR 1.40, 95%CI 0.54-3.66 Cardiovascular mortality, 2 individual studies on hs-CRP: • Ferreira 2024: HR 2.49, 95%CI 0.31-20.03 • Zhou 2024: HR 3.50, 95%CI 1.54-7.96	• Review process by two independent researchers • Restricted to English language • Quality appraisal using Newcastle-Ottawa Scale • Meta-analysis done for all systemic inflammatory markers, here only results of individual studies on CRP reported

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
Hu 2022	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: Jul 2021 • Databases: PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), WanFang Data, and China Biology Medicine disc • Study designs: cohort studies • N included studies: N=36	• Eligibility criteria: adult patients with heart failure, screening or assessment of the nutritional status of heart failure patients using multidimensional evaluation tools or technologies recommended by ASPEN 2012 • Exclusion: (1) Reports did not present the data of all-cause mortality; (2) Subjects were those who received left ventricular assist device or heart transplantation during a follow-up	Malnutrition	All-cause mortality • Poor nutritional status as evaluated by: ○ Prognostic Nutritional Index: 9 studies, HR 1.64, 95%CI 1.32-2.04, p<0.00001, I^2 95% ○ Geriatric Nutritional Risk Index: 16 studies, HR 1.57, 95%CI 1.38-1.79, p<0.00001, I^2 91% ○ Controlling Nutritional Status Score: 9 studies, HR 1.58, 95%CI 1.30-1.92, p<0.00001, I^2 88% ○ Nutritional Risk Index: 3 studies, HR 1.77, 95%CI 1.55-2.03, p<0.00001, I^2 0% ○ Short Form Mini Nutritional Assessment: 3 studies, HR 1.94, 95%CI 1.40-2.70, p<0.001, I^2 0% ○ Mini Nutritional Assessment: 4 studies, HR 2.62, 95%CI 1.11-6.20, p=0.03, I^2 73% ○ Generated Subjective Global Assessment: 3 studies, HR 2.38, 95%CI 1.65-3.44, p<0.00001, I^2 0%	• Selection process by two independent researchers, unclear for data extraction • Restricted to English and Chinese language • Quality appraisal using Newcastle-Ottawa Scale
Kao 2024	• Design: systematic review + meta-analysis • Funding: Chongqing Science and Health Joint Medical Research Project, Grant/Award Number 2023MSXM081; CoI: none • Search date: Sep 2023 • Databases: PubMed, Embase • Study designs: cohort studies or post hoc analysis of clinical trials	• Eligibility criteria: patients with heart failure; study investigating the association between baseline health-related QoL, as measured by the KCCQ, and all-cause mortality or heart failure hospitalisation; reported a multivariate-adjusted risk estimate for the bottom versus the top KCCQ score or for the KCCQ score as continuous data • Exclusion: (1) health-related QoL was measured using other	Quality of life: KCCQ	All-cause mortality • Bottom vs. top KCCQ score: 6 studies, pooled adjusted HR 2.34, 95%CI 2.10-2.60, p<0.00001, I^2 42% • Per 10-point KCCQ score decrease: 7 studies, pooled HR 1.12, 95%CI 1.07-1.16, p<0.00001, I^2 84%	• Selection process by two independent researchers, unclear for data extraction • Language restriction unclear • Quality appraisal using Newcastle-Ottawa Scale

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	• N included studies: N=12	instruments; (2) outcome measures were not of relevant or did not report a risk estimate; (3) only reporting univariate adjusted risk summary			
Ketabi 2024	• Design: systematic review + meta-analysis • Funding: Larestan University of Medical Sciences (Grant No. 206); CoI: none • Search date: Jan 2023 • Databases: PubMed, Embase, Web of Science, ProQuest, Scopus, Science Direct and Google Scholar • Study designs: observational studies • N included studies: N=7	• Eligibility criteria: original studies examining the relationship between recurrent hospitalizations for heart failure and mortality from all causes and cardiovascular causes • Exclusion: case series, case reports, review studies, meta-analyses, letters, short communications, ecologic studies, any duplicate, non-relevant, and abstracts without full text from this systematic review and meta-analysis	Recurrent heart failure hospitalizations	• Cardiovascular mortality: 4 studies, pooled HR 4.28, 95%CI 0.86-7.71, I^2 97.8% ○ Reduction in heterogeneity when stratified by factors such as quality score, sample size, hypertension comorbidity, number of recurrent HFHs, and follow-up time • All-cause mortality: 7 studies, pooled HR 2.76, 95%CI 2.05-3.48, I^2 98.4% ○ Reduction in heterogeneity when stratified by factors such as quality score, sample size, and hypertension comorbidity	• Review process by single reviewer • No language restriction • Quality appraisal using Newcastle-Ottawa Scale
Kyriakou 2016	• Design: systematic review + meta-analysis • Funding: not reported; CoI: not reported • Search date: Jun 2014 • Databases: Pubmed, Cochrane Library and CINAHL • Study designs: all • N included studies: N=26	• Eligibility criteria: studies published between 2004-2014 and that examined clinical outcomes of the comorbidity heart failure - anemia • Exclusion: studies that examined the effectiveness of anemia treatments; articles that have been referred generally for cardiovascular problems and not specifically for heart failure	Anemia	• Pooled RR of mortality at maximal available follow-up, anemia vs. no anemia: 16 studies, RR 1.70, 95%CI 1.47-1.98, I^2 75%	• Unclear if review process was done by independent researchers • Restricted to English language • Quality appraisal using Newcastle-Ottawa Scale

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
Lakhani 2021	• Design: systematic review + meta-analysis • Funding: not reported; CoI: not reported • Search date: Aug 2019 • Databases: PubMed, Embase • Study designs: prospective or retrospective cohort studies • N included studies: N=19	• Eligibility criteria: HFpEF patients, hazard ratios for risk of new onset HFpEF as well as prognostic outcomes including cardiovascular (CV) mortality, long-term CV outcomes, and all-cause mortality	CRP	• Cardiovascular mortality: ○ High vs. low CRP: 2 studies, HR 2.52, 95%CI 1.61-3.96, p<0.0001, I^2 19% ○ CRP as continuous variable: 2 studies, HR 1.24, 95%CI 1.05-1.47, p=0.01, I^2 28% • All-cause mortality: ○ High vs. low CRP: 5 studies, HR 1.78, 95%CI 1.53-2.06, p<0.00001, I^2 0% ○ CRP as continuous variable: 7 studies, HR 1.06, 95%CI 1.02-1.10, p=0.004, I^2 61%	• Unclear if selection process was done by independent researchers • Data extraction done by independent reviewers • No language restriction • Quality appraisal using Newcastle-Ottawa Scale
Lee 2023	• Design: systematic review + meta-analysis • Funding: supported by the National Research Foundation of Korea (NRF) grants funded by the Korea government (MSIT) (2021R1C1C100849812), the BK21 FOUR project (Center for Human-Caring Nurse Leaders for the Future) funded by the Ministry of Education (MOE, Korea) and the NRF, and the 2022 Hannam University Research Fund; CoI: none • Search date: Jan 2014 - Sep 2021	• Eligibility criteria: adult population 18 years or above with heart failure diagnosis; reported original results (e.g., not a literature review, editorial, or case study); reported the relationships between health outcomes and comorbidities, which were defined as clinical diagnoses based on medical records, administration codes, or self-report (e.g., not a condition determined by questionnaires for screening, such as the presence of clinically significant depressive symptoms based on the Patient Health Questionnaire-9); and reported relevant statistical values • Exclusion: studies that reported composite outcomes,	Anemia Obesity	All-cause mortality • Anemia: 5 studies, HR 1.66, 95%CI 0.93-2.97, p=0.09, I^2 88% • Obesity: 2 studies, HR 0.99, 95%CI 0.97-1.00, p=0.06, I^2 0%	• Review process by two independent researchers • Restricted to English language • Quality appraisal using RoBANS tool

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	• Databases: Medline, Embase, Cinahl • Study designs: observational studies • N included studies: N=42	such as combined results of morbidity and hospital readmissions			
Li 2021	• Design: systematic review + meta-analysis • Funding: supported by the Medical Scientific Research Foundation of Zhejiang Province, China (2018KY695) and the Ningbo Health Branding Subject Fund (PPXK2018-01); CoI: none • Search date: Jul 2019 • Databases: PubMed, Embase • Study designs: observational studies • N included studies: N=10	• Eligibility criteria: (1) or retrospective observational study recruiting patients (aged 65 years or older) with heart failure; (2) baseline GNRI as exposure; (3) outcome measures were all-cause mortality and major cardiovascular events (death and hospitalization for heart failure); (4) provided at least age-adjusted risk ratio (RR), hazard ratios (HR) or odds ratios (OR) with 95%CI for outcomes; and (5) length of follow-up no less than one year	Geriatric Nutritional Risk Index	All-cause mortality • Lowest vs. highest GNRI score: 6 studies, pooled RR 2.11, 95%CI 1.72-2.58, I^2 0% • Per category decrease in GNRI: 2 studies, pooled RR 1.29, 95%CI 1.20-1.39, I^2 12% • Each unit reduction in GNRI: 4 studies, pooled RR 1.06, 95%CI 1.03-1.08, I^2 60%	• Review process by two independent researchers • No language restriction • Quality appraisal using Newcastle-Ottawa Scale
Milajerdi 2018	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: Nov 2017 • Databases: PubMed, Scopus, OVID and Google scholar • Study designs: all • N included studies: N=16	• Eligibility criteria: population age more than 18 years, reported number of participants in each BMI categories, reported numbers of deaths due to heart failure or CVD mortality after heart failure diagnosis in each BMI categories, calculated the HR or RR with 95%CI	BMI	• Pre-diagnosis BMI, highest vs. lowest: 7 studies, HR for mortality = 1.24, 95%CI 0.65-2.37, I^2 91% • Post-diagnosis BMI, highest vs. lowest: 10 studies, HR for mortality = 0.69, 95%CI 0.61-0.77, I^2 84% • Non-linear U-shaped association between pre-diagnosis BMI and risk of heart failure mortality (p<0.0001)	• Selection process by two independent researchers, unclear for data extraction • Restricted to English language • Quality appraisal using Newcastle-Ottawa Scale

