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The Effect of Resistance Training on Markers of Cachexia in Patients with Heart Failure: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Cachexia is a metabolic syndrome characterised by muscle wasting that is highly prevalent in subjects with heart failure (HF) and negatively affects physical function, quality of life, morbidity and mortality. Resistance training has been recently incorporated into cardiac rehabilitation exercise programmes to increase muscle strength in patients with HF. This systematic review and meta-analysis aim to assess the effects of resistance training on markers of cachexia in patients with HF.

Methods: Four electronic databases (MEDLINE, Embase, CENTRAL and CINAHL) were searched to identify randomised controlled trials (RCTs) evaluating the effects of resistance training-only programmes on published criteria for cachexia assessment including muscle strength, body composition (e.g. lean mass/muscle mass) or biochemical markers of cachexia (e.g. inflammatory markers) in patients with HF. Studies were selected based on pre-specified inclusion and exclusion criteria, with a risk of bias assessment carried out. Meta-analyses of muscle strength outcomes were completed using RevMan 5.4.1.

Results: Nine studies were included in this review. Pooled analysis of one repetition-maximum strength test of the lower [SMD 0.67 (95% Cl – 0.12, 1.22) p-value = 0.02] and upper extremities [SMD 1.20 (95% Cl – 0.62, 1.79) p-value <0.0001] showed a significant increase in muscle strength associated with resistance training, which are both important indicators of physical function. Resistance training did not increase muscle strength during rapid movements measured via peak torque at 60, 90 or 180°/s. There were no significant results recorded for changes in body composition and biochemical markers of cachexia. There were inconsistent findings for the effect of resistance training on quality of life. No studies reported findings on measures of anorexia or fatigue.

Conclusions: The findings of this review reveal the potential benefits of resistance training in preserving and enhancing muscle strength in patients with HF who are at risk of cardiac cachexia. Despite inconclusive results on body composition and quality of life, the inclusion of resistance training in cardiac rehabilitation guidelines has the potential to address issues of muscle weakness and frailty. Specific resistance training protocol recommendations to prevent or treat the development of cachexia cannot be made without the publication of more robust RCTs, specifically examining cachectic patients with heart failure with careful assessment of clinical outcomes of markers of cachexia.

1 | Background

Heart failure (HF) is a complex and progressive clinical syndrome characterised by the failure of the heart to deliver oxygenated blood to peripheral tissues to meet metabolic demands [1]. Patients with HF are diagnosed based on measurement of left ventricular ejection fraction (LVEF); those with LVEF ≥50% are characterised as HF with preserved ejection fraction (HFpEF), LVEF <40% is HF with reduced ejection fraction (HFrEF), and patients with LVEF of 40–49% are considered HF mid-range ejection fraction (HFmEF) [2, 3]. The classification of patients into different types of HF is also often based on the severity of symptoms and exercise tolerance, based on the New York Heart Association (NYHA) functional classification, with class 'I' being the least severe and 'IV' being the most severe [2, 3]. The prevalence of HF is ever growing among the aging population, leading to constraints on healthcare costs [2]. Despite the development of disease management therapies, HF remains associated with high rates of morbidity and mortality [4]. Patients living with HF often report a poorer quality of life (QoL), reduced functional ability and reduced independence [5].

A subset of patients with HF are at risk of malnutrition [6], frailty [7], cachexia [8] or sarcopenia [9], characterised by certain HF clinical features, such as decreased muscle strength, fatigue and body weight loss, with these conditions frequently overlapping [8, 10]. Cachexia is "a complex metabolic syndrome associated with an underlying illness and characterised by loss of muscle with or without loss of fat mass" [11]. Cardiac cachexia affects a subset of patients, approximately 10–39%, independent of age or severity of disease, and negatively affects function, QoL, morbidity and mortality [8]. Various aspects of the HF syndrome, such as inflammation, nutrient malabsorption, altered endocrine mediators [12] or the potential development of cardio-renal syndrome [13], could contribute to this cardiac cachexia risk. HF creates an environment favouring inflammation, with increased production of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-alpha), low levels of anabolic hormones, such as growth hormone, IGF-1 axis activity, and testosterone in men, anorexia and insulin resistance. These features of illness trigger involuntary and severe body mass loss and muscle wasting, leading to weakness and fatigue [11]. Different diagnostic criteria are used to diagnose cachexia, such as Evan et al.'s, which includes: unintentional weight loss of at least 5% in the previous 12 months, or a body mass index of less than 20 kg/m^2, and three of the following five clinical criteria: decreased muscle strength (such as hand-grip strength), fatigue, anorexia, low-fat free mass index and abnormal biochemistry (increased inflammatory markers, anaemia or low serum albumin) [11].

Several markers of cardiac cachexia have been identified and are used to predict outcomes of HF. Dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging and computed tomography are some tools used to diagnose muscle loss [11]. However, other markers of poor performance, indicated by functional measurements such as poor muscle strength, measured by isokinetic dynamometers, or 1-repetition maximum (RM) tests, and QoL questionnaires could indicate cachexia development and may predict poor HF prognosis [14]. Cardiac cachexia is linked to heightened activity in the sympathetic nervous system. This association is discerned through the measurement of heart rate variability (HRV), which refers to the variation in time intervals between consecutive heartbeats [15]. In the context of cardiac cachexia, abnormal HRV signifies an imbalance in the autonomic nervous system, particularly an overstimulated sympathetic system. Elevated norepinephrine levels, a neurotransmitter associated with the sympathetic response, further contribute to this dysregulation. The resultant diminished HRV indicated an impaired ability of the heart to adapt to changing demands, reflecting the progression of cardiac cachexia and contributing to a poorer prognosis in patients with HF [16, 17].

Exercise, defined as a structured physical activity performed to improve physical function, has been widely incorporated into clinical guidelines of HF care [18]. Systematic reviews assessing the effect of exercise in patients with HF reveal the integral role of exercise in improving QoL, physical capacity, and physiological outcomes [5, 18, 19]. Aerobic training (AT) has been the primary mode of exercise rehabilitation recommended in patients with HF. Evidence on the effects of aerobic training on HF suggests favourable outcomes in cardiovascular mortality rate, aerobic power (VO_2 peak) [20], sympathovagal balance, exercise tolerance [21] and enhanced insulin sensitivity [22]. Alongside the involvement of neuro-hormonal and inflammatory mechanisms, it can be contended that disuse atrophy of skeletal muscle constitutes a facet in the progression of cachexia [14]. Therefore, incorporating muscle strengthening or resistance exercise could potentially be deemed more appropriate to prevent the degradation of skeletal muscle mass and the development of cachexia, and to improve the prognosis of disease in patients with HF.