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
		• Exclusion: outpatients with heart failure		• No significant non-linear association between post-diagnosis and risk of heart failure mortality (p=0.41)	
Osorio 2023	• Design: systematic review + meta-analysis • Funding: supported by the Research Incentive Fund (FIPE) of the Hospital de Clínicas de Porto Alegre and the Coor- dination for the Improvement of Higher Education Personnel (CAPES, Brazil); CoI: none • Search date: Oct 2022 • Databases: Medline, Embase, Web of Science, Lilacs, and Scopus • Study designs: prospective and retrospective observational cohort studies • N included studies: N=38	• Eligibility criteria: (1) patients ≥18 years hospitalized with decompensated heart failure; (2) assessment of nutritional risk with multidimensional tool (more than on isolated parameter/marker); (3) assessment of the following prognostic parameters: all-cause mortality, cardiovascular mortality, and/or rehospitalization	Nutritional screening tools	All-cause mortality • PNI: 2 studies, RR 2.19, 95%CI 1.03-4.65, I^2 89% • GNRI: 6 studies, RR 2.43, 95%CI 1.64-3.60, I^2 81% • CONUT: 6 studies, RR 2.85, 95%CI 1.65-4.92, I^2 91% • MNA-SF: 2 studies, RR 4.85, 95%CI 2.0-11.75, I^2 0%	• Review process by two independent researchers • No language restriction • Quality appraisal using Newcastle-Ottawa Scale
Qin 2017	• Design: systematic review + meta-analysis • Funding: not reported; CoI: none • Search date: Mar 2016 • Databases: PubMed, Embase	• Eligibility criteria: subjects diagnosed with heart failure, BMI reported, adjusted risk estimates with 95%CI on the associations of BMI and the risks of death from all-causes	BMI	All-cause mortality • Pooled HR for every 5 kg/m^2 increment: 14 studies, HR 0.95, 95%CI 0.92-0.97, I^2 90% • Random effects dose-response analysis: non-linear association, p=0.0025	• Selection process by two independent researchers, unclear for data extraction • Unclear language restriction • Quality appraisal using Newcastle-Ottawa Scale

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	• Study designs: prospective cohort studies • N included studies: N=14				
Uchmanowicz 2020	• Design: systematic review + meta-analysis • Funding: funded by the Ministry of Science and Higher Education in Poland as a part of a statutory grant of the Wroclaw Medical University for maintaining research potential (no. SUB.E020.19.003); CoI: none • Search date: May 2019 • Databases: PubMed, Scopus, and Google Scholar • Study designs: case-control, prospective, or retrospective studies • N included studies: N=30	• Eligibility criteria: humans with a definite diagnosis of heart failure and frailty quantified and related to the primary endpoints of all-cause mortality and/or hospitalization • Exclusion: studies on patients with acute heart failure, without well-specified frailty definition/measure, with composite primary endpoints, and without HR values for frailty effect or numbers of frail and non-frail patients who achieved/not achieved the primary endpoint	Frailty	All-cause mortality • Frail vs. non-frail: 29 studies, HR 1.48, 95%CI 1.31-1.65, p<0.001, I^2 54% • Fried-based measures: ○ Outpatient: 5 studies, HR 1.42, 95%CI 1.05-1.79, I^2 32% ○ Inpatient: 8 studies, HR 1.48, 95%CI 1.03-1.93, I^2 30% • Other frailty measures: ○ Outpatient: 6 studies, HR 1.60, 95%CI 1.43-1.77, I^2 12% ○ Inpatient: 10 studies, HR 1.42, 95%CI 1.12-1.72, I^2 0%	• Selection process by two independent researchers, unclear for data extraction • Restricted to English language • Quality appraisal using STROBE criteria
Van Lummel 2022	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: Jan 2021 • Databases: PubMed, Embase, Cochrane	• Eligibility criteria: studies using the surprise question as prognostic indicator with death as outcome • Exclusion: retrospective studies, reversed surprise question	Surprise question	Diagnostic accuracy of the surprise question, cardiac subgroup: 7 studies (4 on heart failure) • Sensitivity: 71.0, 95%CI 60.5-81.5, I^2 82% • Specificity: 73.4, 95%CI 62.2-84.6, I^2 87% • AUC: 0.78, 95%CI 0.69-0.87 Individual results: • Barnes 2008: sensitivity 78.6, specificity 61.3	• Review process by two independent researchers • Restricted to English language • Quality appraisal using QUIPS tool

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	Library, Scopus, Web of Science and CINAHL • Study designs: prospective studies of any design • N included studies: N=59			• Aaronson 2019: sensitivity 78.6, specificity 56.9 • Gastelurrutia 2019: sensitivity 78.7, specificity 69.4 • Straw 2019: sensitivity 84.6, specificity 58.7	
Wang 2018	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: Nov 2017 • Databases: PubMed, Embase, Cochrane Library, and Web of Science • Study designs: prospective studies • N included studies: N=10	• Eligibility criteria: (1) patients: subjects with heart failure, age ≥ 65 years; (2) interventions: subjects with frailty; (3) comparators: subjects without frailty; (4) outcomes: all-cause mortality or all-cause hospitalization or HF-related hospitalization	Frailty	All-cause mortality • 6 studies, HR 1.70, 95%CI 1.41-2.04, p<0.00001, I^2 0%	• Review process by two independent researchers • Restricted to English language • Quality appraisal using Newcastle-Ottawa Scale
Wang 2024	• Design: systematic review + meta-analysis • Funding: grant from the Science and Technology Program of Liaoning Province (No. 2018225003); CoI: none • Search date: Sep 2022 • Databases: Embase, PubMed, and Cochrane Library • Study designs: observational and retrospective studies	• Eligibility criteria: patients with heart failure with preserved ejection fraction (HFpEF)	Anemia Albumine	All-cause mortality • Anemia: 8 studies, HR 1.53, 95%CI 1.41-1.67, I^2 56% • Albumine: 6 studies, HR 1.29, 95%CI 1.14-1.47, I^2 95%	• Selection process by two independent researchers • Unclear if data extraction was done by independent reviewers • Unclear language restriction • No quality appraisal reported

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	• N included studies: N=30				
Wawrzeńczyk 2019	• Design: systematic review • Funding: none; CoI: none • Search date: Jan 2013 - Feb 2019 • Databases: PubMed, Scopus • Study designs: prospective, retrospective, cross-sectional, interventional, and clinical trials, as well as meta-analyses • N included studies: N=75	• Eligibility criteria: (1) studies carried out on human adults of more than 18 years of age with chronic heart failure diagnosis and studies on general population without history of cardiovascular diseases, in order to assess the prognosis factor for CHF with comparison to healthy population or CHF patients with an appropriate nutritional status; (2) studies assessing nutritional interventions in CHF patients (supportive nutritional and dietary treatment in terms of malnutrition, as well as weight reduction in the cases of excessive nutritional status, with the exception of bariatric surgery as an intentional weight-loss intervention in obese patients) as well as observational studies without intervention; (3) studies with the assessment of hard or surrogate endpoints, e.g., mortality rate, frequency of complication (like hospitalizations, severity of symptoms and effectiveness of CHF therapy) being evaluated with evidence-based medicine	Nutritional status	• Narrative overview	• Unclear if selection process was done by independent researchers • Data extraction done by independent reviewers • Restricted to English language • No quality appraisal reported

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
		(EBM) parameters (i.e., relative risk estimates - hazard ratio (HR), risk ratio (RR), and odds ratio (OR)) or log-rank test with 95%CI and/or associated p values			
Wu 2024	• Design: systematic review + meta-analysis • Funding: not reported; CoI: none • Search date: May 2023 • Databases: PubMed, Embase • Study designs: post hoc analysis of RCTs or observational studies • N included studies: N=13	• Eligibility criteria: patients with heart failure; weight loss defined as a loss of at least 5% of usual body weight over a period of 6–12 months as a predictor; cardiovascular or all-cause mortality as the outcome of interest; reported multivariable-adjusted risk estimates for cardiovascular or all-cause mortality associated with weight loss • Exclusion: (1) participants were not restricted to patients with heart failure; (2) intentional weight loss through medications or bariatric surgery as a predictor; (3) weight changes occurring within a period of less than 3 months; and (4) failure to report outcomes of interest	Weight loss	• All-cause mortality: weight loss vs. stable weight, 12 studies, HR 1.75, 95%CI 1.43-2.14, I^2 79% ○ Obesity: 3 studies, HR 1.76, 95%CI 1.41-2.20, I^2 0% ○ Non-obesity: 4 studies, HR 1.90, 95%CI 1.14-3.14, I^2 71% • Cardiovascular mortality: weight loss vs. stable weight, 4 studies, HR 1.75, 95%CI 1.18-2.28, I^2 85%	• Unclear if selection process was done by independent researchers • Data extraction done by independent reviewers • Restricted to English language • Quality appraisal with Newcastle-Ottawa Scale
Xia 2021	• Design: systematic review + meta-analysis • Funding: not reported; CoI: none • Search date: 2008 - Sep 2020	• Eligibility criteria: patients with heart failure and anemia; short- and long-term mortality, and hospitalization outcomes; adjusted hazard ratio	Anemia	Overall mortality, 1-year • 10 studies, OR 1.43, 95%CI 1.25-1.63, p<0.001, I^2 56%	• Selection process by two independent researchers, unclear for data extraction • Restricted to English language • Quality appraisal using ROBINS-I tool