Resistance training (RT) involves the use of resistance to increase strength, power and muscle mass. In healthy older adults, a strong body of evidence suggests that a structured RT programme is associated with muscle hypertrophy and increased muscle strength [23]. RT has also been associated with increased resting metabolic rate and reduced body fat percentage [24]. In patients with HF, concerns about the safety of RT have been one of the main reasons for the favouring of AT in cardiac rehabilitation. However, a study assessing the safety of resistance exercises in patients with chronic heart failure (CHF) allayed the concerns of safety by demonstrating tolerability of RT in all patients with no adverse events concerning left ventricular function, including the development of ventricular arrhythmia [25]. Over the past few decades, studies revealing the safety of RT have been published and exercise programmes incorporating RT have been linked to the reversal of skeletal muscle atrophy, the increase in strength and the improvement of QoL in patients with CHF [26].

Previous systematic reviews and meta-analyses, published in 2016 [27], 2017 [28] and 2021 [29], reported on the effects of RT on aerobic capacity, muscle strength and QoL in patients with HF. However, despite reporting on muscle strength, none of the previous analyses focused primarily on the effects of RT on markers of cachexia in HF, leading to differences in inclusion criteria and outcomes of interest. Furthermore, new research has emerged since the publication of the previous meta-analyses.

This study aims to conduct a systematic analysis of randomised clinical trials to investigate the effects of adhering to an RT protocol on markers of cachexia in patients with HF. These markers include changes in anthropometric measurements, inflammatory markers or muscle strength measurements.

2 | Methods

This systematic review of literature was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30]. This review was registered on PROSPERO (registration number: CRD4202346399) including the detailed prespecified protocol.

2.1 | Search Strategy

For electronic databases (MEDLINE via Ovid, Embase via Ovid, Cumulative Index to Nursing and Allied Health Literature [CINAHL] via EBSCO and Cochrane Central Register of Controlled Trials [CENTRAL]) were searched to identify relevant studies published from inception up until July 2023. The search strategy used was reviewed by an Information Specialist, including – but not limited to – terms such as 'heart failure', 'cardiac failure', 'CHF', 'resistance training', 'strength training' and 'weight lifting'. An example of the search strategy used on MEDLINE via Ovid can be found in Supplementary Materials (S1). Reference lists from previously published systematic reviews [27–29] and reference lists of included studies were reviewed for potential additional studies. No language or publication date restrictions were set.

2.2 | Inclusion and Exclusion Criteria

2.2.1 | Study Design

Only randomised controlled trials (RCTs) were included. Studies with non-human participants or studies where patients were not identified and reported as having HF were excluded.

2.2.2 | Population

Studies including patients, of any gender, aged 18 years or older diagnosed with HF with preserved, moderately reduced and reduced ejection fractions were included. Studies including diagnosis of acute or decompensated HF were excluded. Studies including pregnant women and patients undergoing chemotherapy, or any form of reversible HF, were excluded.

2.2.3 | Intervention

To meet the inclusion criteria, studies must have a defined RT-only intervention group and a non-trained control group, or low-intensity exercise to serve as a placebo intervention. The RT group should undergo a programme where an external force of resistance or body weight resistance is used to complete a set of exercises in circuit form or specific sets/repetitions form. Resistance-based exercises could involve a variety of equipment, including weight-lifting machines or resistance bands. Studies with interventions lasting less than two weeks were excluded. Studies with interventions of different physical conditioning therapies in conjunction with RT, including an intervention of RT and AT combined, versus a control group were excluded.

2.2.4 | Outcomes

The primary outcomes of interest were diagnostic criteria of cachexia. Eligible studies included at least one of the following outcomes:

- Muscle strength measurements — measured using an isokinetic dynamometer, 1-RM test or handgrip strength test.
- Anthropometry measurements — body mass index (BMI), body weight, fat-free mass index (FFMI), DEXA, bioelectrical impedance analysis (BIA) or skeletal muscle mass measurements.
- Biochemical assessment — inflammatory markers (C-reactive protein [CRP], TNF-alpha, IL-6), anaemia or low serum albumin.

The secondary outcomes include QoL, fatigue, anorexia, depression, mortality and hospitalisation.

Studies that did not assess any of the primary outcomes were excluded, given the aim of this study.

2.3 | Study Selection

Rayyan software was employed to consolidate records from the various database searches and remove duplicates. Title screening was performed by one reviewer (RH), using the above states pre-specified eligibility criteria. Full texts of studies considered eligible for inclusion were subsequently screened by three independent reviewers (RH, AS, NMG). Studies that did not have accessible full-text versions were excluded.

2.4 | Data Extraction

Data extraction was conducted by one reviewer (RH), and discussed and corroborated by the two additional investigator reviewers (NM and AS). Data, including author, year of publication, location, study population, sample size, intervention characteristics, control characteristics, period of follow-up, adverse events, outcomes assessed and main findings, were tabulated for each study.

2.5 | Risk of Bias Assessment

The Cochrane risk of bias tool for randomised controlled trials (RoB.2) was used to assess the risk of bias and methodological

quality of the included studies. This assessment accounted for selection bias, performance bias, detection bias, attrition bias and reporting bias [31]. To assess the overall risk of bias for each study, the following classification criteria were used: a study was deemed "low risk of bias" if all domains of the RoB.2 were judged to be low risk, a study was judged as "raising some concerns" if unclear risks or concerning risks were raised for any of the domains, and a study was considered "high risk of bias" if at least one domain was recorded as high risk [32].

2.6 | Measurement of Treatment Effect and Data Synthesis

Revman 5.4.1 was used to perform meta-analysis on outcomes measured when two or more studies assessed the effect of the intervention on said measure with appropriate levels of heterogeneity [33]. Continuous measurements given as mean and standard deviation (SD) were used for assessing data. No dichotomous variables were analysed. In the event of an unreported change in mean or SD, the change in mean was calculated by subtracting the mean prior to intervention from the mean post-intervention. The change in standard deviations was calculated using the formula, $SD = \sqrt{(SD\ at\ baseline)^2 + (SD\ post - treatment)^2 - (2\rho \times SD\ at\ baseline \times SD\ post\ treatment)}$ with the assumption that ρ=0.5 [34]. The I^2 statistical test was used to calculate statistical heterogeneity and pooled data was represented as change in mean and 95% confidence intervals. p-Value <0.05 was deemed statistically significant. Where meta-analysis was not possible, outcome measures were presented as reported in the study or as a narrative description.

3 | Results

3.1 | Selection Process

A PRISMA flow chart showing a summary of the process of study selection is shown in Figure 1. The initial database search identified a total of 2121 studies, and an additional study was identified through a separate reference list search, bringing the total to 2122 studies. After the removal of duplicates (n = 134), 1988 titles were screened, of which 1869 titles were determined to not meet inclusion criteria. Abstract screening for the remaining 119 studies was independently completed by three reviewers (RH, AS, NMG), with 99 further studies excluded, and

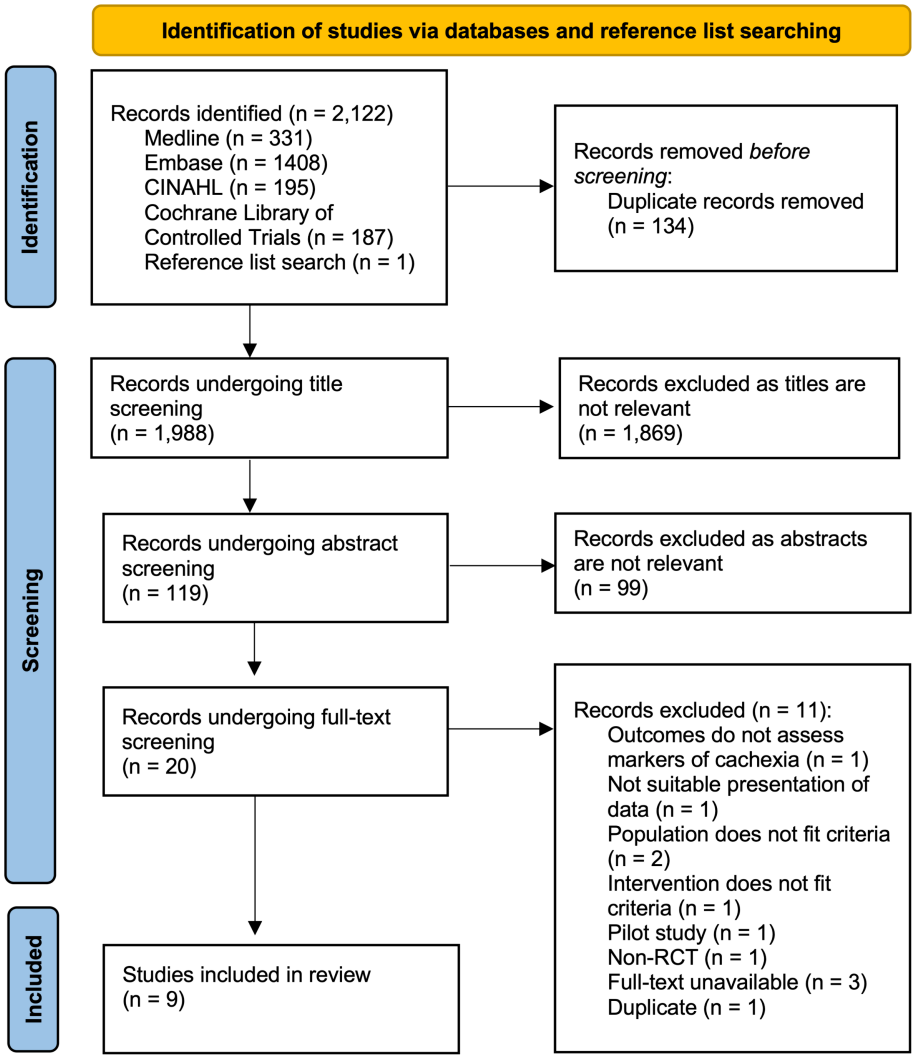

FIGURE 1 | PRISMA flow chart of selection process.

20 full-text studies were retrieved for assessment of eligibility. Eleven of these studies did not meet the criteria and were excluded; two did not assess relevant outcomes [35, 36], two assessed an ineligible population [37, 38], one incorporated an ineligible intervention [39], two were ineligible study designs (pilot study [40], not randomised [41]), one was a duplicate, and three studies were not available in full-text versions, as only the abstracts were published (authors were contacted in an attempt to obtain full-text versions but no response was received). Nine studies were then eligible to be included in this review.

3.2 | Study Characteristics

Characteristics of the included studies can be found in Supplementary Materials (S2). All nine studies were parallel RCTs, published between 1997 and 2021.

3.2.1 | Participants

The study sample sizes ranged from 13 to 39 participants. In total, 200 participants were included, 102 participants were allocated to an RT intervention group and 98 served as control group participants. Seven studies included patients aged 50–85 years old [42–48], while two studies included patients aged 40 years and older [49, 50]. All studies recruited patients previously diagnosed with CHF. All studies included patients with HFrEF only, except one, which also included patients with preserved and mid-range ejection fraction [50]. Four studies included patients with HF of NYHA classes I–III [43, 46, 48, 50], while the other five studies only included patients of classes II–III [42, 44, 45, 47, 49].

3.2.2 | Intervention

There were variations in the interventions used in the included studies. The length of the interventions varied from six weeks to 20 weeks. RT was performed three times a week in all studies, except Cider et al., where it was performed twice a week [45]. The weight lifted by participants progressively increased according to tolerability in all studies, except Groennebaek et al., where the load remained at 30% of 1RM for each individual [43]. Most of the interventions comprised free weights and weighted machines, with some variations; Cider et al. included functional activities, such as getting up from chairs and dressing, into the RT intervention [45]. Cider et al. and Turri-Silva et al. performed the RT programme in circuit form [45, 50]. Groennebaek et al. incorporated pneumatic cuffs to establish a blood-flow-restricted RT programme, where cuffs were placed around the proximal portion of the thighs during exercise [43]. Regarding the comparison group, all studies compared RT to an untrained control group that continued usual care, aside from Pu et al., who incorporated a low-intensity stretching exercise program to serve as a placebo intervention [46].