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	• Databases: Embase, CENTRAL, Scopus, PubMed, Cochrane Library, ISI Web of Science, clinicaltrial.gov, and MEDLINE • Study designs: (quasi-)RCTs, controlled trials, observational prospective or retrospective studies • N included studies: N=11				
Xu 2023	• Design: systematic review + meta-analysis • Funding: not reported; CoI: none • Search date: Dec 2022 • Databases: PubMed, Embase • Study designs: post hoc analysis of clinical trial or cohort study • N included studies: N=25	• Eligibility criteria: patients with a diagnosis of heart failure, predictor = health-related QoL defined by the MLHFQ or KCCQ at baseline, the better versus worse QoL group or QoL score as a continuous variable, all-cause mortality, provided the multivariable-adjusted risk summary of all-cause mortality • Exclusion: 1) QoL was evaluated by other instruments, 2) reported the unadjusted risk estimate,3) outcome measures were not of interest	Quality of life (MLHFQ, KCCQ)	All-cause mortality • MLHFQ, per 10-point score increase: 9 studies, HR 1.12, 95%CI 1.06-1.18 • MLHFQ, top vs. bottom score: 7 studies, HR 1.56, 95%CI 1.26-1.94, I^2 46% • KCCQ, per 10-point score decrease: 6 studies, HR 1.12, 95%CI 1.07-1.16, I^2 77% • KCCQ, bottom vs. top score: 6 studies, HR 2.34, 95%CI 2.10-2.60, I^2 41%	• Unclear if selection process was done by independent researchers • Data extraction done by independent reviewers • Unclear language restriction • Quality appraisal with Newcastle-Ottawa Scale
Yamamoto 2020	• Design: systematic review + meta-analysis • Funding: Japan Society for the Promotion of	• Eligibility criteria: participants of any age who had a history of heart failure; physical performance tests were	Physical performance	All-cause mortality • 6MWD ○ Per 1-m increase: 7 studies, HR 0.99, 95%CI 0.99-1.00, p<0.00001, I^2 86%	• Unclear if selection process was done by independent researchers

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	Science (JSPS), KAKENHI Grant Number JP18K17715, Japan; CoI: none • Search date: Feb 2019 • Databases: Embase, Medline, PubMed, Cochrane Library • Study designs: prospective and retrospective cohort studies • N included studies: N=22	defined as those that measured upper extremity strength (e.g. handgrip strength), lower extremity strength (e.g. isometric or isotonic knee extension), walking speed, or other performance scales [e.g. short physical performance battery (SPPB)] • Exclusion: cohort studies not evaluating hazard ratios; participants who had heart transplantation, implantable ventricular assist devices, orthopedic surgery (e.g. hip or knee arthroplasty and spinal surgery), and paralysis due to stroke		○ Lower vs. higher: 3 studies, HR 2.04, 95%CI 1.48-2.83, p<0.0001, I^2 0% • Walking speed: 3 studies, no meta-analysis ○ Pulignano 2016: each tertile increase in walking speed was associated with a decrease in all-cause mortality (HR 0.620, 95%CI 0.434-0.884) ○ Vidan 2016: participants with slower walking speed (<10% of the gender and height-adjusted reference value) had higher risk for 1-year mortality (HR 1.77; 95%CI 0.95-2.32) compared to those with faster walking speed, albeit not significantly ○ Lo 2015: those with slower walking speed (<0.8 m/s) had a higher risk for all-cause mortality (HR 1.37; 95%CI 1.10-1.70) compared to those with faster walking speed (>0.8 m/s) • Handgrip strength: 2 studies, no meta-analysis ○ Izawa 2009: 1-kg increase in handgrip strength decreased the risk for cardiac death (HR 0.900; 95%CI 0.831-0.976) ○ Vidan 2016: those with a weaker grip strength (<20% of the gender and body mass index adjusted reference value) had higher risk for 1-year mortality (HR 1.46; 95%CI 0.86-2.46) compared to those with stronger grip strength, albeit not significantly • SPPB: 2 studies, no meta-analysis; 1 study only reported combined outcome ○ Chiarantini 2010: those who had 0, 1–4, and 5–8 points had higher risk for all-cause mortality (HR 6.06, 95%CI 2.19-16.76; HR	• Data extraction done by independent reviewers • Unclear language restriction • Quality appraisal with RoBANS tool

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
				4.78, 95%CI1.63-14.02; and HR 1.95, 95%CI 0.67- 5.70, respectively) compared to those who had 9–12 points • Lower extremity strength: 2 studies, no meta-analysis ○ Hulsmann 2004: knee flexor, but not knee extensor, strength was significantly associated with mortality (no results reported) ○ Izawa 2009: 1-Nm/kg increase in strength decreased the risk for cardiac death (HR 1.042; 95%CI, 0.251-4.328), albeit not significantly	
Yang 2018	• Design: systematic review + meta-analysis • Funding: many reported; CoI: none • Search date: Mar 2018 • Databases: Medline, Embase, Cochrane Library • Study designs: all • N included studies: N=14	• Eligibility criteria: (1) frailty assessed using validated assessment instruments; (2) confirmed diagnosis of heart failure on the basis of international criteria and guideline definitions • Exclusion: (1) studies without any relevance to the clinical outcomes of hospitalization and mortality; (2) studies that investigated the effects of medical or surgical intervention, including cardiac resynchronization therapy, LVAD, and cardiac transplantation; (3) data on acute heart failure	Frailty	All-cause mortality • 8 studies, HR 1.54, 95%CI 1.34-1.75, p<0.001, I^2 0% ○ Fried phenotype: 5 studies, HR 1.80, 95%CI 1.41-2.28, p<0.001, I^2 0%	• Review process by two independent researchers • Restricted to English language • Quality appraisal using Newcastle-Ottawa Scale
Zhang 2019	• Design: systematic review + meta-analysis • Funding: not reported; CoI: none	• Eligibility criteria: studies that evaluated the associations between BMI and all-cause mortality in patients either with	BMI	All-cause mortality • Per 5 units increment in BMI: ○ HFpEF: 4 studies, HR 0.93, 95%CI 0.89-0.97, I^2 76%; the dose-response meta-	• Selection process by two independent researchers, unclear for data extraction • No language restriction

Study ID	Methods	Patient characteristics	Prognostic factor(s)	Results	Critical appraisal of study quality
	• Search date: Apr 2017 • Databases: PubMed, Embase • Study designs: prospective cohort studies • N included studies: N=10	heart failure and a reduced (HFrEF; LVEF < 40%) or preserved left ventricular ejection fraction (HFpEF; LVEF ≥ 50%); only studies with at least three categories of BMI were considered • Exclusion: studies with patients with a mean left ventricular ejection fraction (LVEF) close to 45%		analysis showed a U-shaped association between BMI and all-cause mortality with the lowest mortality at a BMI of 32-33 kg/m² (p < 0.01 for non-linearity) ○ HFrEF: 7 studies, HR 0.96, 95%CI 0.92-1.00, I² 95%; the dose-response meta-analysis showed a 'flatter' U-shaped association than for HFpEF with the lowest mortality at a BMI of 32 kg/m² (p < 0.01)	• No quality appraisal reported
Zhang 2024	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: Jan 2023 • Databases: PubMed, Embase • Study designs: retrospective or prospective observational studies • N included studies: N=12	• Eligibility criteria: patients with heart failure; investigated the association of Prognostic Nutritional Index with all-cause mortality and/or combined endpoint of mortality and rehospitalization; reported multivariate adjusted hazard ratio (HR) or risk ratio (RR) with 95%CI associated with Prognostic Nutritional Index • Exclusion: (1) malnutrition was assessed by other nutritional screening tools, (2) provided the univariate adjusted risk summary, (3) outcome measures were not of interest or without reported the risk estimate	Prognostic Nutritional Index	All-cause mortality • Lowest vs. highest category: 7 studies, RR 1.79, 95%CI 1.40-2.30, I² 77% • Per unit reduction: 5 studies, RR 1.08, 95%CI 1.04-1.13, I² 77% In-hospital mortality: 2 studies, no meta-analysis • Alatasa 2020: malnutrition defined by Prognostic Nutritional Index <41.2 was independently associated with an increased risk of in-hospital mortality (HR 1.29; 95%CI 1.13-1.46) among elderly patients with acute heart failure • Candeloro 2020: per unit reduction in Prognostic Nutritional Index was not significantly associated with an increased risk of in-hospital mortality (HR 1.05; 95%CI 0.98-1.14) in elderly patients hospitalized for acute heart failure	• Review process by two independent researchers • Restricted to English language • Quality appraisal using Newcastle-Ottawa Scale

Abbreviations: 6MWD: 6-minute walki g distance; 95%CI: 95% confidence interval; AUC: area under the curve; BMI: body mass index; CoI: conflict of interest; CONUT: Controlling Nutritional Status Score; CRP: C-reactive protein; GNRI: Geriatric Nutritional Risk Index; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction; MLHFQ: Minnesota Living with Heart Failure Questionnaire; MNA-SF: Short Form Mini Nutritional Assessment; NYHA: New York Heart Association; OR: odds ratio; PNI: Prognostic Nutritional Index; RCT: randomised controlled trial; RR: relative risk; SPPB: Short physical performance battery.

References

Ali, A., et al., Prognostic value of quality of life and functional status in patients with heart failure: a systematic review and meta-analysis. Egyptian Heart Journal, 2024. 76(1).

Chen, M.Y., et al., Association Between Prognostic Nutritional Index and Prognosis in Patients With Heart Failure: A Meta-Analysis. Frontiers in Cardiovascular Medicine, 2022. 9.

Chen, X. and X. Meng, A systematic review and meta-analysis of frailty in patients with heart failure. Journal of Evaluation in Clinical Practice, 2024.