3.3 | Risk of Bias

The risk of bias assessment summary for the included studies is presented in Figure 2, with full assessment details found in Supplementary Materials (S3). Random sequence generation, accounting for selection bias, was low risk in three studies [42, 46, 50], unclear in five studies [43–45, 47, 48] and high risk in one study [49]. Allocation concealment, also accounting for selection bias, was low risk in two studies [46, 50], unclear in five studies [42, 44, 45, 47, 48] and high risk in two studies [43, 49]. The blinding of participants and personnel, accounting for performance bias, was low risk in one study [46], as it incorporated a placebo intervention, unclear in seven studies [42, 44, 45, 47–50], as blinding of participants was not fully explained or accounted for clearly, and high risk in one study [43]. Due to the nature of the interventions, control groups in eight studies did not receive an exercise intervention, making it challenging to have blinding of participants. The blinding of outcome assessment, accounting for detection bias, was low risk in five studies [42, 44, 46, 47, 50], unclear in two [45, 49] and high risk in two studies [43, 48]. Incomplete outcome data risk, accounting for attrition bias, was low risk in seven studies [42, 43, 45–48, 50], unclear in one [49] and high risk in one study [44]. Selective reporting risk, accounting for reporting bias, was low risk in one study [50], unclear in seven studies [42–44, 46–49] and high risk in one study [45]. No other biases were reported in any included study. Therefore, the overall risk of bias assessment for the studies is considered as follows: Cider 1977 is considered high risk of bias [45], Pu 2001 is judged to raise some concerns [46], Selig 2004 is high risk of bias [44], Williams 2007 is judged to raise some concerns [42], Palveo 2009 is judged to raise some concerns [47], Feiereisen 2013 is high risk of bias [49], Groennebaek 2019 is high risk of bias [43], Lan 2020 is high risk of bias [48] and Turri-Silva 2021 is judged to raise some concerns [50].

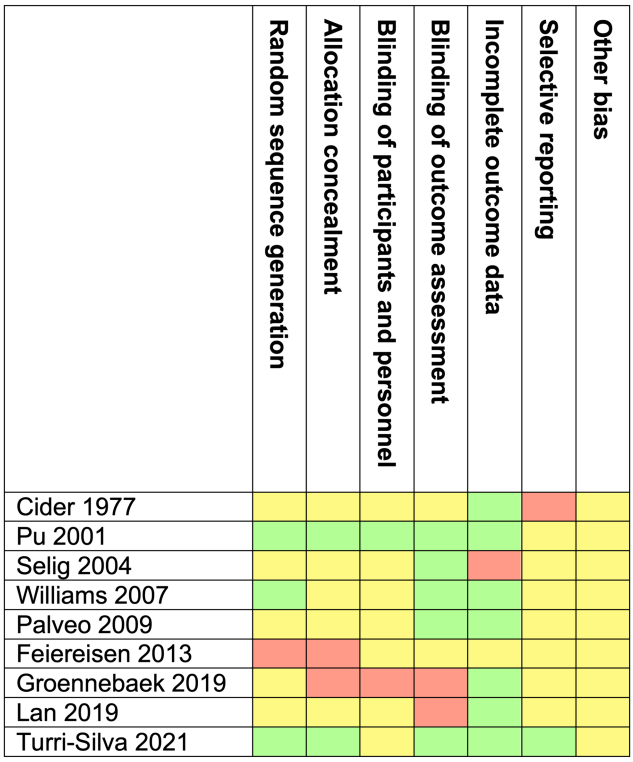

FIGURE 2 | Risk of bias assessment using Cochrane Risk of Bias Tool for RCTs (green indicates low risk, yellow indicated unclear risk and red indicates high risk).

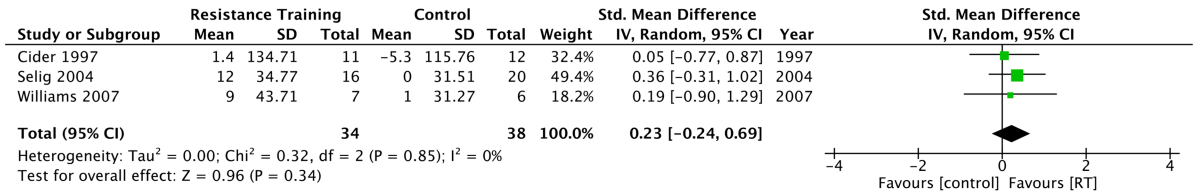

Figure 3(a) - Change in Isokinetic Peak Torque Knee Extensors at 60 degrees/sec

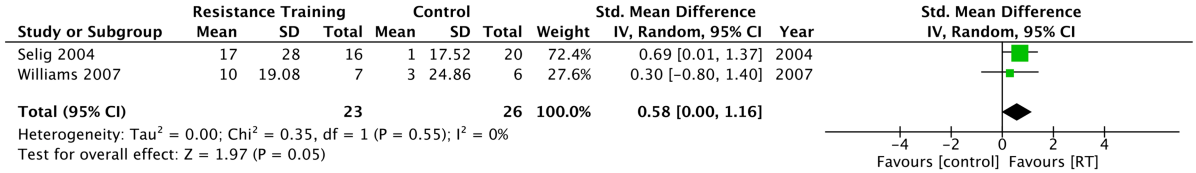

Figure 3(b) - Change in Isokinetic Peak Torque Knee Flexors at 60 degrees/sec

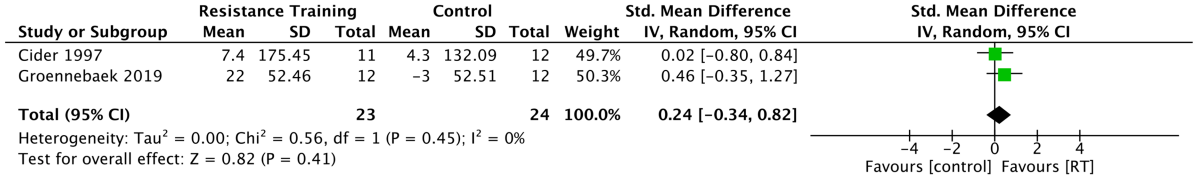

Figure 3(c) - Change in Isometric Peak Torque Knee Extensors at 60 degrees/sec

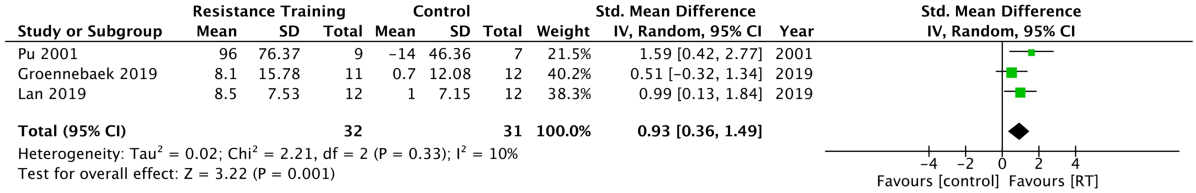

Figure 3(d) - Change in Knee Extensors 1RM Strength

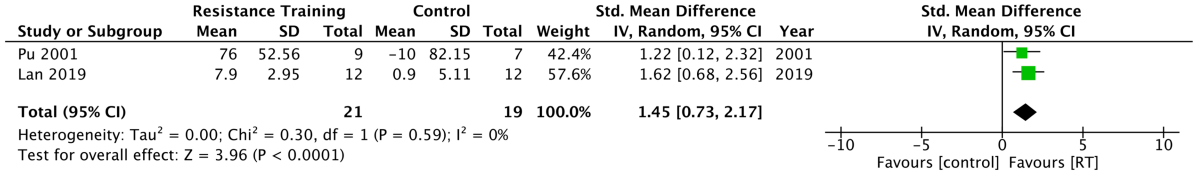

Figure 3(e) - Change in Knee Flexors 1RM Strength

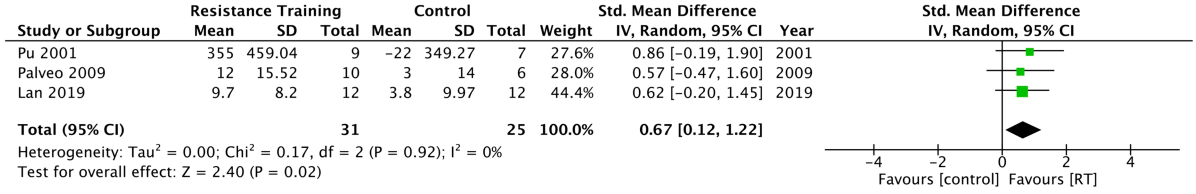

Figure 3(f) - Change in Leg Press 1RM Strength

FIGURE 3 | Change in Lower Body Strength, measured by an isokinetic dynamometer (a–c) or a 1-repetition-maximum test (d–3), showing pooled analysis data as standard mean difference (95% confidence interval) [42–45].

3.4 | Effect of Interventions

3.4.1 | Resistance Training and Muscle Strength

3.4.1.1 | Effects of Resistance Training on Lower Body Strength. Four studies analysed the effect of RT on lower body strength using an isokinetic/isometric dynamometer. A total of 96 participants were included in the meta-analysis of lower body isokinetic/isometric peak torque strength, with 46 participants in the intervention group and 50 in the control group. Cider et al. used a *KINetic COMmunicator II*, an isokinetic hydraulically driven and microcomputer-controlled device [45], while Selig et al. and Williams et al. used the *MERAC isokinetic dynamometer* model [42, 44] and Groennebaek et al. used the *HUMAC* model [43]. The strength of knee extensors measured by isokinetic peak torque at 60°/s (Nm) was measured by three studies [42, 44, 45], and through meta-analysis showed a trend towards improvement in muscle strength associated with RT, compared to the control group and compared to baseline strength of the RT group. However, the results were not statistically significant [SMD 0.23 (95% CI − −0.24, 0.69) p-value = 0.34], as seen in Figure 3(a). Similarly, the isokinetic peak torque strength of knee flexors at 60°/s, measured by two studies [42, 44], showed favourability for RT, compared to the control group, but with statistically nonsignificant results [SMD 0.58 (95% CI − 0.00, 1.16) p-value = 0.55], as seen in Figure 3(b). Change in isometric peak torque strength of knee extensors at 60°/s, measured by two studies [43, 45], was also statistically insignificant [SMD 0.24 (95% CI − −0.34, 0.82) p-value = 0.41], but slightly favouring RT, as seen in Figure 3(c). No heterogeneity was detected ($I^2 = 0\%$) in any pooled results measuring muscle strength using an isokinetic dynamometer ($p = 0.85$, $p = 0.55$ and $p = 0.45$, Figure 3(a) to (c) respectively).

Four studies assessed the effect of RT on lower body strength by using a 1RM test [43, 46–48]. A total of 79 participants were included in the meta-analysis of lower body 1RM strength, with 42 participants in the intervention group and 37 in the control group. The 1RM strength of knee extensors, measured by three studies [43, 46, 48], showed a significant improvement in muscle strength after RT when compared to untrained control groups [SMD 0.93 (95% CI − 0.36, 1.49) p-value = 0.001], with a very low measure of heterogeneity detected ($I^2 = 10\%$, $p = 0.33$), as seen in Figure 3(d). As for the 1RM strength of knee flexors, when analysing the effects of leg curl training on knee flexor strength in two studies [46, 48], RT led to statistically significant improvement in strength, compared to the control group [SMD 1.45 (95% CI − 0.73, 2.17) p-value <0.0001], as seen in Figure 3(e). Change in overall lower body strength was analysed by a 1RM leg press test, done by three studies [46–48]. Results showed significant improvement in strength after RT compared to control groups [SMD 0.67 (95% CI − 0.12, 1.22) p-value = 0.02], as seen in Figure 3(f). No heterogeneity was detected in measures of knee flexors and leg press 1RM ($I^2 = 0\%$, $p = 0.59$ and $p = 0.92$ in Figure 3(e) and (f)).

Two studies recorded measurements of muscle strength but were ineligible to be included in the meta-analysis due to an insufficient number of studies assessing the same outcome [45, 50]. Cider et al. measured the strength of knee extensor muscles by isokinetic peak torque at 180°/s (Nm) [45]. RT showed no significant improvement compared to the control group in the isokinetic peak torque knee extensor strength at 180°/s (Table 1). Turri-Silva et al. calculated the isokinetic peak torque strength of knee extensors at 90°/s (Nm), showing no significant improvement in strength after RT when compared to untrained individuals [50] (Table 1).

3.4.1.2 | Effects of Resistance Training on Upper Body Strength. Three studies assessed the effects of RT on upper body strength by measuring the 1RM of the pectoralis

TABLE 1 | Change in muscle strength outcomes assessed by included studies and not included in meta-analysis [45, 50].

Study	Sample size	Outcome assessed	Findings	Measure of assessment
Cider 1997	$N = 34$ RT − 12 Control − 12	Isokinetic peak torque of knee extensors at 180°/s (Nm)	No improvement in strength	Mean ± SD RT: 2.7 ± 114.32 Control: −2.8 ± 88.34 p-value > 0.05
Turri-Silva 2021	$N = 14$ CRT − 6 CG − 8	Isokinetic peak torque of knee extensors at 90°/s (Nm)	No improvement in strength	MD (95% CI) 1.8 (−66.2–69.8)

Abbreviations: CG, control group; CRT, circuit resistance training; MD, mean difference; Nm, newton-meter; RT, resistance training; SD, standard deviation.