Chokshi, N.B.K., et al., A Systematic Review of Frailty Scores Used in Heart Failure Patients. Heart Lung and Circulation, 2023. 32(4): p. 441-453.

Dhaliwal, S. and A.P. Kalogeropoulos, Markers of Iron Metabolism and Outcomes in Patients with Heart Failure: A Systematic Review. International Journal of Molecular Sciences, 2023. 24(6): p. 15.

El Iskandarani, M., et al., Prognostic role of albumin level in heart failure: A systematic review and meta-analysis. Medicine (United States), 2021. 100(10): p. E24785.

Fan, Y., X. Gu, and C. Zou, Prediction of all-cause and cardiovascular mortality with weight loss in patients with chronic heart failure: a meta-analysis. European Journal of Preventive Cardiology, 2020. 27(19): p. 2155-2158.

Fan, Y., X. Gu, and H. Zhang, Prognostic value of six-minute walk distance in patients with heart failure: A meta-analysis. European Journal of Preventive Cardiology, 2019. 26(6): p. 664-667.

Fu, Z., et al., Association of systemic inflammatory markers with clinical adverse prognosis and outcomes in HFpEF: a systematic review and meta-analysis of cohort studies. Frontiers in Cardiovascular Medicine, 2024. 11.

Hu, Y., et al., Prediction of all-cause mortality with malnutrition assessed by nutritional screening and assessment tools in patients with heart failure:a systematic review. Nutrition, Metabolism and Cardiovascular Diseases, 2022. 32(6): p. 1361-1374.

Kao, G., et al., Predictive value of quality of life as measured by KCCQ in heart failure patients: A meta-analysis. European Journal of Clinical Investigation, 2024. 54(9): p. e14233.

Ketabi, M., et al., The Effect of Recurrent Heart Failure Hospitalizations on the Risk of Cardiovascular and all-Cause Mortality: a Systematic Review and Meta-Analysis. Current Cardiology Reports, 2024. 26(10): p. 1113-1122.

Kyriakou, M. and P.F. Kiff, Prognosis of the comorbid heart failure and Anemia: A systematic review and meta-analysis. Clinical Trials and Regulatory Science in Cardiology, 2016. 16: p. 12-21.

Lakhani, I., et al., Diagnostic and prognostic value of serum C-reactive protein in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart Failure Reviews, 2021. 26(5): p. 1141-1150.

Lee, K.S., et al., Relationship between comorbidity and health outcomes in patients with heart failure: a systematic review and meta-analysis. BMC Cardiovascular Disorders, 2023. 23(1): p. 498.

Li, H., et al., Prognostic value of geriatric nutritional risk index in elderly patients with heart failure: a meta-analysis. Aging Clinical and Experimental Research, 2021. 33(6): p. 1477-1486.

Milajerdi, A., et al., Pre- and post-diagnosis body mass index and heart failure mortality: a dose-response meta-analysis of observational studies reveals greater risk of being underweight than being overweight. Obesity Reviews, 2018. 20(2): p. 252-261.

Osório, A.F., et al., Prognostic value of nutritional screening tools in hospitalized patients with decompensated heart failure: A systematic review and meta-analysis. Nutrition Research, 2023. 120: p. 1-19.

Qin, W., F. Liu, and C. Wan, A U-shaped association of body mass index and all-cause mortality in heart failure patients: A dose-response meta-analysis of prospective cohort studies. Cardiovascular therapeutics, 2017. 35(2).

Uchmanowicz, I., et al., Frailty and the risk of all-cause mortality and hospitalization in chronic heart failure: a meta-analysis. ESC Heart Failure, 2020. 7(6): p. 3427-3437.

Van Lummel, V., et al., The utility of the surprise question: A useful tool for identifying patients nearing the last phase of life? A systematic review and meta-analysis. Palliative medicine, 2022. 36(7): 1023-1046.

Wang, C., et al., Systematic review and meta-analysis to predict mortality in heart failure with preserved ejection fraction: Development and validation of the HF-DANAS score. ESC Heart Failure, 2024. 11(6): p. 4104-4115.

Wang, X., et al., Prognostic Value of Frailty for Older Patients with Heart Failure: A Systematic Review and Meta-Analysis of Prospective Studies. BioMed Research International, 2018. 2018: p. 8739058.

Wawrzeńczyk, A., et al., Clinical significance of nutritional status in patients with chronic heart failure—a systematic review. Heart Failure Reviews, 2019. 24(5): p. 671-700.

Wu, X., Y. Wang, and X. Hu, Association of weight loss with cardiovascular or all-cause mortality in patients with heart failure: A meta-analysis. International Journal of Obesity, 2024. 48(5): p. 626-634.

Xia, H., et al., The Prognostic Significance of Anemia in Patients With Heart Failure: A Meta-Analysis of Studies From the Last Decade. Frontiers in Cardiovascular Medicine, 2021. 8.

Xu, J., et al., Association Between Disease-specific Health-related Quality of Life and All-cause Mortality in Patients with Heart Failure: A Meta-analysis. Current Problems in Cardiology, 2023. 48(4).

Yamamoto, S., et al., Impact of physical performance on prognosis among patients with heart failure: Systematic review and meta-analysis. Journal of Cardiology, 2020. 76(2): p. 139-146.

Yang, X., et al., Impact of Frailty on Mortality and Hospitalization in Chronic Heart Failure: A Systematic Review and Meta-Analysis. Journal of the American Heart Association, 2018. 7(23): p. e008251.

Zhang, J., et al., Body mass index and all-cause mortality in heart failure patients with normal and reduced ventricular ejection fraction: a dose–response meta-analysis. Clinical Research in Cardiology, 2019. 108(2): p. 119-132.

Zhang, X. and Y. Su, Low Prognostic Nutritional Index Predicts Adverse Outcomes in Patients With Heart Failure: A Systematic Review and Meta-analysis. Angiology, 2024. 75(4): p. 305-313.

Evidence tabel module Proactieve zorgplanning

Vraag 2: Leidt proactieve zorgplanning bij patiënten met hartfalen (NYHA-klasse III-IV of advanced) tot een betere kwaliteit van leven en/of hogere tevredenheid van de patiënt en de naasten?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Delmaczynska 2020	• Design: systematic review	• Eligibility criteria: LVAD implemented as bridge to transplantation (BTT), bridge to	Advance care planning	• See description of individual studies below	• Unclear if review process was done by independent researchers

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Funding: not reported; CoI: none • Search date: Jan 2018 • Databases: CINAHL, Medline, PubMed, PsycINFO • Study designs: all • N included studies: N=1 RCTs	recovery (BTR) or destination therapy (DT) and diverse study designs • Exclusion: palliative care impact on patients' quality of life, not exploring the use of ACP and those focused on how to support families in making decision regarding deactivation of LVAD at the time when patients are critically ill and no advance directives are in place; paediatric patients			• Quality appraisal with Mixed Methods Appraisal Tool • Restricted to English language • No relevant included RCTs
Kernick 2018	• Design: systematic review • Funding: none; CoI: none • Search date: Mar 2017 • Databases: Medline, Cochrane Library, CENTRAL, CINAHL, Elsevier Scopus • Study designs: RCTs, quasi-experimental studies and single-arm observational studies • N included studies: N=4 RCTs	• Eligibility criteria: participants with all causes and classifications of heart failure (preserved systolic function included) • Exclusion: studies involving paediatric, cardiac transplant and left ventricular devices	Advance care planning	• See description of individual studies below	• Study selection and data extraction done by independent reviewers • Quality appraisal with Cochrane Risk of Bias Tool • No language restrictions • Relevant included RCTs: Rogers 2017
Nishikawa 2020	• Design: systematic review + meta-analysis • Funding: National Institute for Health Research (NIHR); CoI: none • Search date: Oct 2019	• Eligibility criteria: adults (18 years of age or older) with a clinical diagnosis of heart failure (all types)	Advance care planning	• See description of individual studies below	• Complete review process done by independent researchers • Quality appraisal with Cochrane Risk of Bias Tool • No language restrictions

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Databases: CENTRAL, Medline, Embase, CINAHL, Social Work Abstracts • Study designs: RCTs • N included studies: N=9 RCTs				• Relevant included RCTs: O'Donnell 2018, Rogers 2017
Schichtel 2020	• Design: systematic review + meta-analysis • Funding: unclear; CoI: none • Search date: July 2018 • Databases: Medline, CINAHL, CENTRAL, DARE, Embase, ERIC, Science Citation Index, Social Science Citation Index & Conference Proceedings, PsycINFO • Study designs: RCTs • N included studies: N=14 RCTs	• Eligibility criteria: patients were eligible if they suffered from heart failure defined as a complex syndrome in which the ability of the heart to maintain the circulation of blood is impaired as a result of a structural or functional impairment of ventricular filling or ejection • Exclusion: studies involving people under the age of 18 years and suffering from congenital heart disease; interventions that only dealt with do-not-attempt cardio-pulmonary resuscitation	Advance care planning	• See description of individual studies below	• Study selection and data extraction done by independent reviewers • Quality appraisal with GRADE • Unclear if language restrictions were used • Relevant included RCTs: Rogers 2017
Williams 2020	• Design: systematic review • Funding: none; CoI: none • Search date: 2009 – Sep 2019 • Databases: PubMed, CINAHL, Embase, Web of Science, Cochrane Library, Johanna Briggs Institute	• Eligibility criteria: adult patients with heart failure or COPD • Exclusion: non-peer reviewed articles and studies without full text	Advance care planning	• See description of individual studies below	• Study selection done by one reviewer, unclear for the rest of the methodology • Quality appraisal with Johns Hopkins Nursing Evidence-Based Practice Evidence Rating Scale • Restricted to English language and studies conducted in the United States

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: all • N included studies: N=1 RCTs				• No relevant included RCTs