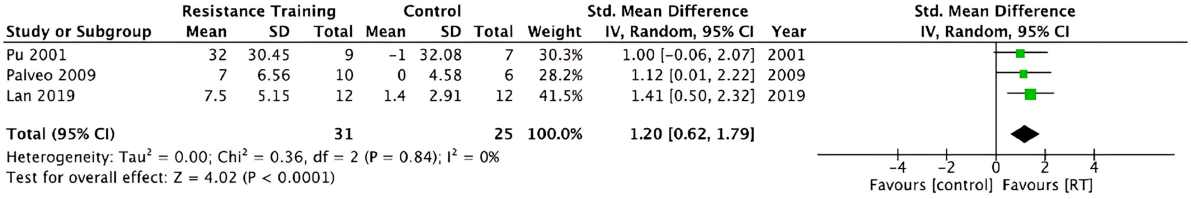

FIGURE 4 | Change in Upper Body Strength, pectoralis strength measured using a 1-repetition maximum test, showing pooled analysis data as standard mean difference (95% confidence interval) [46–48].

muscles, using a bench/chest press exercise test [46–48]. In total, 56 participants were included in the meta-analysis, with 31 participants in the RT group and 25 participants in the control group. Results show that RT was associated with a significant improvement in upper body strength compared to the control group [SMD 1.20 (95% CI − 0.62, 1.79) p-value <0.0001], as seen in Figure 4, with no heterogeneity detected in the pooled analysis ($I^2 = 0\%$, $p = 0.84$).

3.5 | Resistance Training on Anthropometry and Body Composition

Three studies assessed the effects of RT on different measures of body composition [46, 47, 50]. Pu et al. assessed total body muscle mass (kg) using a 24-hour urine creatinine test, collected following a three-day meat-free diet [46]. No significant change in body muscle mass was detected when comparing RT to untrained participants ($p > 0.05$). Palveo et al. assessed changes in body fat percentage from body density measurements derived from a seven-site skinfold assessment, using skinfold callipers at the abdomen, chest, maxillary, subscapular, supra iliac, thigh and triceps sites [47]. No significant change in body fat percentages was observed ($p > 0.05$). Turri-Silva et al. used DEXA scans to assess percentages of total body fat mass and total body lean mass [50]. No significant changes were observed in either measure of body composition. Further details on these results can be found in Table 2.

3.6 | Resistance Training on Biochemical Markers of Cachexia

Fasting blood samples were used by Feiereisen et al. to assess serum levels of TNF-alpha and IL-6 [49]. The decrease in TNF-alpha levels in the RT group from baseline to post-intervention was not statistically significant (p-value = 0.08). When comparing the change in TNF-alpha levels in the RT group to the control group, the difference was not statistically significant as well. As for IL-6 levels, RT caused a significant decrease in IL-6 levels post-training compared to baseline levels in the intervention group. However, when compared to the control group, the decrease in IL-6 levels was not significant (p-value >0.05) [49]. Further details on the results can be found in Table 3.

3.7 | Resistance Training on Quality of Life

Two studies reported measurements of psychosocial parameters at baseline and post-training [43, 45]. Cider et al. used the Quality of Life Questionnaire – Heart Failure (QLQ-HF) to assess self-reported life satisfaction, physical activity, somatic symptoms and emotions of participants [45]. No improvement in any measure of the QoL was detected in the RT group post-training compared to control participants, as seen in Table 4. Groennebaek et al. used the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) to measure the self-reported QoL before and after the six-week intervention [43]. Self-reported disease-related QoL significantly improved in the blood-flow restricted resistance exercise (BFRRE) group compared to participants in the control group. Due to the use of different questionnaires and the assessment of different psychosocial parameters, a meta-analysis was not performed.

3.8 | Resistance Training on Fatigue, Anorexia, Depression, Mortality and Hospitalisation

No studies included in this review reported measures of fatigue, anorexia or depression. Adverse events were recorded in three studies [44, 45, 50]. Further details on the adverse events recorded can be found in Supplementary Materials (S2). Selig

TABLE 2 | Change in anthropometry outcomes assessed by included studies [46, 47, 50].

Study	Sample size	Outcome assessed	Findings	Measure of assessment
Pu 2001	N = 16 RT – 9 Control – 7	Body muscle mass (kg)	No significant change was observed	Mean ± SE RT: 1.81 ± 1.07 Control: −0.18 ± 1.6 p-value > 0.05
Palveo 2009	N = 16 ST – 10 Control – 6	Body fat (%)	No statistically significant decrease in body fat % recorded	Mean ± SD ST: −1 ± 6.56 Control: 0 ± 4.58 p-value > 0,05
Turri-Silva 2021	N = 14 CRT – 6 CG – 8	Fat mass (%)	No significant changes were observed	Mean ± SD CRT: −0.30 ± 0.72 CG: −0.71 ± 1.92
		Lean mass (%)	No significant changes were observed	Mean ± SD CRT: 0.75 ± 1.45 CG: 0.30 ± 1.78

Abbreviations: CG, control group; CRT, circuit resistance training; DEXA, dual energy X-ray absorptiometry; RT, resistance training; SD, standard deviation; SE, standard error; ST, strength training.

TABLE 3 | Change in biochemistry outcomes assessed by included studies [49].

Study	Sample size	Outcome assessed	Findings	Measure of assessment
Feiereisen 2013	$N = 30$ ST – 15 Control – 15	TNF-alpha levels pg/mL	A nonsignificant decrease between ST results at baseline and post-training was recorded (p-value = 0.08). No significant difference when compared to untrained individuals.	Mean ± SD ST: −1.17 ± 2.05 Control: −0.27 ± 1.06 ($p > 0.05$)
		IL-6 levels pg/mL	A significant difference was recorded when comparing ST at baseline to ST post-training ($p = 0.05$). No significant difference was recorded when compared to the control group.	Mean ± SD ST: −1.68 ± 3.01 Control: 0.12 ± 1.82 ($p > 0.05$)

Abbreviations: IL-6, interleukin-6; SD, standard deviation; ST, strength training; TNF, tumour necrosis factor.

et al. recorded one sudden death of a participant in the RT group [44]. Two studies stated no records of hospitalisations or death [46, 47].

4 | Discussion

4.1 | Analysis of Findings

Due to the previously explained detrimental effects of muscle wasting on the functional capacity, QoL, morbidity and mortality of patients with HF, this review aimed to investigate the effects of RT on markers of cachexia in patients with HF. As of yet and to our knowledge, no published reviews have investigated the effects of RT in patients with HF with a specific focus on its effect on markers of cachexia. Additionally, it is important to note that due to the lack of clinical studies examining cachectic patients with HF, this review investigated the effects of RT on markers of cachexia in patients with HF, rather than the effects of RT on cachectic patients with HF specifically.

Nine RCTs were identified that assessed the effect of RT on markers of cachexia in patients with HF. One of the main findings of this review is the significant improvement in lower and upper body 1RM muscle strength post-RT intervention. Pooled analysis of data from four studies revealed a significant increase in the load lifted at 1RM using the knee extensor muscles, knee flexor muscles, overall leg muscles and pectoralis muscles associated with RT. Reduced lower and upper body muscle strength is undoubtedly a detrimental factor potentially linked to reduced independence, mobility, QoL and functional capacity of older patients generally [51, 52], and especially in HF, where muscle strength is strongly associated with morbidity and mortality [53–55]. Muscle strength is also a significant component of sarcopenia, a progressive skeletal muscle wastage disorder associated with increased physical disability, fractures and mortality [56]. Irrespective of the type of HF, sarcopenia is prevalent in approximately 34% of patients with HF [57]. Therefore, the preservation and strengthening of muscle is important in patients with HF and can potentially be achieved through RT, based on the findings of this review. Nevertheless, the strengthening of muscle was only detected in studies where patients were performing 1RM tests, which are relatively slower movements compared to the isokinetic/isometric 60, 90 and 180°/s movements. Pooled analysis of data from four studies investigating the effect of RT on lower body strength using an isokinetic dynamometer at 60°/s showed favourability for RT; however, the results were not significant. Comparably, isolated studies that were ineligible to be included in a pooled analysis showed no improvement in strength measured using an isokinetic dynamometer at 90 and 180°/s [45, 50]. These findings suggest that skeletal muscle was strengthened when performing slower movements in strength tests, but when performing rapid movements, no significant improvements were detected. This could potentially have clinical and functional significance, as it has been shown that the reduced ability of the lower body muscle to generate rapid movements and power is associated with an increased risk of falls in older people [58]. Therefore, results from this meta-analysis suggest that RT could potentially increase muscle strength in slower movements, which improves the functional capacity of patients to perform daily activities, such as lifting objects or standing up from

TABLE 4 | Change in psychosocial parameters and quality of life measurements in included studies [43, 45].

Study	Sample size	Outcome assessed	Findings	Measure of assessment
Cider 1997	*N* = 24 RT – 12 Control – 12	Life satisfaction	No significant improvement detected	Mean ± SD RT: 0 ± 16.8 Control: 1.4 ± 16.87 ($p > 0.05$)
		Physical activity	No significant improvement detected	Mean ± SD RT: 2.6 ± 20.31 Control: 3.5 ± 25.98 ($p > 0.05$)
		Somatic symptoms	No significant improvement detected	Mean ± SD RT: 1 ± 20.07 Control: 1.4 ± 18.03 ($p > 0.05$)
		Emotions	No significant improvement detected	Mean ± SD RT: 0.7 ± 18.71 Control: 0.4 ± 15.44 ($p > 0.05$)
Groennebaek 2019	N = 24 BFRRE – 12 Control – 12	Quality of life	BFRRE improved self-reported disease-related quality of life compared to control participants	Points (95%CI) 5.4 (−0.04, 10.9) 0.05

Abbreviations: BFRRE, blood flow restricted resistance exercise; CI, confidence interval; RT, resistance training; SD, standard deviation.

a chair but has limited effects on rapid muscle movements, linked to muscle strength in preventing falls. Further research is needed to test the ability of RT to improve muscle strength during rapid movements, as well as reach recommendations of RT to increase muscle strength in slower movements.

Interestingly, despite the significant improvement in muscle strength, included studies assessing measures of body composition detected no significant increase in anthropometric measurements, including skeletal muscle mass measured using a 24-hour urine creatinine test, body fat percentage using skinfold measurements and fat mass and lean mass measured using DEXA scan. In previous literature, RT has been associated with an increase in skeletal muscle mass, lean body mass and fat-free mass in healthy adults [59–61]. Nevertheless, in certain clinical populations, such as in older patients with cancer [62, 63], RT has been shown to increase skeletal muscle strength, but not consistently increase muscle hypertrophy. Therefore, chronic diseases, such as cancer or CHF, may impact an individual's response to exercise and ability to induce muscle hypertrophy, as the effects of chronic diseases, including increased catabolic drive, are known to have a detrimental impact on muscle protein synthesis/increasing proteolysis and muscle hypertrophy [64]. Further studies investigating the effect of RT on body composition in patients with CHF are needed, potentially in combination with multimodal therapies, such as the use of nutrition interventions and anabolic agents. This has been suggested and trialled in other conditions such as cancer and chronic obstructive pulmonary disease [65].

The findings of this review showed that RT interventions had a significant decrease in cytokines post-training compared to baseline, in patients with HF, but showed no significant difference when compared to levels of the change in cytokines of the untrained group [49]. Previous literature assessing the effects of RT on inflammatory markers in various populations shows conflicting results. Ogawa et al. [66] found no significant changes in plasma concentrations of TNF-alpha and IL-6 after 12 weeks of RT in older women, whereas Phillips et al. [67] recorded a significant reduction in TNF-alpha after 10 weeks of RT in the same population. Several reasons, such as methodological differences, could explain the conflicting results. However, to our knowledge, studies investigating the effect of RT on cytokines in patients with HF are very limited. Our findings are based on only one study with a small sample size and high risk of bias. Nevertheless, given the mechanisms involved in exercise training that modulate the inflammatory state, incorporating exercise into HF rehabilitation could theoretically be beneficial. A potential mechanism is that contracting skeletal muscle, through strength training, leads to the activation of a cascade of events that stimulates the production of the transcriptional coactivator peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha, which prevents protein catabolism and muscle wasting, and decreases the expression

of inflammatory marker genes, leading to the suppression of chronic inflammation [68]. However, there is currently inadequate evidence available to recommend RT interventions to reduce inflammatory cytokine levels in patients with HF. Further studies with a larger sample size are necessary.

Conflicting results were recorded in included studies in this review assessing psychosocial parameters and self-reported QoL. Three studies that were excluded from this systematic review due to not assessing primary markers of cachexia assessed the effect of RT on self-reported quality of life in patients with HF using the MLWHFQ. Significant increases in QoL were recorded in each study's RT group when compared to baseline QoL measurements and when compared to the control group [35, 69, 70], which is comparable to the findings in the included study by Groennebaek et al., using the MLWHFQ as well. The variation in these results may therefore be attributed to the differing questionnaires used in the included studies; however, currently, there is inadequate evidence to recommend RT to improve QoL in patients with HF.

4.2 | Critical Appraisal of Included Studies

Results of the risk of bias assessment show variation in the level of risk of bias each study possesses. The sequence generation of randomisation was not fully explained by most included studies [43–45, 47, 48], meaning that the level of randomisation and allocation concealment is questionable. Blinding of participants was difficult to establish due to the nature of the intervention, but most studies incorporated blinding of outcome assessors [42, 44, 46, 47, 50]. Furthermore, this meta-analysis under-represented the local population of patients with HF, as patients with advanced HF, class IV of the NYHA, were not included in any RT trial, and only one study included patients with preserved ejection fraction [50]. This limits the application and interpretation of results to the overall CHF population guidelines.