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Cheng 2024	• Design: RCT • Funding: Taipei Veterans General Hospital (V109A-021); CoI: none • Setting: cardiology wards of a large medical center, Taiwan • Sample size: N=82 • Duration: conducted between Jan and Dec 2020	• Eligibility criteria: hospitalized patients with heart failure, older than 20 years, ICD-10 codes I50.0, I50.1, or I50.9, physically able to endure the questionnaire interview or self-administer the questionnaire • Exclusion criteria: if they could not read because of poor eyesight, had severe hearing loss, orwere unable to communicate in Chinese or Taiwanese • *A priori* patient characteristics: ○ Mean age: 69.12 vs. 68.07y ○ M/F: 10/31 vs. 8/33 ○ NYHA class: not reported	ACP intervention (N=41): (1) Motivational video: aimed at stimulating the participants' motivations for EOL dialogue (2) Cartoon version educational brochure about ACP (3) Facilitating a guided discussion After watching the video, the researchers discussed the brochure with the participants. The participants were asked to think about their experiences, current health status, future health status, and their practical needs; the participants then recorded their thoughts in writing on the brochure.	• Patient satisfaction: not reported • Family satisfaction: not reported • Care provider satisfaction: not reported • Quality of life: not reported • Quality of dying: not reported • Hospital readmission: not reported • Resuscitation end-of-life ○ Preferences regarding CPR (LSPQ): change from baseline -5.78 vs. -1.05, z = 3.775, p<0.001	Level of evidence: high risk of bias • Opaque sealed envelopes were used to randomly assign participants to the experimental or control groups at a ratio of 1:1 • The researcher responsible for allocating participants was not involved in participant recruitment, data collection, or data analysis • No blinding of participants • Unclear blinding of assessors • ITT analysis • LSPQ scores: 5-point Likert-type scale, a higher score indicates that participants are more inclined to use medical measures

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
			vs. Routine care (N=41)		
Liu 2023	• Design: RCT • Funding: none; CoI: none • Setting: single centre, China • Sample size: N=116 • Duration: conducted between Jan 2022 and Apr 2023	• Eligibility criteria: patients with chronic heart failure NYHA III-IV, cognitive and independent behavioral abilities • Exclusion criteria: malignant tumors, significant organic lesions, history of alcohol and drug dependence, mental illness, previously undergone heart transplant treatment, thyroid system diseases, hematological disorders • *A priori* patient characteristics: ○ Mean age: 73.19 vs. 74.20y ○ M/F: 32/22 vs. 24/25 ○ NYHA: III N=53, IV N=50	Usual care + palliative care intervention (N=54): (1) Palliative care group: 1 cardiologist, 4 nurses, 1 psychological counselor, 1 nutritionist (2) Specific intervention measures for the following 5 aspects: authorization management, symptom management, early care plans, death education, emotional support Content of early care plans: patients were guided to present relevant content in written form when they were in a good state of consciousness, including basic information and future wishes, and were assisted in developing practical and feasible	• Patient satisfaction: not reported • Family satisfaction: not reported • Care provider satisfaction: ○ Nursing satisfaction: total satisfaction 94.44% vs. 81.63%, p=0.043 • Quality of life: MLHFQ (only reported in graph) ○ After the intervention, the MLHFQ scores of the 2 groups decreased compared to those before the intervention, and the study group was significantly lower than the control group (p<0.05) • Quality of dying: not reported • Hospital readmission: not reported • Resuscitation end-of-life: not reported	Level of evidence: high risk of bias • Computer-generated random number table • Unclear allocation concealment • No blinding • 13/116 patients not included in analysis • Nursing satisfaction: doctor-patient relationship and communication, healthcare services, information acquisition support, continuity and cooperation of medical services, with a total score of 100, divided into very satisfied (90–100 scores), satisfied (70–89 scores), and dissatisfied (≤69 scores), with satisfaction and very satisfied included in the total satisfaction

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
			goals and plans, including intubation procedures, refusal of medication rescue, etc. vs. Usual care (N=49)		
Malhotra 2020	• Design: RCT • Funding: Lien Centre for Palliative Care of Duke-NUS Medical School (LCPC-IN14-0001) and Ministry of Health - Health Services Research of Singapore (NMRC/HSRG/0053/2016); CoI: none • Setting: hospital setting, Singapore • Sample size: N=282 • Duration: conducted between Mar 2015 and June 2018	• Eligibility criteria: heart failure inpatients NYHA III-IV aged at least 21 years • *A priori* patient characteristics: ○ Mean age: 64 vs. 65y ○ M/F: 74/19 vs. 146/43 ○ EF <40%: 9.7% vs. 7.9%	ACP intervention, based on the Respecting Choices Model (N=93): (1) Facilitator explored and documented patient preferences for EOL treatments (comfort care/limited additional treatment/full treatment), cardiopulmonary resuscitation (CPR; yes/no) and place of death (2) Patients nominated a surrogate who was encouraged to be present during ACP discussion (3) Facilitators discussed with the treating physician,	• Patient satisfaction: not reported • Family satisfaction: not reported • Care provider satisfaction: not reported • Quality of life: Kansas City Cardiomyopathy Questionnaire, raw data only presented in graph ○ No significant differences during follow-up • Quality of dying: ○ Preferred place of death respected: 52% vs. 51%, p=1.00 ○ EOL treatments consistent with preference: 35% vs. 44%, p=0.47 • Hospital readmission: not reported • Resuscitation end-of-life ○ Preference for CPR respected: 83% vs. 62%, p=0.12	Level of evidence: high risk of bias • Methods of randomization and allocation concealment not described • Blinded assessors • Primary outcomes only assessed for deceased patients (27 vs. 70) • Outcomes assessed every 4 months

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
			who was involved in outpatient medical decision-making, any issues raised during the session (4) The ACP document, signed by patient, surrogate, facilitator, and physician, was filed in national electronic health records vs. Control group (N=189)		
O'Donnell 2018	• Design: RCT • Funding: Watkins Discovery Award from Brigham and Women's Hospital; CoI: none • Setting: single center, US • Sample size: N=50 • Duration: recruitment Sep 2014 – Dec 2015	• Eligibility criteria: patients hospitalized with heart failure at high risk for mortality; at least 1 poor prognostic indicator • Exclusion criteria: already enrolled in hospice or palliative care or anticipated to require cardiac surgery during the 6-month study duration • *A priori* patient characteristics: ○ Mean age: 74.7 vs. 69.2y ○ M/F: 14/12 vs. 15/9 ○ NYHA: III N=32, IV N=18	Social worker-aided palliative care intervention (N=26): (1) Structured goals of care discussion based on the framework of the Serious Illness Conversation Guide conducted by a social worker with 5 years of palliative care experience and training in use of this approach; education was provided around the importance of advanced care planning, the role of	• Patient satisfaction: not reported • Family satisfaction: not reported • Care provider satisfaction: not reported • Quality of life: ○ KCCQ-12, overall score, change from baseline at 6 months: +11.5 vs. +13.9, p=0.95 • Quality of dying: not reported • Hospital readmission: not reported • Resuscitation end-of-life: not reported	Level of evidence: high risk of bias • Permuted block randomization scheme • All patients were identified and enrolled by the study coordinator, who was blinded to the allocation sequence • Blinded assessors • 6-months outcomes only assessed in survivors

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
			health care proxy, and the need for other legal documents such as Power of Attorney (2) Further guidance by palliative care physician (3) Subsequent patient contacts at the discretion of the patient, social worker or physician vs. Usual care (N=24)		
Rogers 2017	• Design: RCT • Funding: National Institute of Nursing Research (NINR).; CoI: many authors with CoI • Setting: single centre, US • Sample size: N=150 • Duration: recruitment Aug 2012 – June 2015	• Eligibility criteria: age > 18 years, hospitalization for acute heart failure (either systolic or with preserved ejection fraction) or within 2 weeks of discharge of a hospitalization for acute heart failure, dyspnea at rest or minimal exertion plus at least 1 sign of volume overload (jugular venous pressure greater than 10 cm, peripheral edema, congestion on chest x-ray), previous heart failure hospitalization within the past 1 year, ESCAPE risk score ≥4 indicating >50% predicted 6-month mortality, anticipated discharge from hospital with anticipated ability	Palliative care intervention for 6 months (N=75): (1) Team: nurse practitioner (coordinator), hospice and palliative care board-certified physician, trained counselor (2) Symptom management using treatment algorithms; self-management with handout (3) Spiritual assessment	• Patient satisfaction: not reported • Family satisfaction: not reported • Care provider satisfaction: not reported • Quality of life: at 6 months ○ KCCQ, overall score: MD 9.49, 95%CI 0.94-18.05, p=0.03 ○ FACIT-Pal: MD 11.77, 95%CI 0.84-22.71, p=0.035 • Quality of dying: not reported • Hospital readmission: total number of hospital encounter records, mean (SE) of per/patient record-counts: 2.5 (0.45) vs. 2.4 (0.35) • Resuscitation end-of-life: not reported	Level of evidence: high risk of bias • Subjects are assigned treatment using a complete randomization scheme • Allocation concealment unclear • Unblinded • Not all patients included in QOL analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		to return to outpatient follow-up appointments; OR, subjects >18 years of age, hospitalized with acute heart failure with signs/symptoms of volume overload who do not meet all other eligibility criteria may also be considered for enrollment if they can be categorized into one of the following high risk groups: (1) support with chronic inotropes without plans for cardiac transplant or cardiac assist device and anticipated discharge from hospital, (2) multiple hospitalizations for heart failure in the past 12 months (minimum 3) and anticipated discharge from hospital, (3) no prior hospitalization for heart failure in the past 12 months but with an ESCAPE score > 4 and anticipated discharge from hospital • Exclusion criteria: acute coronary syndrome within 30 days; cardiac resynchronization therapy within the past 3 months or current plan to implant; active myocarditis, constrictive pericarditis; severe stenotic valvular disease amendable to surgical intervention;	(4) End-of-life preparation using Outlook Intervention (5) Goals of care vs. Usual care (N=75)		

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		anticipated heart transplant or ventricular assist device within 6 months; renal replacement therapy; non-cardiac terminal illness; women who are pregnant or planning to become pregnant; inability to comply with study protocol • *A priori* patient characteristics: ○ Mean age: 71.9 vs. 69.8y ○ M/F: 79/71 ○ NYHA: III N=112, IV N=20			

Abbreviations: 95%CI: 95% confidence interval; ACP: advance care planning; CoI: conflict of interest; CPR: cardiopulmonary resuscitation; EOL: end of life; FACIT-Pal: Functional Assessment of Chronic Illness Therapy - Palliative Care; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVAD: left ventricular assist device; LSPQ: Life Support Preferences Questionnaire; MD: mean difference; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; QOL: quality of life; RCT: randomised controlled trial; SE: standard error.

References

Cheng, H.C., et al., Advance Care Planning Affects End-of-Life Treatment Preferences Among Patients With Heart Failure: A Randomized Controlled Trial. Journal of Hospice & Palliative Nursing, 2024. 26(1): p. E13-E19.

Delmaczynska, E. and R. Newham, To explore the prevalence and outcomes of advance care planning for patients with left ventricular assist devices: A review. Journal of Clinical Nursing, 2019. 28(9-10): p. 1365-1379.

Kernick, L.A., et al., Does advance care planning in addition to usual care reduce hospitalisation for patients with advanced heart failure: A systematic review and narrative synthesis. Palliative Medicine, 2018. 32(10): p. 1539-1551.

Liu, Y., et al., The impact of palliative care on the physical and mental status and quality of life of patients with chronic heart failure: A randomized controlled trial. Medicine, 2023. 102(50): p. e36607.

Malhotra, C., et al., Impact of a Formal Advance Care Planning Program on End-of-Life Care for Patients With Heart Failure: Results From a Randomized Controlled Trial. Journal of Cardiac Failure, 2020. 26(7): p. 594-598.

Nishikawa, Y., et al., Advance care planning for adults with heart failure. Cochrane Database of Systematic Reviews, 2020. 2020(2).

O'Donnell, A.E., et al., Social worker-aided palliative care intervention in high-risk patients with heart failure (SWAP-HF). A pilot randomized clinical trial. JAMA Cardiology, 2018. 3(6): p. 516-519.

Rogers, J.G., et al., Palliative Care in Heart Failure: The PAL-HF Randomized, Controlled Clinical Trial. Journal of the American College of Cardiology, 2017. 70(3): p. 331-341.

Schichtel, M., et al., The Effect of Advance Care Planning on Heart Failure: a Systematic Review and Meta-analysis. Journal of General Internal Medicine, 2020. 35(3): p. 874-884.

Williams, M.T., et al., Advance Care Planning in Chronically Ill Persons Diagnosed With Heart Failure or Chronic Obstructive Pulmonary Disease: An Integrative Review. American Journal of Hospice & Palliative Medicine, 2020. 37(11): p. 950-956.

Evidence tabel module Medicamenteuze behandeling

Vraag 3: Wat is het effect van staken van de volgende medicatie op de kwaliteit van leven bij patiënten met hartfalen NYHA klasse III-IV in de fase voor het overlijden?
- diurectica (eplerenone, spironolacton, furosemide, bumetanide, hydrochlorothiazide, sglt2-remmers [empagliflozine, dapagliflozine])
- beta-blokkers (metoprolol, carvedilol, nebivolol en bisoprolol)
- ace-remmers, angiotensine receptor antagonisten of angiotensin receptor/neprilysin inhibitor (arni (entresto ®)]
- antistolling (thrombocytenaggregatieaggregatieremmers [acetylsalicyslzuur, clopidogrel, prasugrel, ticagrelor], vitamin k-antagonisten [fenprocoumon, acenocoumarol], directe orale anti-coagulantia [dabigatran, rivaroxaban, apixaban, edoxaban])
- inotropica (dobutamine, dopamine, fosfodi-esterase-3-remmers [enoximone, milrinone])

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Kornholt 2022	• Design: systematic review • Funding: Velux Foundation (grant number 00025835) and the Capital Region of Denmark (E-12825-01-12-01), Tværspuljen, Helsefonden,	• Eligibility criteria: randomized discontinuation trials in older patients defined as patients aged at least 65 years • Exclusion: more than 1 medicine or medicine class discontinued; discontinued medicines targeting cancer, transplant complications, or	Discontinuation of a single medicine or a single medicine class	-	• Study selection by two independent reviewers • Unclear if data extraction was done by two reviewers • Quality appraisal with Cochrane Risk of Bias tool by two independent reviewers • Limited to English literature

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Copenhagen University Hospital Bispebjerg and Frederiksberg, and Aase and Ejnar Foundation; CoI: none • Search date: June 2021 • Databases: PubMed, Embase, Cochrane Library • Study designs: RCTs • N included studies: N=40 RCTs	infections, because these treatments are highly specialized or of limited duration; temporary discontinuation, that is, pausing of medicines			• No relevant RCTs: two RCTs (van Kraaij 1999, Nijst 2020) included patients with heart failure, but not within a palliative or end-of-life context
Reeve 2020	• Design: systematic review • Funding: National Health and Medical Research Council (NHMRC) - Australian Research Council (ARC) Dementia Research Development Fellowship, Australia; CoI: none • Search date: Apr 2019 • Databases: Cochrane Hypertension Specialised Register, CENTRAL, Medline, Embase, WHO-ICTR • Study designs: RCTs • N included studies: N=6 RCTs	• Eligibility criteria: adults aged 50 years and over prescribed one or more antihypertensive medication(s) for hypertension or primary prevention of cardiovascular disease living in the community, residential aged care facilities or in hospital settings	Withdrawal of antihypertensive medications in older adults prescribed for hypertension or primary prevention of cardiovascular disease	-	• Complete review was done by independent reviewers • Quality appraisal with Cochrane Risk of Bias tool • No relevant RCTs

Abbreviations: CoI: conflict of interest; RCT: randomised controlled trial.

References

Kornholt, J., et al., Scoping Review of Randomized Trials With Discontinuation of Medicines in Older Adults. Journal of the American Medical Directors Association, 2022. 23(12): p. 1926.e11-1926.e35.

Reeve, E., et al., Withdrawal of antihypertensive drugs in older people. Cochrane Database of Systematic Reviews, 2020. 2020(6).

Evidence tabel module Niet-medicamenteuze behandeling

Vraag 4: Wat is het effect van niet-medicamenteuze behandeling bij patiënten met hartfalen (NYHA III-IV en advanced) op kwaliteit van leven en aantal heropnames?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Hasegawa 2023	• Design: systematic review + meta-analysis • Funding: Japanese Society for Palliative Medicine; CoI: one author with several conflicts • Search date: Sep 2019 • Databases: CENTRAL, Medline, Embase, Ichushi-Web of the Japan Medical Abstracts Society • Study designs: RCTs • N included studies: N=39 RCTs	• Eligibility criteria: adults with any type of advanced progressive illness with dyspnea • Exclusion: RCTs wherein acute respiratory failure was involved in the development of dyspnea and those exploring dyspnea in the emergency department and/or intensive care unit; high-flow nasal cannula oxygen therapy and non-invasive ventilation	Non-invasive supplemental oxygen therapy (nasal cannula, medium concentration, or fixed concentration Venturi or non-rebreather masks)	• See below for individual results	• Review process done by independent reviewers • Unclear if language restriction was applied • Relevant included RCT: Clark 2015
IQWIG 2019	• Design: systematic review • Funding: not reported; CoI: none • Search date: May 2019 • Databases: Medline, Embase, Cochrane Library	• Eligibility criteria: studies with patients with advanced cardiac failure	Telemonitoring	-	• Selection process done by independent reviewers • Unclear if data extraction was done by independent reviewers • Restricted to English and German • No relevant RCTs included

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: RCTs • N included studies: N=4 RCTs				
Jones 2016	• Design: systematic review • Funding: list in article; CoI: list in article • Search date: Jan 2016 • Databases: CENTRAL, Medline, Embase, CDSR, DARE, Cinahl, PsycInfo, BNI, Web of Science • Study designs: RCTs and quasi-RCTs • N included studies: N=18 RCTs	• Eligibility criteria: adults with advanced diseases where muscle loss and weakness is common, that is cancer, COPD, chronic heart failure (NYHA 3/4), or HIV/AIDS	Neuromuscular electrical stimulation	• See below for individual results	• Review process done by independent reviewers • No language restriction • Relevant included RCT: Quittan 2001
Kwekkeboom 2016	• Design: systematic review • Funding: National Institute of Nursing Research of the National Institutes of Health under awards number R01NR013468 (Kwekkeboom, PI) and R00NR012773 (Bratzke, PI); CoI: not reported • Search date: Dec 2014 • Databases: Medline, Cinahl, PsycINFO • Study designs: all • N included studies: N=13, of which 6 RCTs	• Eligibility criteria: adults with heart failure	Cognitive-behavioural therapy	• See below for individual results	• Review process done by independent reviewers • Restricted to English language • Relevant included RCT: Beniaminovitz 2002

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Lorenz 2008	• Design: systematic review • Funding: National Institute of Nursing Research and the Agency for Healthcare Research and Quality (grant no. 290-02-0003); CoI: Amgen (Lorenz) • Search date: Jan 2007 • Databases: Medline, DARE, National Consensus Project for Quality Palliative Care bibliography • Study designs: all • N included studies: unclear	• Eligibility criteria: patients at the end of life	Interventions for improving palliative care	-	• Review process done by independent reviewers • Restricted to English language • No relevant RCTs included
Mo 2022	• Design: systematic review • Funding: Marie Curie I-CAN-CARE Program grant (MCCC-FPO-16-U); CoI: none • Search date: Mar 2021 • Databases: Medline, Embase, AMED, PsycINFO, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science • Study designs: RCT, non-RCT, pre-post design	• Eligibility criteria: palliative care patients	Virtual reality	• See below for individual results	• Review process done by independent reviewers • Restricted to English language • Relevant included RCT: Groninger 2021