4.3 | Comparison With Previous Systematic Reviews

Three systematic reviews were published previously assessing the effects of RT on HF [27–29]. Our findings on the effects of RT on 1RM leg press strength in HF mirrored that of the previous most recent analyses in 2017 [28] and 2021 [29]. However, the improvement in 1RM strength of knee flexors detected in our analysis was only assessed in the 2021 analysis and was then found insignificant [29]. The isokinetic peak torque of knee flexors was not recorded in any previous analysis. The findings of our analysis recorded a higher improvement in the 1RM strength of the pectoralis muscles compared to the most recent analysis, which was the first to address the effects of RT on upper body strength [29]. This systematic review is the first to address the effects of RT on anthropometric measurements and cytokines in HF, due to its focus on markers of cachexia in HF. Improvement in QoL was assessed in all previous analyses and, similar to our findings, was found significant in studies using the MLWHFQ [27–29]. Despite some overlap in outcomes of the meta-analysis with previous systematic reviews, this study introduces novelty by evaluating the effects of resistance training on muscle strength in HF through the lens of Evans et al.'s definition of cachexia [11].

4.4 | Strengths and Limitations

Previous published systematic reviews have provided strong evidence of the effect of RT on various outcomes of HF. However, due to the wide prevalence of cachexia in HF and its debilitating effect on functional capacity, QoL and disease prognosis, it is crucial to primarily assess the effect of interventions on markers of cachexia in HF. For that reason, this review is of great importance, being the first systematic review focusing on the effect of RT on markers of cachexia in patients with HF. Other strengths of this review include the rigorous methodology that was followed to complete this analysis, which included three independent reviewers (RH, AS and NM) involved in the screening and interpreting of data.

However, this review has some limitations that affect the strength and implementation of the results. Methodological heterogeneity and study design variability exist between the included studies, such as the models of isokinetic dynamometers used, the length and intensity of the training and the exercises incorporated in the RT protocol. Some studies, such as Palveo et al., included participants who were being treated by an afterload-reducing agent, such as a beta-adrenergic blocker, which has been linked to improved exercise tolerance and breathlessness [71]. Beta-blockers have also been shown to have a positive effect in reducing cachexia in patients with HF [72]. This further introduces variability in study designs that could impact the interpretation of our findings. Nevertheless, it is important to note that future multi-modal interventions incorporating beta-blockers and RT could potentially show significant positive effects in reducing cachexia in patients with HF. Furthermore, the data extraction process involved one reviewer. To improve reliability of results, two or more reviewers should independently extract data following a consensus process. Unfortunately, the number of RCTs that incorporate an RT-only programme, compared to an aerobic training or combined programme, is limited, which affected the number of studies included in this review. Furthermore, most of the studies included relatively small sample sizes, with the smallest being 13 participants in both control and intervention groups [42] and the largest being 39 participants [44]. Larger sample sizes could allow for more significant trends to be detected. Additionally, results should be interpreted with caution due to the risk of bias in the studies included. At present, to our knowledge, there have been no studies that specifically examined the effects of RT on cachectic patients with HF. Therefore, some outcomes of interest were not assessed by any study included, such as body weight change or BMI, which are key prognostic markers of cachexia [11].

4.5 | Implications for Practice and Future Research

Despite the recorded improvement of muscle strength associated with RT, the methodological variations of published RCTs, the low number of trials and small sample sizes make it challenging to identify a specific optimal RT programme to incorporate into the cardiac rehabilitation of patients with HF. The 2023 British Association for Cardiovascular Prevention and Rehabilitation (BACPR) guidelines highlight

the importance of physical activity and exercise training in HF [73]. However, due to the lack of clinical trials assessing the various forms of exercise in patients with HF, including RT, AT and combined training, no specific recommendations regarding RT are provided in these guidelines. Further research to validate the benefits of RT in regulating markers of cachexia in HF is necessary to determine an optimal RT protocol. As for the safety of RT programmes in HF, the findings of this review show that RT programmes were safely performed by participants in all included trials. Adverse events occurred in some studies, but they were all non-exercise- and non-cardiac-related. Nonetheless, studies including patients with severe HF (NYHA IV) and patients with preserved ejection fraction are needed to deem RT safe for the general HF population.

Furthermore, future research assessing the cardiorespiratory reflex control and autonomic balance of patients with HF in response to training would provide further insights into the effect of RT on cardiac cachexia. Patients with cardiac cachexia demonstrate impairment of the cardiorespiratory reflex control and autonomic derangements, closely linked to a neuro-hormonal activation of a catabolic state of wasting [17, 74]. As a response to left ventricular dysfunction, the sympathetic nervous system is activated to maintain cardiac output. However, with the progression of the disease, overactivation of the sympathetic nervous system takes place, alongside impairment of the neurohormonal activation of neurotransmitters and hormones, such as norepinephrine and epinephrine, which is linked to the progression of HF to cardiac cachexia [17]. This is thought to be associated with abnormal sympathovagal control of HRV in patients, favouring the sympathetic nervous system, characterised by shifts in the low-frequency to high-frequency ratio (LF/HF), an increase in low-frequency (LF) and a decrease in high-frequency (HF) [75]. Trials investigating the effect of AT on patients with CHF demonstrated a decrease in LF and an increase in HF, accompanied by a decrease in whole-body norepinephrine, after exercise training [21]. Studies investigating the effects of RT on HRV and its components in patients with HF are limited. Therefore, future research involving spectral analysis of HRV could potentially provide a clearer understanding of the effect of RT on the sympathovagal balance, neurohormonal activation and development of cardiac cachexia in patients with HF.

5 | Conclusions

RT has shown potential benefits in safely preserving and enhancing lower and upper body 1RM muscle strength in patients with HF who are at risk of cardiac cachexia. Despite recording insignificant associations between RT and anthropometric measurements, the inclusion of RT in guidelines of cardiac rehabilitation has the potential to address issues of muscle weakness and frailty. However, specific RT protocol recommendations to prevent the development of cachexia cannot be made without the publication of more robust RCTs, with an adequate power size calculation and careful assessment of clinical outcomes of markers of cachexia.

Author Contributions

Adrian Slee: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, writing – original draft, writing – review and editing.

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Conflicts of Interest

None declared.

Ethical Standards

The manuscript does not contain clinical studies or patient data.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.