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• N included studies: N=2 RCTs				
Yu 2024	• Design: systematic review • Funding: none; CoI: none • Search date: 2018-2023 • Databases: PubMed, Web of Science, Scopus, and Cochrane Library • Study designs: RCTs • N included studies: N=19 RCTs	• Eligibility criteria: adults with heart failure; RCTs with a Jadad score >3	Dietary interventions or oral nutritional supplements	-	• Selection process done by independent reviewers • Unclear if data extraction was done by independent reviewers • Restricted to English language • No relevant RCTs included

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Beniaminovitz 2002	• Design: RCT • Funding: grant from the New York City American Heart Association Grant-in-Aid and the Division of Research Resources, General Clinical Research Centers Program, N.I.H. 5 M01 RR00645; CoI: not reported • Setting: single centre, US • Sample size: N=29 • Duration: unclear	• Eligibility criteria: patients with moderate to severe heart failure • *A priori* patient characteristics: ○ Mean age: 50 vs. 48y ○ M/F: 18/7 ○ Mean LVEF (%): 20 vs. 18%	Exercise training (N=20): - Supervised training sessions, 3 times/week - 15 min each of bicycle and treadmill exercise at a workload corresponding to 50% of peak VO2 with a minute ventilation <25 l/min and a heart rate <120 beats/min - Series of leg calisthenics, including hip flexion and extension with ankle	• Patient satisfaction: not reported • Family satisfaction: not reported • Care provider satisfaction: not reported • Quality of life: ○ MLHFQ: mean change 13 vs. 7, no p-value ▪ Pre: 50 vs. 41 ▪ Post: 37 vs. 33 ○ Guyatt Respiratory Scale: ▪ Pre: 74 vs. 79 ▪ Post: 88 vs. 82 • Quality of dying: not reported • Hospital readmission: not reported • Resuscitation end-of-life: not reported	Level of evidence: unclear risk of bias • Poor description of methods • 2:1 randomization for training versus active control groups, method unclear • Unclear allocation concealment • Unclear blinding • 4/29 patients not included in analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
			weights (5 lb/leg) and thigh muscle contraction using therabands - Each month, an additional set of exercises was added and ankle weights were increased by 2 lb/leg; the resistance of the theraband was also increased vs. Guided imagery (N=9): - 90-min, weekly therapist-guided sessions for 1 month - were taught a series of relaxation/imagery exercises that promoted stress reduction - 15-min tape of the images learned during the session: instruction to listen to the tapes on an audiocassette at least twice daily - patients were encouraged to perform the mental exercises twice daily		

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality

Bourge 2008	• Design: RCT
	• Funding: supported by Medtronic Inc., Minneapolis, Minnesota; CoI: most authors received grants from Medtronic Inc.
	• Setting: multicentre study, US
	• Sample size: N=274
	• Duration: 6 months follow-up
		• Eligibility criteria: at least 18 years old; NYHA class III or IV heart failure (regardless of ejection fraction); managed in centers with an advanced HF program; received optimized standard medical therapy (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a beta-blocker; all medications as tolerated) for at least 3 months before enrollment; at least 1 HF-related hospitalization or emergency department visit necessitating intravenous treatment (e.g., diuretic administration) within the previous 6 months
		• Exclusion criteria: severe chronic obstructive pulmonary or severe restrictive airway disease; pulmonary arterial hypertension; major cardiovascular event (other than hospitalization) within 3 months before enrollment; known atrial or ventricular septal defects; tricuspid or pulmonary stenosis; mechanical right heart valves; severe, noncardiac condition limiting 6-month survival; serum creatinine ≥3.5 mg/dl or chronic renal dialysis; likely to undergo cardiac transplantation within 6 months of randomization; receiving continuous positive inotropic therapy; presently implanted with an incompatible pacemaker or implantable cardioverter-defibrillator (ICD);
			Chronicle group (N=134): monitoring using implantable continuous hemodynamic monitor
			
			vs.
			
			Control group (N=140)
				• Patient satisfaction: not reported
				• Family satisfaction: not reported
				• Care provider satisfaction: not reported
				• Quality of life: not reported
				• Quality of dying: not reported
				• Hospital readmission:
				  ○ After implantation, there were 11 hospitalizations for device-related complications and 4 hospitalizations for procedure-related complications that resulted in a total of 40 additional hospitalization days in 13 of the 274 successful implantation patients
				  ○ During the randomized period, 37 patients in the Chronicle group were hospitalized for HF, compared with 57 patients in the control group; HR 0.64, 95%CI 0.42-0.96, p=0.03)
				• Resuscitation end-of-life: not reported
					Level of evidence: high risk of bias
					
					• Unclear method of randomisation and allocation concealment
					• Single-blinded (patients only)
					• 29/274 patients not included in analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		receiving cardiac resynchronization therapy (CRT) that had not achieved optimal programming for 3 months; of childbearing age without reliable contraceptive measures • *A priori* patient characteristics: ○ Mean age: 58 vs. 58y ○ M/F: 178/96 ○ NYHA class III: 84% vs. 87%			
Clark 2015	• Design: RCT • Funding: funded by the National Institute for Health Research; CoI: none • Setting: multicentre, UK • Sample size: N=139 (of which 25 in a nocturnal oxygen therapy arm that was not included in the analysis) • Duration: follow-up of 24 months	• Eligibility criteria: aged 18 years or over; heart failure from any aetiology; NYHA class III/IV; LV systolic dysfunction confirmed by echocardiography, with LVEF less than 40% or graded as at least 'moderately' impaired on visual inspection if an accurate ejection fraction could not be calculated; receiving maximally tolerated medical management of their heart failure as reached target dose of (or be on maximally tolerated dose of, or be intolerant of) an inhibitor of the renin–angiotensin system shown to improve prognosis, a beta-adrenoceptor antagonist shown to improve prognosis, an aldosterone antagonist • Exclusion criteria: unable to provide written informed consent; had had a cardiac resynchronisation therapy device implanted within the previous 3 months; had coexisting malignant disease if this would affect the study in the investigators' opinion; had interstitial lung disease; had COPD	Home oxygen therapy (N=57) vs. Best medical therapy (N=57)	• Patient satisfaction: not reported • Family satisfaction: not reported • Care provider satisfaction: not reported • Quality of life: ○ MLHFQ: adjusted MD (95%CI) ▪ 3 months: -5.5 (-10.5 to -0.4), p=0.03 ▪ 6 months: -0.1 (-6.9 to 6.7), p=0.98 ▪ 12 months: -2.6 (-11.0 to 5.8), p=0.54 ○ EQ-5D: unadjusted mean (SD) ▪ 6 months: 0.55 (0.23) vs. 0.54 (0.30) ▪ 12 months: 0.46 (0.36) vs. 0.57 (0.25) ▪ 18 months: 0.63 (0.30) vs. 0.65 (0.12) ▪ 24 months: 0.83 (0.02) vs. 0.73 • Quality of dying: not reported • Hospital readmission: ○ Mean number of days alive and out of hospital: 312.8 vs. 329 • Resuscitation end-of-life: not reported	Level of evidence: high risk of bias • Patients were randomised by a member of the research team at the recruiting site using the secure, telephone-based randomisation service at the York Trials Unit • No blinding • 12/114 patients not included in analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		likely to fulfil criteria for LTOT; forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) < 70% and FEV1 < 40% predicted and hypoxia [partial pressure of arterial oxygen (PaO2) < 7.3kPa or saturations < 90%]; were using any device or medication that would impede their ability to use LTOT or NOT, such as continuous positive airway pressure; were unwilling or unable to comply with safety regulations regarding oxygen use, particularly smoking; were unable to complete patient-related information on entry • *A priori* patient characteristics: ○ Mean age: 72.3y ○ M/F: 80/34 ○ NYHA III: 94.7%			
Groninger 2021	• Design: RCT • Funding: grant from the Charles and Mary Latham Fund; CoI: none • Setting: single tertiary centre, US • Sample size: N=94 • Duration: recruitment Oct 2018 – Mar 2020	• Eligibility criteria: age 18 or older, able to complete surveys in English, diagnosed with ACC/AHA stage C or D heart failure, and reported pain 4/10 or greater within the last 24 hours • Exclusion criteria: if they already used virtual reality for personal use, had intractable nausea/vomiting, history of motion sickness, history of seizures or epilepsy, had anatomical cranial structural abnormalities that prevented use of virtual reality headset, were on contact isolation, and/or were participating in another pain management study • *A priori* patient characteristics:	Virtual reality session for 10' (N=54): - Equipment: Facebook Oculus Go - Software: Forest of Serenity vs. Guided imagery session for 10' on portable tablet (N=40)	• Patient satisfaction: ○ Willingness to use the intervention again: 88% vs. 89% • Family satisfaction: not reported • Care provider satisfaction: not reported • Quality of life: FACIT-Pal 14, total score, mean (SD) ○ Post-intervention: 25.8 (5.1) vs. 27.6 (4.9), p=0.0863 • Quality of dying: not reported • Hospital readmission: not reported • Resuscitation end-of-life: not reported	Level of evidence: high risk of bias • Enrolled subjects were randomized by the study coordinator 1:1 using a computerized randomized scheme • Unclear allocation concealment • Subjects and study coordinator not blinded to assigned interventions • Data collection was blinded to the study coordinator; final analysis was

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		○ Mean age: 56.1y ○ M/F: 53/35 ○ NYHA class 2/3: 71.9% ○ NYHA class 4: 28.1% ○ LVAD: 51.1%			completed using a de-identified data set by a statistician blinded to the participants • 6/94 patients not included in analysis
Gulbahar 2022	• Design: RCT • Funding: unclear; CoI: none • Setting: multicentre study, Turkey • Sample size: N=72 • Duration: Oct 2019 – June 2020	• Eligibility criteria: (*a*) 18 years and older, (*b*) diagnosed with NYHA classification stages III and IV HF (who are patients with HFrEF and their left ventricular ejection fraction ≤40% by echocardiography in the past year, and those on a stable medical regimen), (*c*) hospitalized at present due to active HF symptoms, and (*d*) not using a nonpharmacologic approach including herbal therapies, physical activity or exercises, acupuncture, reflexology, meditation, guided imagery or another massage, and relaxation technique during the research process • Exclusion criteria: (*a*) advanced stage chronic obstructive pulmonary disease, asthma, cancer, (*b*) NYHA classification stages I and II HF, and (*c*) active thrombosis or coagulation; patients hospitalized for less than 1 week, who were discharged before 7 days, and who could not complete 14 sessions of CM or BRE • *A priori* patient characteristics: ○ Mean age: 67.4 vs. 63.0 vs. 65.5y ○ M/F: 32/40 ○ NYHA class IV: N=38	Classical massage (N=24): applied on both the hand and foot, twice a day for 30 minutes each for 7 days vs. Benson relaxation exercise (N=26): twice a day for 20 minutes each for 7 days vs. Routine care (N=22)	• Patient satisfaction: not reported • Family satisfaction: not reported • Care provider satisfaction: not reported • Quality of life: ○ SSQ-HF: mean (SD) ▪ Week 1: 39.5 (10.37) vs. 39.61 (8.82) vs. 46.27 (9.47), p=0.028 ▪ Week 3: 36.91 (10.95) vs. 37.7 (8.32) vs. 42.4 (9.53), p=0.123 ○ MLHQF: mean (SD) ▪ Week 1: 65.5 (10.08) vs. 66.15 (9.88) vs. 66.54 (9.76), p=0.066 ▪ Week 3: 61 (10.57) vs. 62.92 (10.07) vs. 63.45 (8.65), p=0.405 • Quality of dying: not reported • Hospital readmission: not reported • Resuscitation end-of-life: not reported	Level of evidence: high risk of bias • Stratified allocation using a computer program • Independent statistician, who was not involved in the interventional procedures and was blind to the study groups, allocated the participants • No blinding of participants and principal investigator • A single independent statistician analyzed the data • 2/72 patients not included in analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Quittan 2001	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single university centre, Austria • Sample size: N=42 • Duration: follow-up of 8 weeks	• Eligibility criteria: patients diagnosed with severe chronic heart failure, making the patients listed for heart transplantation; an established and optimized drug therapy, including chronic intravenous bridging therapy to heart transplantation with prostaglandin E1 or in combination with dobutamine via a portable pump • Exclusion criteria: pacemakers, peripheral edemas counteracting NMES, unstable disease course including signs of acute heart failure or severe arrhythmia, and disorders that counteracted strength testing or NMES of the thigh muscles • *A priori* patient characteristics: ○ Mean age: 59 vs. 57y ○ M/F: 21/12 ○ NYHA: II N=8, III N=19, IV N=6	Neuromuscular Electrical Stimulation, up to 60' per day, 5 days per week, during 8 weeks (N=17) vs. Control group (N=16)	• Patient satisfaction: not reported • Family satisfaction: not reported • Care provider satisfaction: not reported • Quality of life: SF-36, median change from baseline at 8 weeks ○ Physical functioning: 7.5 vs. -5.0 ○ Physical role: 0 vs. 0 ○ Emotional role: 33.3 vs. 0 ○ Social functioning: 18.8 vs. -12.5 • Quality of dying: not reported • Hospital readmission: not reported • Resuscitation end-of-life: not reported	Level of evidence: high risk of bias • Block-wise randomization list (groups of six) provided by the Department of Medical Statistics • The physician doing the randomization was not further involved in practical aspects of the trial and kept the code locked until the end of the study period • Patients not blinded • The personnel performing all measurements were not aware of the patients' group assignments • 9/42 patients not included in analysis
Yang 2024	• Design: RCT • Funding: National Natural Science Foundation of China (71904143 and 71974142), the Youth Program of Tianjin Nursing Association (tjhlky2022QN08) and Nursing Special Development Fund of Tianjin Medical University (2022XKZX-04); CoI: none	• Eligibility criteria: patients: (1) inpatients had a diagnosis of HF classified as NYHA Class Ⅲ–Ⅳ and ejection fraction ≤40%, (2) aged 18 years or older; (3) able to express themselves, (4) able to use a smartphone; caregivers: (1) patient's family members or close relatives, (2) providing care free of charge and spending at least 24 hours per week caring for patients with HF, (3) able to express themselves; (4) able to use a smartphone • Exclusion criteria: (1) taking psychotropic drugs and (2)	Dignity therapy (N=35): four sessions including one face-to-face session before discharge and three online sessions over 1 week after discharge vs. Usual care (N=35)	• Patient satisfaction: not reported • Family satisfaction: not reported • Care provider satisfaction: not reported • Quality of life: ○ MLHQF: mean (SD) ▪ 1 week: 69.92 (10.96) vs. 70.97 (12.53), t=-0.762, p=0.449 ▪ 4 weeks: 70.00 (10.64) vs. 70.47 (12.53), t=-0.350, p=0.727 ▪ 8 weeks: 70.25 (10.89) vs. 70.63 (12.49), t=-0.273, p=0.786 ▪ ANOVA: between groups F=0.057 (p=0.812); interaction effect F=8.426 (p=0.007) • Quality of dying: not reported	Level of evidence: high risk of bias • Randomisation using Research Randomizer website • To ensure allocation concealment, the random numbers were packaged by a third party in sequentially numbered, sealed and opaque envelopes • Patients not blinded • The data was collected by a research assistant who was

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Setting: single university centre, China • Sample size: N=70 dyads • Duration: May – Dec 2021	participating in other studies in the last 3 months • *A priori* patient characteristics: ○ Mean age patients: 72.4y ○ Mean age family caregivers: 57.1y ○ M/F patients: 39/25 ○ M/F family caregivers: 26/38		• Hospital readmission: not reported • Resuscitation end-of-life: not reported	blind to the between-group assignment • 8 dyads not included in analysis

Abbreviations: 95%CI: 95% confidence interval; ACC/AHA: American College of Cardiology/American Heart Association; CoI: conflict of interest; FACIT-Pal: Functional Assessment of Chronic Illness Therapy - Palliative Care; HR: hazard ratio; MD: mean difference; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; QOL: quality of life; RCT: randomised controlled trial; SD: standard deviation.

References

Beniaminovitz A, Lang CC, LaManca J, Mancini DM. Selective low-level leg muscle training alleviates dyspnea in patients with heart failure. J Am Coll Cardiol. 2002; 40(9):1602–1608.

Bourge, R.C., et al., Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. Journal of the American College of Cardiology, 2008. 51(11): p. 1073-9.

Clark AL, Johnson M, Fairhurst C, Torgerson D, Cockayne S, Rodgers S, et al. Does home oxygen therapy (HOT) in addition to standard care reduce disease severity and improve symptoms in people with chronic heart failure? A randomised trial of home oxygen therapy for patients with chronic heart failure. Health Technol Assess 2015;19:1-120.

Groninger, H., et al., Virtual reality for pain management in advanced heart failure: A randomized controlled study. Palliative Medicine, 2021. 35(10): p. 2008-2016.

Gulbahar Eren, M. and Z. Gok Metin, Classical Massage and Relaxation Exercise on Symptom Status and Quality of Life in Advanced Stage Patients With Heart Failure: A Randomized Controlled Trial. Holistic Nursing Practice, 2022. 36(3): p. E1-E11.

Hasegawa, T., et al., Efficacy of supplemental oxygen for dyspnea relief in patients with advanced progressive illness: A systematic review and meta-analysis. Respiratory Investigation, 2023. 61(4): p. 418-437.

IQWIG, Data-supported timely management in cooperation with a physician-staffed centre for telemedicine in advanced cardiac failure. Institute for Quality and Efficiency in Health Care, 2019. 11: p. 28.

Jones, S., et al., Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. Cochrane Database of Systematic Reviews, 2016. 2016(10).

Kwekkeboom, K.L. and L.C. Bratzke, A Systematic Review of Relaxation, Meditation, and Guided Imagery Strategies for Symptom Management in Heart Failure. Journal of Cardiovascular Nursing, 2016. 31(5): p. 457-68.

Lorenz, K.A., et al., Evidence for improving palliative care at the end of life: a systematic review. Annals of Internal Medicine, 2008. 148(2): p. 147-59.

Mo, J., et al., How effective is virtual reality technology in palliative care? A systematic review and meta-analysis. Palliative Medicine, 2022. 36(7): p. 1047-1058.

Quittan M, Wiesinger GF, Sturm B, Puig S, Mayr W, Sochor A, et al. Improvement of thigh muscles by neuromuscular electrical stimulation in patients with refractory heart failure: a single-blind, randomised, controlled trial. American Journal of Physical Medicine and Rehabilitation 2001;80:206-14.

Yang, W., et al., Advanced heart failure patients and family caregivers health and function: randomised controlled pilot trial of online dignity therapy. BMJ Supportive and Palliative Care, 2024. 14(e1): p. E1361-E1371.

Yu X, Chen Q, Lou IX. Dietary strategies and nutritional supplements in the management of heart failure: a systematic review. Front Nutr. 2024 Oct 11;11:1428010. doi: 10.3389/fnut.2024.1428010.